

A new insight in PK distribution volume metrics, V_{ss} and V_z : theory and in-silico study Supplementary material

Manuel Prado-Velasco, Laura García-Ruesgas

1 Terminal volume estimation from extravascular profiles

We derive here the semi-NCA methodology to estimate the terminal apparent volume $V_z^{(C)}$ from an extravascular (EV) profile measured through the declared scalar observable

$$c(t) = C\mathbf{A}(t).$$

For central observation, $C = V_1^{-1}\mathbf{e}_1^T$ and $c(t) = c_p(t)$. For a non-central or composite observable, all terminal intercepts and clearances below refer to $c_z(t) = C\mathbf{A}_z(t)$, not necessarily to central plasma concentration. The objective is not to identify the full absorption model, but to recover a biologically interpretable estimate of the terminal volume of the PK subsystem, correcting the standard estimator $CL_z/\lambda_z^{\text{EV}}$ when the terminal EV slope is absorption-controlled. The method extends the terminal mass-balance identity in equation (M24) to several parallel depots, each one possibly receiving either an impulse input or a finite rectangular input window. The estimated $V_z^{(C)}$ always refers to the PK subsystem excluding depots; consequently, the clearance used below is the PK-subsystem terminal clearance relative to the same observable, CL_z , not the extended-system clearance obtained after appending absorption states.

Step 0: observable consistency and identifiability. The same observable row C must be used for the IV and EV profiles, for the terminal intercept, for $V_{ss}^{(C)}$ if it is used as an anchor, and for the terminal clearance CL_z . The method requires $C\mathbf{A}_z(t) \neq 0$ in the terminal phase. With only a non-central concentration profile $C\mathbf{A}(t)$, CL_z is generally not identifiable from D/AUC_C , because D/AUC_C is an input-dependent average apparent clearance, whereas

$$CL_z = \frac{r_z(t)}{C\mathbf{A}_z(t)} \quad (1)$$

is a terminal-mode clearance, consistent with equation (M18). Thus, CL_z must either be known from the structure, estimated from an additional measurement of elimination rate or total amount, or justified by a special condition. The common NCA substitution $CL_z = D/AUC$ is valid without qualification only when the elimination rate is proportional to the measured observable throughout the relevant response, as in central observation with central elimination.

Step 1: terminal regime and flip-flop detection. Let λ_z^{EV} and λ_z^{IV} be the terminal slopes obtained from semi-logarithmic regression of the EV and IV profiles measured as $c(t) = C\mathbf{A}(t)$. If $\lambda_z^{\text{EV}} \approx \lambda_z^{\text{IV}}$, the terminal phase is treated as non-flip-flop and equation (M20) is used:

$$\hat{V}_z^{(C),\text{NFF}} = \frac{CL_z}{\lambda_z^{\text{EV}}}. \quad (2)$$

If $\lambda_z^{\text{EV}} < \lambda_z^{\text{IV}}$, flip-flop is assumed and the controlling terminal rate is

$$k_* = \lambda_z^{\text{EV}}. \quad (3)$$

The EV terminal intercept defines

$$c_z^{\text{EV}}(t) = c_{z,0}^{\text{EV}} e^{-k_* t}, \quad c_{z,0}^{\text{EV}} = C\mathbf{A}_z^{\text{EV}}(0). \quad (4)$$

Step 2: aggregate terminal depot correction. Let $\mathcal{R}$ be the set of depot branches whose absorption rate is indistinguishable from the controlling value k_* . The individual branches in $\mathcal{R}$ are not identifiable from the terminal slope alone. For the semi-NCA methodology proposed here, the controlling aggregate is additionally assumed to belong to a single terminal input class. That is, all branches in $\mathcal{R}$ are assumed to arise either from bolus-loaded depots or from rectangular depot-input windows. Mixed terminal classes within the controlling aggregate are not treated as identifiable within the semi-NCA framework, because the terminal mass-balance correction would then depend on several independent temporal-shape contributions that cannot be resolved from the terminal slope and intercept alone. In such cases, the preferred strategy is explicit model-based identification of the absorption structure. What enters the mass-balance correction is only the aggregate terminal absorbed-dose amplitude

$$\Theta_z = \sum_{j \in \mathcal{R}} F_j D_j \eta_j, \quad (5)$$

where D_j is the nominal dose entering depot branch j , F_j is the fraction of that branch entering the PK subsystem, and η_j is the terminal shape factor of the input to the depot. With this definition, the semi-NCA flip-flop identity becomes

$$\boxed{\hat{V}_z^{(C),\text{FF}} = \frac{CL_z}{k_*} - \frac{\Theta_z}{c_{z,0}^{\text{EV}}}}. \quad (6)$$

For a known depot input $w_j(t)$, using the same time origin as the terminal intercept in equation (4),

$$\eta_j = \frac{1}{D_j} \int_0^\infty e^{k_* t} w_j(t) dt, \quad D_j = \int_0^\infty w_j(t) dt. \quad (7)$$

Thus, a bolus input to the depot at the time origin gives $\eta_j = 1$, whereas a rectangular input of width T_j starting at the time origin gives

$$\eta_j(T_j) = \frac{e^{k_* T_j} - 1}{k_* T_j} = F_{\text{abs}}(k_*) e^{k_* T_j}, \quad (8)$$

with F_{abs} as defined in equation (MB20). This is the semi-NCA counterpart of equation (MB21). If the rectangular input starts at t_{0j} , the factor in equation (8) must be multiplied by $e^{k_* t_{0j}}$. For $T_j > 0$, $\eta_j(T_j) > 1$ and $\eta_j(T_j) \rightarrow 1$ as $T_j \rightarrow 0^+$.

Step 3: primary estimators when the terminal form is known. Under the homogeneous terminal-class assumption introduced above, the aggregate correction can be represented by a single correction family. If the controlling aggregate is known to arise from bolus-loaded depot branches, then $\eta_j = 1$ and

$$\hat{V}_z^{(C), \text{bolus}} = \frac{CL_z}{k_*} - \frac{\sum_{j \in \mathcal{R}} F_j D_j}{c_{z,0}^{\text{EV}}}. \quad (9)$$

If the controlling aggregate is known to arise from rectangular depot-input windows, then

$$\hat{V}_z^{(C), \text{rect}} = \frac{CL_z}{k_*} - \frac{\sum_{j \in \mathcal{R}} F_j D_j \eta_j(T_j)}{c_{z,0}^{\text{EV}}}. \quad (10)$$

These formulas identify only the aggregate correction, not each branch-specific contribution. This is sufficient for estimating $V_z^{(C)}$ from the terminal mass balance if CL_z is available.

Relation with the terminal input direction. If the structural depot directions $\mathbf{B}_j$ are known and $\mathbf{1}^T \mathbf{B}_j = 1$, the absorption-controlled terminal direction is

$$\mathbf{b}_{\text{FF}} = \frac{\sum_{j \in \mathcal{R}} F_j D_j \eta_j \mathbf{B}_j}{\sum_{j \in \mathcal{R}} F_j D_j \eta_j}. \quad (11)$$

The corresponding resolvent identity is

$$V_z^{(C), \text{FF}}(\mathbf{b}_{\text{FF}}) = \frac{\mathbf{1}^T G_* \mathbf{b}_{\text{FF}}}{C G_* \mathbf{b}_{\text{FF}}}, \quad G_* = -(K + k_* I)^{-1}. \quad (12)$$

Equation (12) is not an additional NCA estimator unless K and the depot directions are known; it is a consistency check linking the semi-NCA correction to equation (M28) and to the parallel-depot formulation in Appendix (MB.2).

Step 4: $V_{ss}^{(C)}$ -anchored exploratory branch when the terminal form is unknown.

If flip-flop is detected but the temporal form of the controlling terminal contribution is not known, the problem is not identifiable from the EV terminal slope and intercept alone. A practical regularized estimate can be obtained by using an external steady-state anchor. Let $V_{ss}^{(C),\text{ref}}$ denote the selected anchor, ideally $V_{ss}^{(C)}(\mathbf{b}_{\text{FF}})$ if the terminal direction is known. This anchor must be computed with the same observable C :

$$V_{ss}^{(C)}(\mathbf{b}) = \frac{\mathbf{1}^T G_0 \mathbf{b}}{C G_0 \mathbf{b}}, \quad G_0 = -K^{-1},$$

consistent with equation (M9). The aggregate correction compatible with the anchor is

$$\hat{\Theta}_{V_{ss}} = c_{z,0}^{\text{EV}} \left(\frac{CL_z}{k_*} - V_{ss}^{(C),\text{ref}} \right). \quad (13)$$

Let

$$S_{\text{ctrl}} = \sum_{j \in \mathcal{R}} F_j D_j. \quad (14)$$

If S_{ctrl} is known and positive, the implied aggregate shape factor is

$$\hat{\eta}_{V_{ss}} = \frac{\hat{\Theta}_{V_{ss}}}{S_{\text{ctrl}}}. \quad (15)$$

The interpretation is diagnostic. If $\hat{\eta}_{V_{ss}} \approx 1$, the data are compatible with a bolus-type terminal correction and equation (9) is used. If $\hat{\eta}_{V_{ss}} > 1$, the data are compatible with an extended depot-input window. This exploratory branch is intended only to discriminate between homogeneous terminal correction classes. It must not be interpreted as evidence that several heterogeneous terminal-input classes coexist within the controlling aggregate. If the data require simultaneous bolus-type and extended-window terminal corrections to explain the same terminal regime, the semi-NCA framework is considered structurally insufficient and explicit model-based identification is recommended.

In both cases the $\hat{\eta}_{V_{ss}}$ should be used to select the correction class, but the final estimate should use an externally justified T_{abs} , not the value of T_{abs} fitted to force $\hat{V}_z^{(C)} = V_{ss}^{(C),\text{ref}}$:

$$\hat{V}_z^{(C),\text{rect}}(T_{\text{abs}}) = \frac{CL_z}{k_*} - \frac{S_{\text{ctrl}}}{c_{z,0}^{\text{EV}}} \frac{e^{k_* T_{\text{abs}}} - 1}{k_* T_{\text{abs}}}. \quad (16)$$

Finally, if $\hat{\eta}_{V_{ss}} < 1$ beyond numerical and experimental tolerance, no bolus or rectangular-window terminal correction is compatible with the selected CL_z , $c_{z,0}^{\text{EV}}$, S_{ctrl} , and $V_{ss}^{(C),\text{ref}}$.

Step 5: compatibility checks and final fallback. When central observation, central input, and the assumptions underlying the central comparison are part of the model, the estimate should satisfy the corresponding ordering within tolerance. This ordering must

not be imposed for arbitrary non-central observables or arbitrary depot directions, because the exact sign of $V_z^{(C),\text{FF}} - V_{ss}^{(C)}$ is determined by equation (MB29) and can change with C and $\mathbf{b}$.

If the aggregate correction cannot be determined, if the implied $\hat{\Theta}_{V_{ss}}$ is non-positive, if $\hat{\eta}_{V_{ss}}$ is incompatible with the admissible correction class, or if the resulting $\hat{V}_z^{(C)}$ fails the applicable physical checks, the method returns the anchor V_{ss} .

$$\boxed{\hat{V}_z^{(C),\text{fallback}} = V_{ss}^{(C),\text{ref}}}. \quad (17)$$

This fallback is motivated by the convergence of V_z to V_{ss} for small k_a .

Remarks.

- The method estimates the terminal volume of the PK subsystem relative to the selected observable C and never the terminal volume of the extended depot-plus-PK system.
- The IV profile is used to distinguish intrinsic terminal disposition from absorption-controlled terminal behavior and to support the clearance estimate. If observation and elimination are central, $CL_z = CL$; otherwise, CL_z must be supplied or approximated with an explicit diagnostic flag.
- The method does not require identifying each terminal depot contribution separately. The identifiable object for the semi-NCA correction is the aggregate Θ_z .
- The $V_{ss}^{(C)}$ -anchored branch is exploratory and regularized. It should be used to select a plausible correction class or to provide a fallback when the terminal absorption form is not identifiable from concentration data alone.

2 Omalizumab TMDD model

In the present supplement, the distinction between *core* and *extended* models follows the implementation philosophy of the PyxCybSim tool used for the in-silico studies. The extended model is just the core model, increased by an additional subsystem. In this study the core model denotes the PK disposition subsystem needed to describe the drug disposition after IV administration, whereas the extended model appends auxiliary input, and depot structures required to reproduce the EV administration process. The same convention is used for all models below.

2.1 Model type and structural philosophy

The current implementation defines a linear time-invariant (LTI) approximation of the target-mediated drug disposition (TMDD) model for omalizumab/IgE from Straube (2025). The structural realization is a three-compartment mammillary model with:

- central free-drug amount state A_{D_c} ,
- central drug–target complex amount state A_{DR} ,
- peripheral free-drug amount state A_{D_p} ,
- and an optional depot amount state A_d for extravascular administration.

The starting point is the published three-state nonlinear TMDD model in the central compartment:

$$\begin{aligned}\frac{dD}{dt} &= -k_{\text{on}}DR + k_{\text{off}}DR - k_{eD}D, \\ \frac{dR}{dt} &= -k_{\text{on}}DR + k_{\text{off}}DR + k_{\text{syn}} - k_{eR}R, \\ \frac{dDR}{dt} &= k_{\text{on}}DR - k_{\text{off}}DR - k_{eDR}DR,\end{aligned}$$

with basal target

$$R_b = \frac{k_{\text{syn}}}{k_{eR}}.$$

Introducing total drug and total target concentrations,

$$D_T = D + DR,$$

$$R_T = R + DR,$$

yields

$$\begin{aligned}\frac{dD_T}{dt} &= -k_{eD}D_T + (k_{eD} - k_{eDR})DR, \\ \frac{dR_T}{dt} &= k_{\text{syn}} - k_{eR}R_T + (k_{eR} - k_{eDR})DR, \\ \frac{dDR}{dt} &= k_{\text{on}}(D_T - DR)(R_T - DR) - (k_{\text{off}} + k_{eDR})DR.\end{aligned}$$

Under the total quasi-steady-state approximation,

$$\frac{dDR}{dt} \approx 0,$$

one obtains the quadratic equation

$$DR^2 - DR(D_T + R_T + K_M) + D_T R_T \approx 0,$$

with

$$K_M = K_d \left(1 + \frac{k_{eDR}}{k_{\text{off}}} \right), \quad K_d = \frac{k_{\text{off}}}{k_{\text{on}}}.$$

For the high-affinity regime emphasized by Straube (2025),

$$DR \approx \begin{cases} D_T, & D_T \leq R_T, \\ R_T, & D_T \geq R_T. \end{cases}$$

The current implementation does not retain this piecewise system explicitly. Instead, it constructs an LTI operating-point approximation by fixing the free-target concentration at its basal value R_b and embedding binding into constant micro-rates. Hence the nonlinear term $k_{\text{on}}DR$ is replaced by a linear capture term $k_{\text{on}}R_bD$.

2.2 Core LTI disposition model

The core state vector is

$$\mathbf{A}_{\text{core}}(t) = \begin{pmatrix} A_{D_c}(t) \\ A_{DR}(t) \\ A_{D_p}(t) \end{pmatrix},$$

and the dynamics are written as

$$\frac{d\mathbf{A}_{\text{core}}}{dt} = K_{\text{core}}\mathbf{A}_{\text{core}} + B_{\text{core}}u_c(t).$$

Using the exact parameter mapping in the code,

$$k_{10} = k_{eD}, \quad k_{20} = k_{eDR}, \quad k_{12} = k_{\text{on}}R_b, \quad k_{21} = k_{\text{off}}, \quad k_{13} = \frac{Q}{V_c}, \quad k_{31} = \frac{Q}{V_p},$$

the core matrix is

$$K_{\text{core}} = \begin{pmatrix} -(k_{10} + k_{12} + k_{13}) & k_{21} & k_{31} \\ k_{12} & -(k_{21} + k_{20}) & 0 \\ k_{13} & 0 & -k_{31} \end{pmatrix},$$

and the central-input vector is

$$B_{\text{core}} = \begin{pmatrix} 1 \\ 0 \\ 0 \end{pmatrix}.$$

The corresponding state equations are

$$\frac{dA_{D_c}}{dt} = -(k_{10} + k_{12} + k_{13})A_{D_c} + k_{21}A_{DR} + k_{31}A_{D_p} + u_c(t),$$

$$\frac{dA_{DR}}{dt} = k_{12}A_{D_c} - (k_{21} + k_{20})A_{DR},$$

$$\frac{dA_{D_p}}{dt} = k_{13}A_{D_c} - k_{31}A_{D_p}.$$

The observation matrices defined in the code are

$$C_{D_c} = \begin{pmatrix} 1/V_c & 0 & 0 \end{pmatrix}, \quad C_{DR_c} = \begin{pmatrix} 0 & 1/V_c & 0 \end{pmatrix}, \quad C_{D_p} = \begin{pmatrix} 0 & 0 & 1/V_p \end{pmatrix},$$

and the total amount in the central subsystem is

$$A_{c,\text{total}} = A_{D_c} + A_{DR}.$$

2.3 Extended depot realization

The extended state vector is

$$\mathbf{A}_{\text{ext}}(t) = \begin{pmatrix} A_{D_c}(t) \\ A_{DR}(t) \\ A_{D_p}(t) \\ A_d(t) \end{pmatrix},$$

where A_d denotes the depot amount.

The code splits depot loss into an absorbed branch and a non-absorbed branch:

$$k_{a1} = Fk_a, \quad k_{a0} = (1 - F)k_a, \quad k_a = k_{a1} + k_{a0}.$$

Therefore the extended system is

$$\frac{d\mathbf{A}_{\text{ext}}}{dt} = K_{\text{ext}}\mathbf{A}_{\text{ext}} + B_{\text{ext}}u_d(t),$$

with

$$K_{\text{ext}} = \begin{pmatrix} -(k_{10} + k_{12} + k_{13}) & k_{21} & k_{31} & k_{a1} \\ k_{12} & -(k_{21} + k_{20}) & 0 & 0 \\ k_{13} & 0 & -k_{31} & 0 \\ 0 & 0 & 0 & -(k_{a1} + k_{a0}) \end{pmatrix},$$

and

$$B_{\text{ext}} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 1 \end{pmatrix}.$$

Equivalently,

$$\frac{dA_{D_c}}{dt} = -(k_{10} + k_{12} + k_{13})A_{D_c} + k_{21}A_{DR} + k_{31}A_{D_p} + k_{a1}A_d,$$

$$\begin{aligned}\frac{dA_{DR}}{dt} &= k_{12}A_{D_c} - (k_{21} + k_{20})A_{DR}, \\ \frac{dA_{D_p}}{dt} &= k_{13}A_{D_c} - k_{31}A_{D_p}, \\ \frac{dA_d}{dt} &= -k_a A_d + u_d(t).\end{aligned}$$

Thus the depot is a first-order absorption compartment with explicit availability split:

$$\text{absorbed fraction rate} = k_{a1}A_d, \quad \text{lost fraction rate} = k_{a0}A_d.$$

2.4 Parameter mapping

The structural parameter class contains the following nominal fields:

$$k_{\text{on}}, k_{\text{off}}, k_{eD}, k_{eDR}, R_b, V_c, V_p, Q, k_a, F, MW_D, MW_R.$$

The nominal values are:

$$\begin{aligned}k_{\text{on}} &= 1.01 \text{ nM}^{-1}\text{d}^{-1}, & k_{\text{off}} &= 1.98 \text{ d}^{-1}, & k_{eD} &= 0.10 \text{ d}^{-1}, & k_{eDR} &= 0.167 \text{ d}^{-1}, \\ R_b &= 1.1 \text{ nM}, & V_c &= 1.34 \text{ L}, & V_p &= 4.41 \text{ L}, & Q &= 4.3 \text{ L d}^{-1}, \\ k_a &= 0.31 \text{ d}^{-1}, & F &= 0.42, & MW_D &= 149000 \text{ g mol}^{-1}, & MW_R &= 190000 \text{ g mol}^{-1}.\end{aligned}$$

From these defaults, the nominal derived rates are

$$\begin{aligned}k_{12} &= k_{\text{on}}R_b = 1.111 \text{ d}^{-1}, & k_{21} &= 1.98 \text{ d}^{-1}, \\ k_{13} &= \frac{Q}{V_c} = \frac{4.3}{1.34} = 3.208955 \text{ d}^{-1}, & k_{31} &= \frac{Q}{V_p} = \frac{4.3}{4.41} = 0.975057 \text{ d}^{-1}, \\ k_{a1} &= Fk_a = 0.1302 \text{ d}^{-1}, & k_{a0} &= (1 - F)k_a = 0.1798 \text{ d}^{-1}.\end{aligned}$$

2.5 Three nominal scenario definitions used in the study

The notebook uses three structural scenario definitions, but one of them is combined with the no-elimination toggle to produce four operative cohorts in the sweep.

Nominal scenario The deterministic nominal operating point is exactly the default structural parameter set above:

$$(k_{\text{on}}, k_{\text{off}}, k_{eD}, k_{eDR}, R_b, V_c, V_p, Q, k_a, F) = (1.01, 1.98, 0.10, 0.167, 1.1, 1.34, 4.41, 4.3, 0.31, 0.42),$$

using the units stated in previous sections.

Hyper-IgE scenario The hyper-IgE scenario was defined as a mechanistically anchored stress configuration of the omalizumab–IgE TMDD system, not as an independently fitted population model. The systemic TMDD structure and the binding/disposition parameterization were based on the mechanism-based omalizumab model of Hayashi et al. (2007), using Table 3 as the primary reference for the omalizumab, IgE, and omalizumab–IgE complex parameters. The scenario preserves this model structure but shifts the operating point to a markedly elevated baseline IgE condition, $R_b = 10.95$ nM, in order to explore the behavior of the anti-IgE system under high target burden.

For the extravascular input, a slow first-order absorption setting was selected because regulatory clinical pharmacology information for Xolair describes subcutaneous omalizumab as slowly absorbed, with peak concentrations reached approximately 6–8 days after dosing, and reports an average absolute subcutaneous bioavailability of $F = 0.62$ (FDA 2013). Therefore, the hyper-IgE scenario uses $k_a = 0.071$ d^{−1} together with $F = 0.62$ as a conservative absorption-limited configuration. All systemic clearance and volume quantities used in this operating point were treated as bioavailability-corrected quantities, rather than apparent subcutaneous parameters, so that the derived microconstants remain internally consistent. Under the combined conditions of high IgE burden and slow extravascular input, the terminal slope can become absorption-controlled, making this scenario suitable for evaluating the emergence of flip-flop behavior in the omalizumab TMDD model.

The deterministic hyper-IgE operating point is defined by the following overrides:

$$\begin{aligned} k_a &= 0.071 \text{ d}^{-1}, \quad F = 0.62, \quad V_c = 3.0 \text{ L}, \quad k_{eD} = 0.059 \text{ d}^{-1}, \quad Q = 0.5 \text{ L d}^{-1}, \quad R_b = 10.95 \text{ nM}, \\ k_{\text{on}} &= 10^5 \text{ M}^{-1}\text{s}^{-1} = 8.64 \text{ nM}^{-1}\text{d}^{-1}, \quad K_d = 1.07 \text{ nM}, \quad k_{\text{off}} = K_d k_{\text{on}} = 9.2448 \text{ d}^{-1}, \\ V_{DR} &= 2.25 \text{ L}, \quad CL_{DR} = (5.86 + 7.32) \text{ mL h}^{-1} = 13.18 \text{ mL h}^{-1}, \\ k_{eDR} &= \frac{CL_{DR}}{V_{DR}} = 0.140587 \text{ d}^{-1}. \end{aligned}$$

In this deterministic hyper-IgE point, only the listed quantities are overridden; any unspecified parameter remains at the structural default.

No-complex-elimination scenario The third structural scenario is the no-complex-elimination variant:

$$k_{eDR} = 0.$$

This configuration should not be interpreted as a fitted clinical phenotype, but as an idealized case representing strongly reduced immune-complex removal, motivated by pathological settings that may perturb mononuclear phagocytic handling or FcRn-mediated recycling of IgG-containing species.

This scenario is applied to both operating points above, producing the two derived deterministic cases:

$$\text{nominal_no_elim} = \text{nominal with } k_{eDR} = 0,$$

hyperIgE_no_elim = hyperIgE with $k_{eDR} = 0$.

Hence the scenario uses:

- three conceptual scenario definitions: nominal, hyper-IgE, and no-complex-elimination;
- four operative cohorts for the Monte Carlo sweep: `nominal`, `hyperIgE`, `nominal_no_elim`, and `hyperIgE_no_elim`.

3 Omalizumab TMDD model with presystemic lymphatic transit

3.1 Model type and structural philosophy

The implemented model is:

- **Systemic block:** the LTI approximation of the omalizumab/IgE TMDD model.
- **Presystemic block:** a Zhao et al. (2013)-inspired subcutaneous absorption structure with depot, lymphatic transit, presystemic lymphatic loss, and an optional tiny direct vascular branch.

Core realization (4 states). The core includes the presystemic lymphatic state by design:

$$\mathbf{A}_{\text{core}}(t) = \begin{pmatrix} A_{D_c}(t) \\ A_{DR}(t) \\ A_{D_p}(t) \\ A_{D_L}(t) \end{pmatrix},$$

where:

- A_{D_c} : free-drug amount in the central compartment,
- A_{DR} : central drug-target complex amount,
- A_{D_p} : free-drug amount in the peripheral compartment,
- A_{D_L} : presystemic lymphatic transit amount.

Extended realization (5 states). The full extravascular realization adds the injection-site depot:

$$\mathbf{A}_{\text{ext}}(t) = \begin{pmatrix} A_{D_c}(t) \\ A_{DR}(t) \\ A_{D_p}(t) \\ A_{D_L}(t) \\ A_d(t) \end{pmatrix},$$

where A_d is the depot amount.

3.2 Published model lineage and reduction path

The Zhao et al. (2013) model describes subcutaneous absorption with vascular, endothelial, interstitial, and lymphatic states before systemic entry. The key lymphatic transport equation in the published absorption block is

$$\frac{dX_L}{dt} = ((1 - s_L) r L C_I) - \left(K_{\text{Lymph}} + \frac{1}{t} \right) X_L,$$

and the systemic entry term from lymph is

$$\frac{1}{t} X_L.$$

In the simplified discussion of Zhao et al. (2013), once drug is in the lymphatic transport state, the bioavailability to systemic circulation is

$$f = \frac{1/t}{1/t + K_{\text{Lymph}}} = \frac{1}{1 + tK_{\text{Lymph}}}.$$

Zhao et al. (2013) also shows that, under the published skin physiological parameters, the fraction initially entering the endothelial route is only

$$\frac{R_1 V_I}{R_1 V_I + (1 - s_L) L} = 0.00102 = 0.102\%.$$

This is the published quantitative reason why a dominant lymphatic route is justified for skin subcutaneous absorption.

The model used in the second scenario does **not** attempt to reproduce the full PBPK endothelial-interstitial system. Instead, it performs the following reduction:

1. Preserve two essential absorption motifs from Zhao et al. (2013):
 - a. dominant lymphatic presystemic transport,
 - b. negligible direct vascular entry.

2. Lump the local injection site into a first-order depot state A_d .
3. Lump lymphatic transport into a single presystemic amount state A_{DL} with two exits:

$$A_{DL} \xrightarrow{k_{LC}} A_{Dc}, \quad A_{DL} \xrightarrow{k_{L0}} \emptyset.$$

4. Preserve the original Straube (2025) systemic TMDD block after systemic entry.

The transport rate parameters follow:

$$k_{DC} = f_{\text{vascular}} k_a,$$

$$k_{DL} = (1 - f_{\text{vascular}}) k_a,$$

$$k_{LC} = \frac{1}{\tau_{\text{lymph}}},$$

$$F_{\text{lymph}} = \frac{k_{LC}}{k_{LC} + k_{L0}},$$

which implies

$$k_{L0} = k_{LC} \left(\frac{1}{F_{\text{lymph}}} - 1 \right).$$

Two presystemic quantities are taken almost directly from (Zhao et al. 2013):

- $F_{\text{lymph}} = 0.62$ is carried over from the reported omalizumab subcutaneous bioavailability.
- $f_{\text{vascular}} = 0.00102$ comes from the published 0.102% endothelial uptake fraction in (Zhao et al. 2013), which has been neglected to zero for the objective of the current study.

Two quantities are modeling choices of the new model:

- $k_a = 0.31 \text{ d}^{-1}$ is retained from the original (Straube 2025) depot time scale, not from (Zhao et al. 2013).
- $\tau_{\text{lymph}} = 2.5 \text{ h}$ was chosen as a representative value within the short transit-time range reported by (Zhao et al. 2013) of roughly 2–3 h; the table itself lists $t = 3 \text{ h}$.

Therefore, the lymphatic block is Zhao et al. (2013)-inspired and physiologically anchored.

3.3 Equations of the extended model

Core 4-state realization The core matrix form is

$$\frac{d\mathbf{A}_{\text{core}}}{dt} = K_{\text{core}} \mathbf{A}_{\text{core}} + \mathbf{B}_{\text{core}} u_c(t),$$

with

$$K_{\text{core}} = \begin{pmatrix} -(k_{10} + k_{12} + k_{13}) & k_{21} & k_{31} & k_{LC} \\ k_{12} & -(k_{20} + k_{21}) & 0 & 0 \\ k_{13} & 0 & -k_{31} & 0 \\ 0 & 0 & 0 & -(k_{LC} + k_{L0}) \end{pmatrix}, \quad \mathbf{B}_{\text{core}} = \begin{pmatrix} 1 \\ 0 \\ 0 \\ 0 \end{pmatrix}.$$

Equivalently, the state equations are

$$\frac{dA_{D_c}}{dt} = -(k_{10} + k_{12} + k_{13})A_{D_c} + k_{21}A_{DR} + k_{31}A_{D_p} + k_{LC}A_{D_L} + u_c(t),$$

$$\frac{dA_{DR}}{dt} = k_{12}A_{D_c} - (k_{20} + k_{21})A_{DR},$$

$$\frac{dA_{D_p}}{dt} = k_{13}A_{D_c} - k_{31}A_{D_p},$$

$$\frac{dA_{D_L}}{dt} = -(k_{LC} + k_{L0})A_{D_L}.$$

3.4 Extended 5-state realization

The extended extravascular realization is

$$\frac{d\mathbf{A}_{\text{ext}}}{dt} = K_{\text{ext}} \mathbf{A}_{\text{ext}} + \mathbf{B}_{\text{ext}} u_d(t),$$

with

$$K_{\text{ext}} = \begin{pmatrix} -(k_{10} + k_{12} + k_{13}) & k_{21} & k_{31} & k_{LC} & k_{DC} \\ k_{12} & -(k_{20} + k_{21}) & 0 & 0 & 0 \\ k_{13} & 0 & -k_{31} & 0 & 0 \\ 0 & 0 & 0 & -(k_{LC} + k_{L0}) & k_{DL} \\ 0 & 0 & 0 & 0 & -k_a \end{pmatrix}, \quad \mathbf{B}_{\text{ext}} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 1 \end{pmatrix}.$$

The corresponding state equations are

$$\frac{dA_{D_c}}{dt} = -(k_{10} + k_{12} + k_{13})A_{D_c} + k_{21}A_{DR} + k_{31}A_{D_p} + k_{LC}A_{D_L} + k_{DC}A_d,$$

$$\frac{dA_{DR}}{dt} = k_{12}A_{D_c} - (k_{20} + k_{21})A_{DR},$$

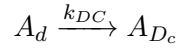
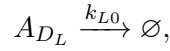
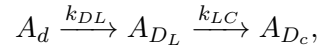
$$\frac{dA_{D_p}}{dt} = k_{13}A_{D_c} - k_{31}A_{D_p},$$

$$\frac{dA_{D_L}}{dt} = k_{DL}A_d - (k_{LC} + k_{L0})A_{D_L},$$

$$\frac{dA_d}{dt} = -k_a A_d + u_d(t).$$

3.5 Depot structure and systemic fraction

The depot structure is therefore a two-branch first-order depletion process:



The total fraction of depot material that reaches the systemic TMDD block is

$$F_{SC} = f_{\text{vascular}} + (1 - f_{\text{vascular}})F_{\text{lymph}}.$$

For this study $f_{\text{vascular}} = 0$ and $F_{SC} = 0.62$.

3.6 Parameters and nominal values

3.7 Systemic block

The systemic parameters are exactly the same as in the previous LTI model.

Table 1: Exact nominal systemic parameters preserved from the Straube (2025) LTI model.

Parameter	Nominal value	Comment
k_{on}	$1.01 \text{ nM}^{-1} \text{ d}^{-1}$	Linear capture uses $k_{12} = k_{\text{on}} R_b$
k_{off}	1.98 d^{-1}	Complex dissociation
k_{eD}	0.10 d^{-1}	Free-drug elimination
k_{eDR}	0.167 d^{-1}	Complex elimination
R_b	1.1 nM	Basal target concentration
V_c	1.34 L	Central volume
V_p	4.41 L	Peripheral volume
Q	4.3 L d^{-1}	Intercompartmental distribution flow
MW_D	$149000 \text{ g mol}^{-1}$	Drug molecular weight
MW_R	$190000 \text{ g mol}^{-1}$	Target molecular weight

The exact derived systemic micro-rates are

$$k_{10} = 0.10 \text{ d}^{-1}, \quad k_{20} = 0.167 \text{ d}^{-1}, \quad k_{12} = k_{\text{on}} R_b = 1.111 \text{ d}^{-1},$$

$$k_{21} = 1.98 \text{ d}^{-1}, \quad k_{13} = \frac{Q}{V_c} = \frac{4.3}{1.34} = 3.208955 \text{ d}^{-1}, \quad k_{31} = \frac{Q}{V_p} = \frac{4.3}{4.41} = 0.975057 \text{ d}^{-1}.$$

3.8 Presystemic lymphatic block

Table 2: Exact nominal presystemic parameters used by the lymphatic extension.

Parameter	Nominal value	Comment
k_a	0.31 d^{-1}	Retained from the original Straube depot time scale
F_{lymph}	0.62	Zhao-inspired lymphatic survival fraction
τ_{lymph}	2.5 h	Code choice inside Zhao's reported short 2–3 h transit range
f_{vascular}	0	Preset dependent: simplified

From these definitions, the exact derived lymphatic rates are

$$k_{LC} = \frac{1}{\tau_{\text{lymph}}} = \frac{1}{2.5 \text{ h}} = 0.4 \text{ h}^{-1} = 9.6 \text{ d}^{-1},$$

$$k_{L0} = k_{LC} \left(\frac{1}{F_{\text{lymph}}} - 1 \right) = 0.245161 \text{ h}^{-1} = 5.883871 \text{ d}^{-1},$$

$$k_{LC} + k_{L0} = 0.645161 \text{ h}^{-1} = 15.483871 \text{ d}^{-1}.$$

Note that Zhao et al. (2013) table gives $t = 3 \text{ h}$ and $K_{\text{Lymph}} = 0.00338 \text{ min}^{-1}$, which correspond to $k_{LC} = 0.333333 \text{ h}^{-1}$ and $K_{\text{Lymph}} = 0.2028 \text{ h}^{-1}$. The code intentionally changes the transit time to 2.5 h in the nominal parameterization, while keeping $F_{\text{lymph}} = 0.62$, so its implied loss rate becomes slightly larger than the value tabulated by Zhao et al. (2013).

3.9 Preset-specific derived rates

Table 3: Exact preset-dependent presystemic branch rates.

Preset	f_{vascular}	$k_{DC} \text{ (d}^{-1}\text{)}$	$k_{DL} \text{ (d}^{-1}\text{)}$	F_{SC}
simplified	0.000000	0.0000000	0.3100000	0.6200000
zhao_skin_vascular	0.001020	0.0003162	0.3096838	0.6203876

Our study uses the simplified preset.

4 Buprenorphine long-acting injectable model

4.1 Model type and structural philosophy

The scenario is based on a linear time-invariant population pharmacokinetic structure for buprenorphine based on a three-compartment mammillary disposition model with first-order elimination from the central compartment (Bjornsson et al. 2023). The disposition model is extended with three auxiliary absorption/depot states, giving the extended amount-state vector

$$\mathbf{A}_{\text{ext}}(t) = \begin{bmatrix} A_c(t) & A_2(t) & A_3(t) & A_{\text{seq}}(t) & A_{d1}(t) & A_{d2}(t) \end{bmatrix}^T.$$

Core disposition model The core PK subsystem is the three-compartment mammillary model

$$\frac{d}{dt} \begin{bmatrix} A_c \\ A_2 \\ A_3 \end{bmatrix} = K_{\text{core}} \begin{bmatrix} A_c \\ A_2 \\ A_3 \end{bmatrix} + B_{\text{core}} u_c(t),$$

with

$$K_{\text{core}} = \begin{bmatrix} -(k_{10} + k_{12} + k_{13}) & k_{21} & k_{31} \\ k_{12} & -k_{21} & 0 \\ k_{13} & 0 & -k_{31} \end{bmatrix}, \quad B_{\text{core}} = \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix},$$

and

$$k_{10} = \frac{CL}{V_c}, \quad k_{12} = \frac{Q_2}{V_c}, \quad k_{21} = \frac{Q_2}{V_2}, \quad k_{13} = \frac{Q_3}{V_c}, \quad k_{31} = \frac{Q_3}{V_3}.$$

The corresponding state equations are

$$\frac{dA_c}{dt} = -(k_{10} + k_{12} + k_{13})A_c + k_{21}A_2 + k_{31}A_3 + u_c(t), \quad (18)$$

$$\frac{dA_2}{dt} = k_{12}A_c - k_{21}A_2, \quad (19)$$

$$\frac{dA_3}{dt} = k_{13}A_c - k_{31}A_3. \quad (20)$$

The plasma concentration observable is

$$C_p(t) = \frac{A_c(t)}{V_c}.$$

Extended absorption/depot structure The extended realization keeps three absorption/depot states. The autonomous extended matrix contains first-order depletion of the three absorption states and their first-order transfer into the central compartment:

$$\frac{dA_c}{dt} = -(k_{10} + k_{12} + k_{13})A_c + k_{21}A_2 + k_{31}A_3 + k_{a,\text{seq}}A_{\text{seq}} + k_{a,d1}A_{d1} + k_{a,d2}A_{d2} + u_c(t), \quad (21)$$

$$\frac{dA_2}{dt} = k_{12}A_c - k_{21}A_2, \quad (22)$$

$$\frac{dA_3}{dt} = k_{13}A_c - k_{31}A_3, \quad (23)$$

$$\frac{dA_{\text{seq}}}{dt} = -k_{a,\text{seq}}A_{\text{seq}} + u_{\text{seq}}(t), \quad (24)$$

$$\frac{dA_{d1}}{dt} = -k_{a,d1}A_{d1}, \quad (25)$$

$$\frac{dA_{d2}}{dt} = -k_{a,d2}A_{d2}. \quad (26)$$

The default continuous input vector for the extended model is intentionally reduced to

$$u_{\text{ext}}(t) = \begin{bmatrix} u_c(t) \\ u_{\text{seq}}(t) \end{bmatrix}, \quad B_{\text{ext}} \in \mathbb{R}^{6 \times 2},$$

with

$$B_{\text{ext}} = \begin{bmatrix} 1 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 1 \\ 0 & 0 \\ 0 & 0 \end{bmatrix}.$$

Thus, $u_c(t)$ injects directly into A_c , whereas $u_{\text{seq}}(t)$ injects into the sequential absorption state A_{seq} . The direct absorption branches A_{d1} and A_{d2} remain structural states, but in the default interface they are loaded by initial conditions or state jumps rather than by separate continuous input functions.

Direct branches are represented as initial depot loads,

$$A_{d1}(0) = D_{d1}, \quad A_{d2}(0) = D_{d2}, \quad A_{\text{seq}}(0) = 0.$$

Route-dependent administration mapping The route-mapping layer distributes a nominal dose D as

$$D_{\text{abs}} = FD, \quad D_{\text{seq}} = f_{\text{seq}}D_{\text{abs}}, \quad D_{d1} = f_{d1}D_{\text{abs}}, \quad D_{d2} = f_{d2}D_{\text{abs}}.$$

For the sequential branch, the scenario builds the finite zero-order input

$$u_{\text{seq}}(t) = \begin{cases} D_{\text{seq}}/T_{\text{seq}}, & t_{\text{lag,seq}} \leq t < t_{\text{lag,seq}} + T_{\text{seq}}, \\ 0, & \text{otherwise,} \end{cases}$$

where $t_{\text{lag,seq}}$ and T_{seq} are route-specific lag and zero-order duration values.

The nominal route presets are as follows. For sublingual dosing (SL),

$$F = 0.14, \quad f_{\text{seq}} = 0.759, \quad f_{d1} = 0.241, \quad f_{d2} = 0,$$

$$t_{\text{lag,seq}} = 0.171 \text{ h}, \quad T_{\text{seq}} = 0.419 \text{ h}, \quad k_{a,\text{seq}} = 1.72 \text{ h}^{-1}, \quad k_{a,d1} = 0.0875 \text{ h}^{-1}.$$

For weekly subcutaneous dosing (Q1W),

$$F = 1, \quad f_{\text{seq}} = 0.455, \quad f_{d1} = 0.545, \quad f_{d2} = 0,$$

$$t_{\text{lag,seq}} = 0, \quad T_{\text{seq}} = 10.1 \text{ h}, \quad k_{a,\text{seq}} = 0.0401 \text{ h}^{-1}, \quad k_{a,d1} = 0.00565 \text{ h}^{-1}.$$

For monthly subcutaneous dosing (Q4W),

$$F = 1, \quad f_{\text{seq}} = 0, \quad f_{d1} = 0.0863, \quad f_{d2} = 0.9137,$$

$$t_{\text{lag,seq}} = 0, \quad T_{\text{seq}} = 0, \quad k_{a,d1} = 0.0441 \text{ h}^{-1}, \quad k_{a,d2} = 0.00166 \text{ h}^{-1}.$$

Structural nominal parameters The nominal disposition values are

$$CL = 52.1 \text{ L/h}, \quad V_c = 64.3 \text{ L}, \quad Q_2 = 186 \text{ L/h}, \quad V_2 = 130 \text{ L}, \quad Q_3 = 60.3 \text{ L/h}, \quad V_3 = 1580 \text{ L}.$$

The absorption parameters are route-dependent and are applied through the route administration mapping.

Population covariates and inter-individual variability The scenario implements the population layer externally to the structural model. The active subject-level disposition equations are

$$\begin{aligned} CL_i &= 52.1 \left(\frac{\text{Age}_i}{35} \right)^{-0.233} \left(\frac{\text{WT}_i}{72.4} \right)^{0.413} \exp(\eta_{CL,i}), \\ V_{c,i} &= 64.3 (1 + 2.69 \text{ OUD}_i) \exp(\eta_{Vc,i}), \\ Q_{3,i} &= 60.3 \exp(\eta_{Q3,i}), \quad V_{3,i} = 1580 \exp(\eta_{V3,i}). \end{aligned}$$

The random effects are

$$\begin{aligned} \eta_{CL,i} &\sim \mathcal{N}(0, 0.2067701313^2), & \eta_{Vc,i} &\sim \mathcal{N}(0, 0.6935882994^2), \\ \eta_{Q3,i} &\sim \mathcal{N}(0, 0.3672607823^2), & \eta_{V3,i} &\sim \mathcal{N}(0, 0.2916844976^2). \end{aligned}$$

The structural values Q_2 and V_2 remain fixed in the current population study.

Bioavailability and route-fraction covariate functions The scenario includes the published dose-dependent sublingual bioavailability function

$$F_{\text{SL}}(D) = 0.14 \left(\frac{D}{16 \text{ mg}} \right)^{-0.371}.$$

For the nominal 16 mg dose, this gives $F_{\text{SL}} = 0.14$.

In addition:

$$\text{logit}(F_{\text{Q1W1},i}) = \text{logit}(0.455) - 0.671 \text{ OUD}_i + 0.576 \text{ Female}_i + \eta_{F,i}.$$

where $F_{\text{Q1W1},i}$ is used as the subject-specific Q1W sequential fraction,

$$f_{\text{seq},i} = F_{\text{Q1W1},i}, \quad f_{d1,i} = 1 - F_{\text{Q1W1},i}, \quad f_{d2,i} = 0.$$

5 Additional Results

5.1 Omalizumab TMDD model

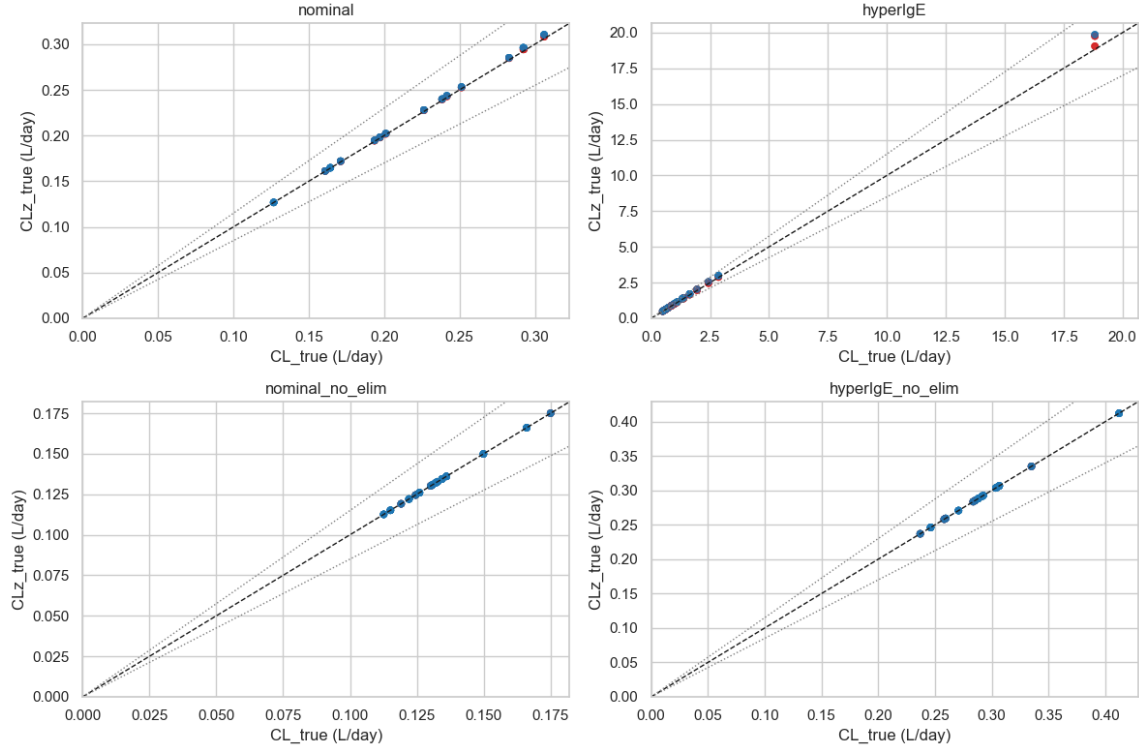


Figure 1: Structural terminal clearance CL_z versus exposure clearance CL in the omalizumab TMDD model. Points are stratified by cohort and flip-flop status, with red denoting flip-flop cases and blue denoting non-flip-flop cases. The identity line and $\pm 15\%$ bands show that CL_z and CL coincide in the no-elimination variants, whereas moderate deviations are retained when peripheral complex elimination is active.

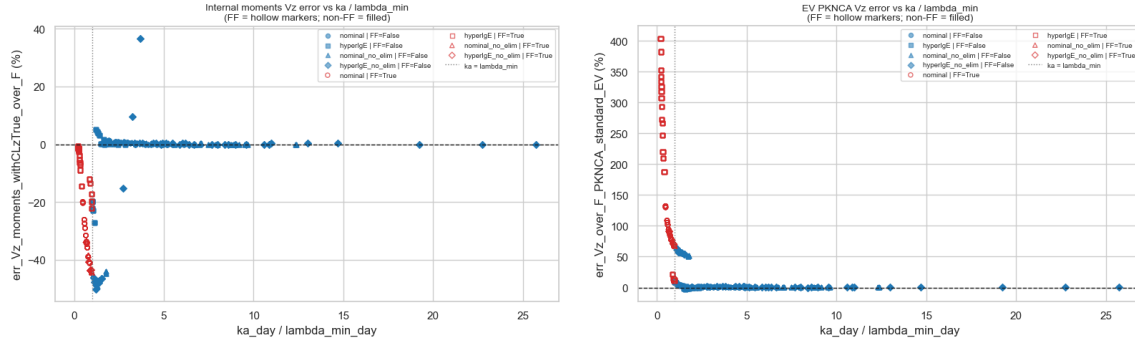


Figure 2: EV terminal-volume error versus $k_a/\lambda_{\min}$ in the omalizumab TMDD model. The left panel shows the relative error of the semi-NCA V_z/F estimator using supplied CL_z , whereas the right panel shows the corresponding standard PKNCA EV V_z/F error. Symbols identify cohorts; blue points denote non-flip-flop cases and red points denote flip-flop cases. The semi-NCA correction remains aligned with the structural reference, while the standard terminal estimator deteriorates under absorption-controlled terminal phases.

Under extravascular flip-flop conditions, the terminal slope identified by standard NCA becomes absorption-driven, such that

$$\lambda_z^{(\text{EV})} \approx k_a \quad (27)$$

instead of reflecting the true systemic terminal eigenvalue $\lambda_{\min}$. Since standard terminal-volume estimation follows

$$V_z \propto \frac{1}{\lambda_z}, \quad (28)$$

the resulting bias is governed approximately by

$$\frac{V_{z,\text{est}}}{V_{z,\text{true}}} \sim \frac{\lambda_{\min}}{k_a}. \quad (29)$$

Consequently, the error structure is controlled primarily by the dimensionless ratio $k_a/\lambda_{\min}$, rather than by k_a alone. This normalization justifies the interest in plotting the relative error against $k_a/\lambda_{\min}$.

5.2 Omalizumab TMDD model with presystemic lymphatic transit

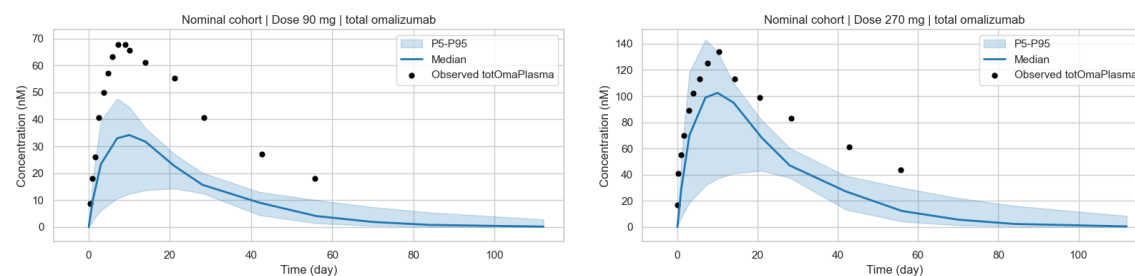


Figure 3: Physiological validation profiles for the nominal omalizumab TMDD model with presystemic lymphatic transit, shown together with the Meno-Tetang observations used in the main manuscript validation figure. The model underpredicts the $D = 90$ mg observations, but both simulated profiles retain a plausible disposition pattern and therefore provide a suitable route-matched setting for evaluating distribution-volume metrics after non-central administration.

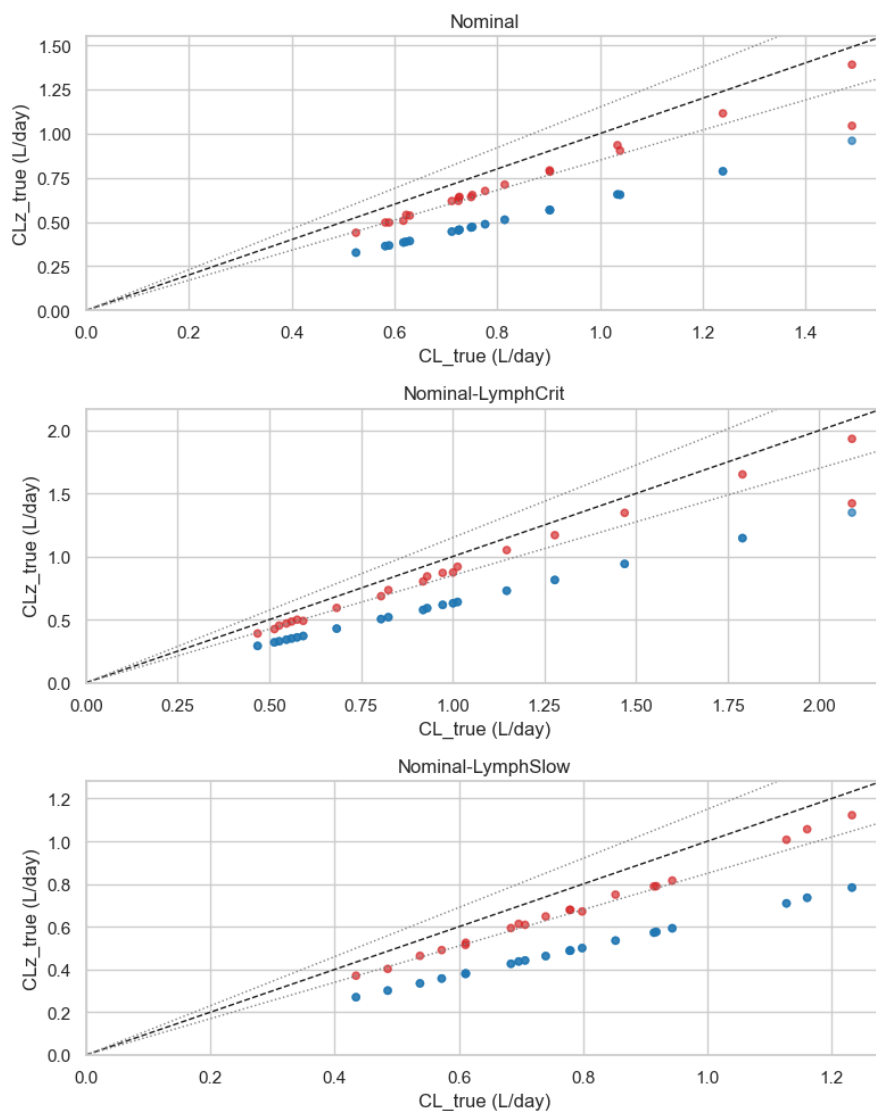


Figure 4: Structural terminal clearance CL_z versus exposure clearance CL in the omalizumab TMDD model with presystemic lymphatic transit. Red points denote flip-flop cases and blue points denote non-flip-flop cases; the identity line and $\pm 15\%$ bands are shown for reference. In this route-matched lymphatic core, CL_z is clearly lower than CL , especially in non-flip-flop profiles, so an AUC-based clearance used as a proxy for CL_z would markedly overestimate the terminal clearance.

The larger separation between CL_z and CL in the lymphatic scenario is mechanistically expected. The presystemic lymph compartment acts as a slow upstream reservoir that de-

couples global exposure from terminal disposition. The AUC-based clearance CL averages the whole response after entry through the lymphatic route, whereas CL_z is evaluated on the terminal core distribution observed centrally. When terminal mass is enriched in the non-central lymphatic pathway, the terminal elimination flux per unit central concentration is reduced and CL_z becomes smaller than CL .

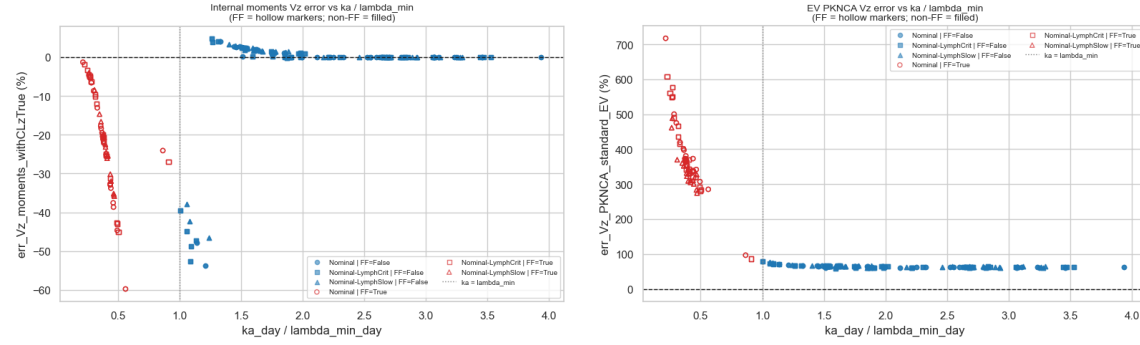


Figure 5: EV terminal-volume error versus $k_a/\lambda_{\min}$ in the omalizumab TMDD model with presystemic lymphatic transit. The left panel reports the relative error of the semi-NCA V_z estimator using supplied CL_z , and the right panel reports the standard PKNCA EV V_z error. The color code distinguishes non-flip-flop cases in blue from flip-flop cases in red, with symbols identifying cohorts. The comparison isolates the effect of absorption-controlled terminal behavior from the additional lymphatic decoupling between CL and CL_z .

5.3 Buprenorphine long-acting injectable model

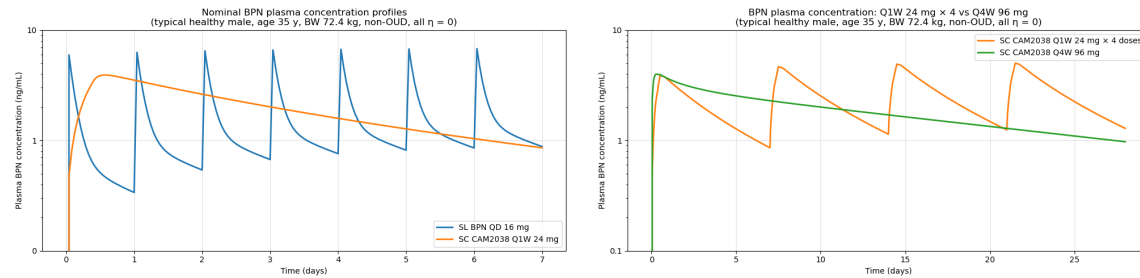


Figure 6: Simulated plasma buprenorphine profiles for a typical subject. The left panel compares SL 16 mg with Q1W 24 mg over one week, and the right panel compares Q1W 24 mg with Q4W 96 mg over 28 days. These profiles illustrate the transition from a relatively rapid non-flip-flop input to long-acting depot input that controls the observed terminal phase.

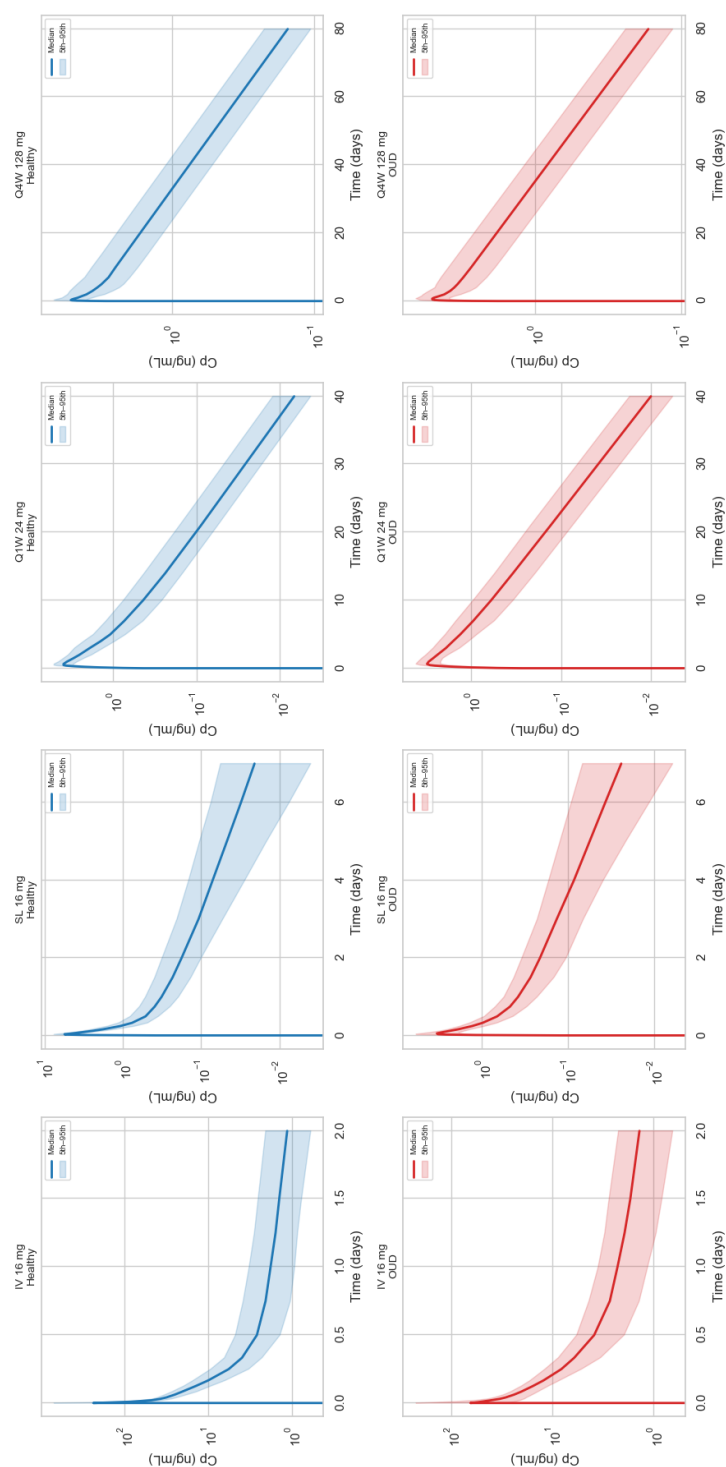


Figure 7: Population single-dose buprenorphine profiles after bolus IV, SL, Q1W, and Q4W administration, summarized as median and 5th–95th percentile bands for the healthy and OUD cohorts. The rotated layout preserves the route-specific profile shapes and highlights the longer terminal persistence of the long-acting injectable regimens.

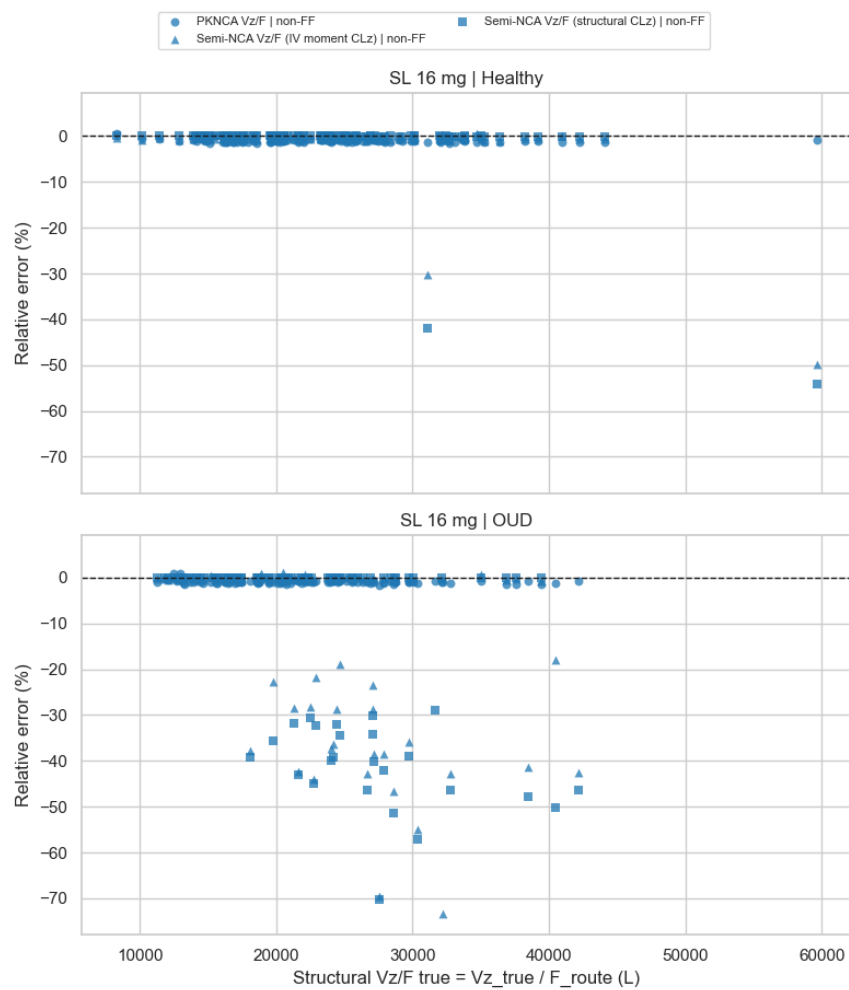


Figure 8: Route-specific relative error of apparent V_z/F estimates after SL 16 mg buprenorphine. The upper and lower panels correspond to the healthy and OUD cohorts, respectively. All profiles are non-flip-flop, and both the semi-NCA and standard PKNCA estimators remain close to the structural reference.

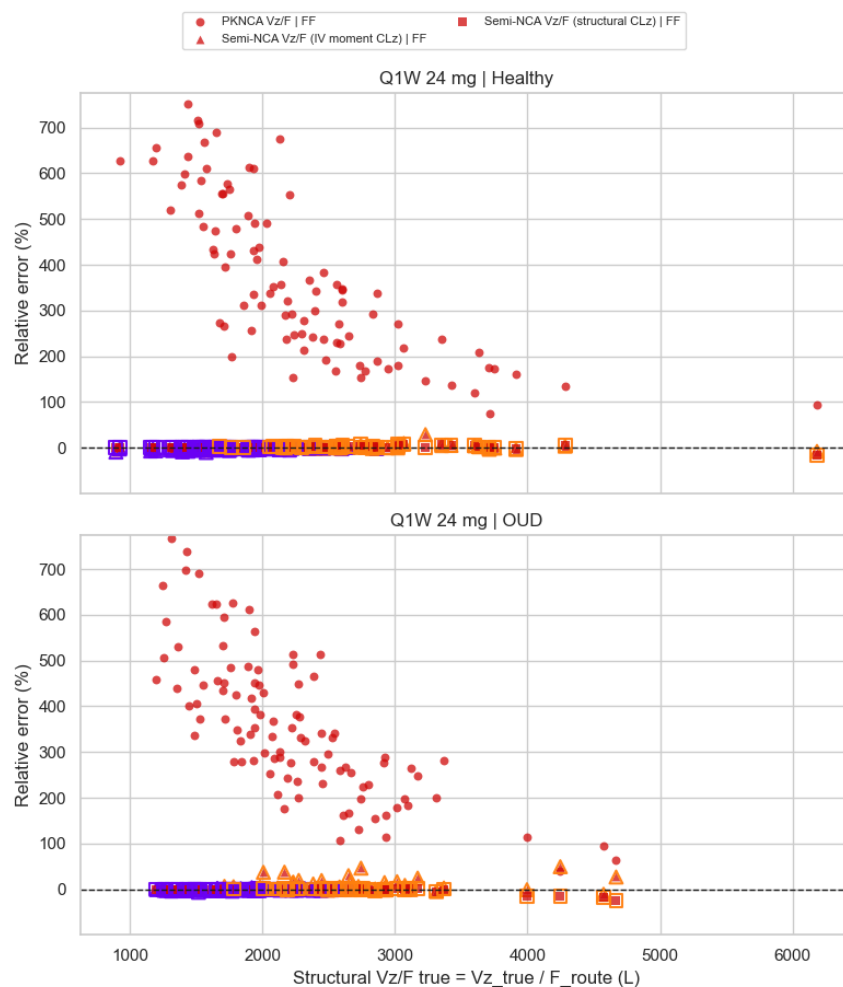


Figure 9: Route-specific relative error of apparent V_z/F estimates after Q1W 24 mg buprenorphine. The upper and lower panels correspond to the healthy and OUD cohorts. All profiles are flip-flop, shown in red; hollow overlays reproduce the V_{ss} -anchored depot-shape diagnostics used in Figure (M10). The semi-NCA estimator remains close to the structural reference, whereas standard PKNCA shows the expected large terminal-volume error under absorption-controlled disposition.

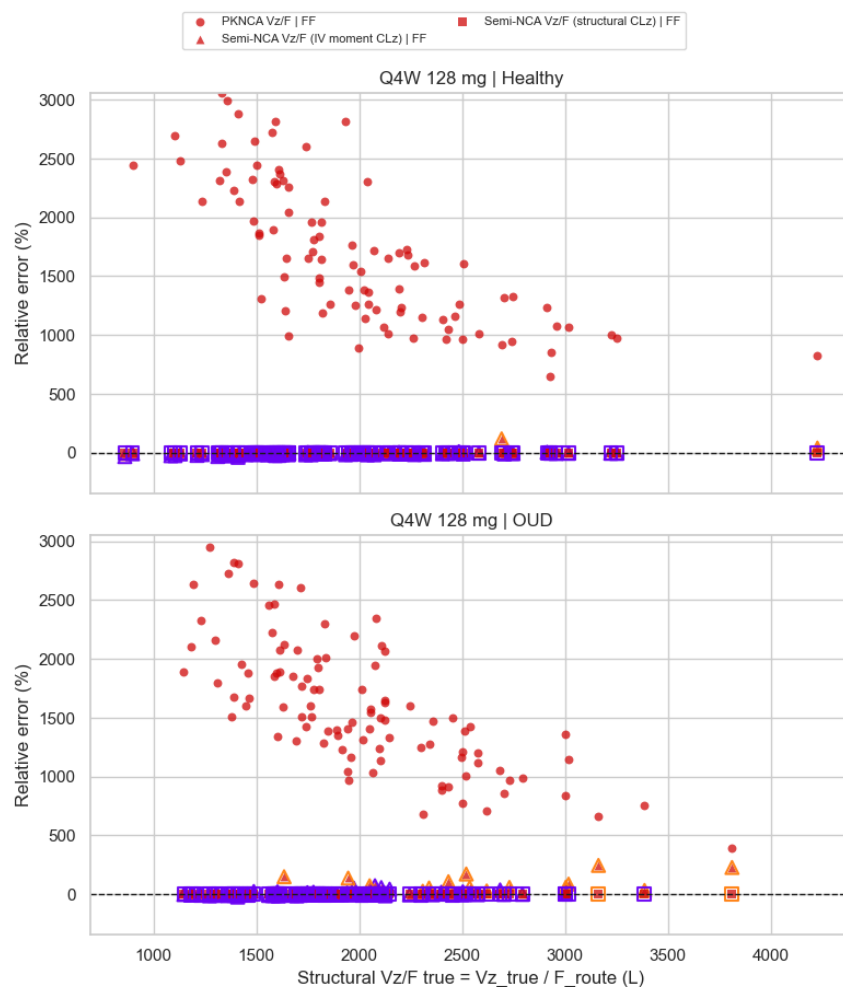


Figure 10: Route-specific relative error of apparent V_z/F estimates after Q4W 128 mg buprenorphine. The panel structure and diagnostic overlays are the same as for Q1W. The long depot-controlled terminal phase again preserves the semi-NCA correction while inducing large errors in the standard PKNCA terminal-volume estimator.

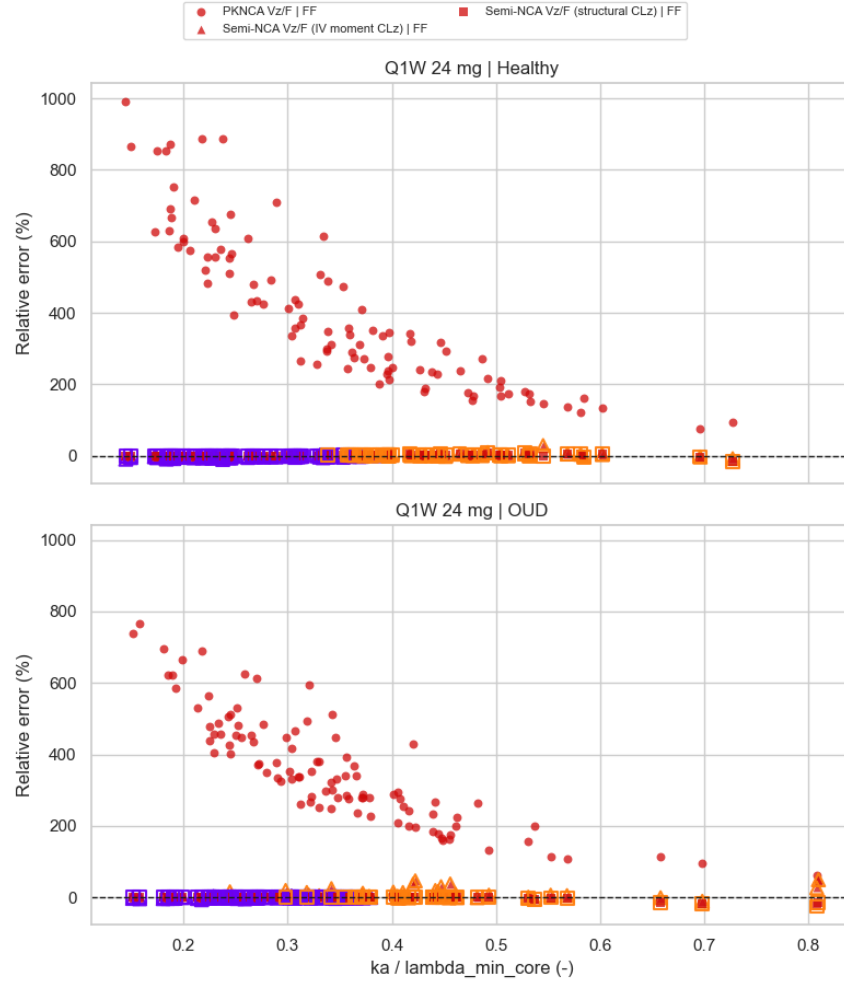


Figure 11: Relation between apparent V_z/F error and $k_a/\lambda_{\min}$ after Q1W 24 mg buprenorphine. The upper and lower panels correspond to the healthy and OUD cohorts. All profiles are flip-flop, with the same hollow bolus and rectangular-window diagnostics used in Figure 10. The semi-NCA estimator remains stable, whereas the PKNCA error increases as the absorption process becomes slower relative to the terminal disposition rate.

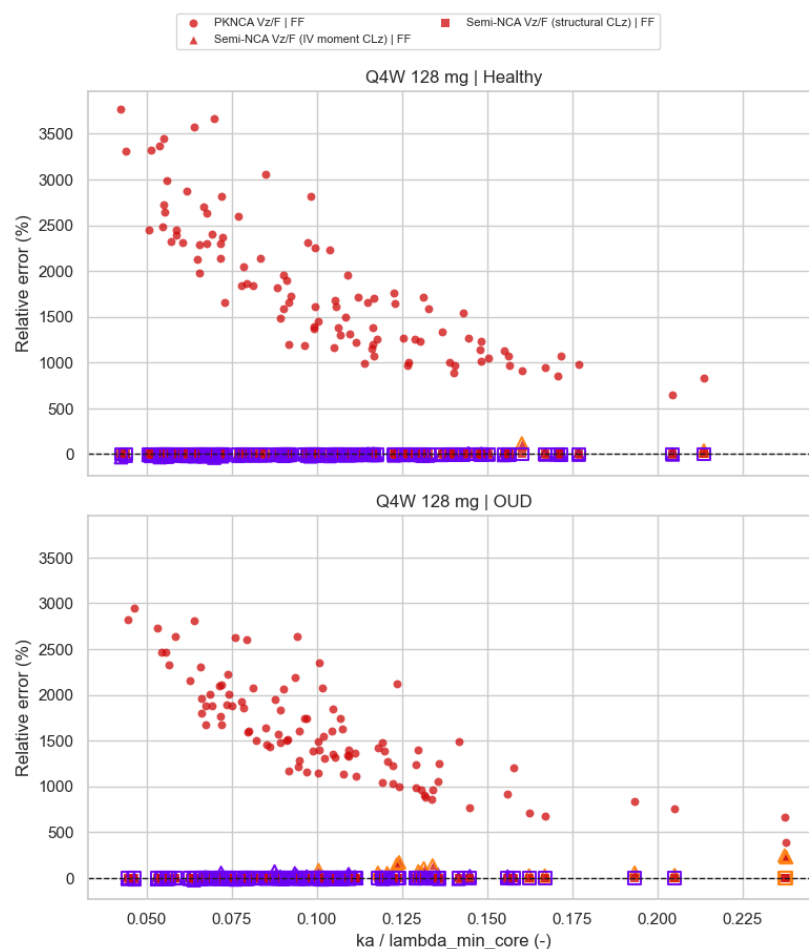


Figure 12: Relation between apparent V_z/F error and $k_a/\lambda_{\min}$ after Q4W 128 mg buprenorphine. The behavior mirrors the Q1W case: the semi-NCA correction remains close to the structural reference, while the standard PKNCA estimator is increasingly biased as the depot-controlled terminal phase becomes more dominant.

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