

BACKGROUND

What is Target Mediated Drug Disposition (TMDD)

- TMDD is a concept first proposed by Levy G *et al.* It is a phenomenon that occurs when a potent and specific drug binds to the target site with high affinity, leading to changes in its pharmacokinetic characteristics.
- TMDD has been proposed to explain a wide range of ligand-target binding in tissues when the affinity with the target is high, regardless of whether synthetic or biopharmaceutical, but it is mainly applied to biopharmaceuticals, especially peptides, proteins, and antibody drugs.

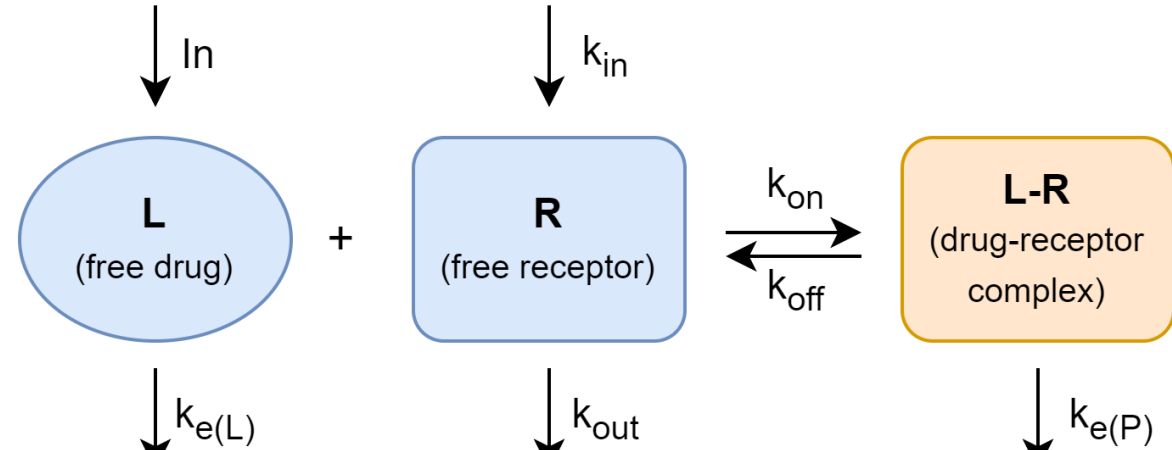


Figure. One compartment TMDD model
k_{on} : binding rate of the drug and target, koff : dissociation rate of the drug-target complex, ke(L) : degradation rate of the free drug, ke(P) : internalization rate of the drug-target complex, kin : synthesis of the drug receptor, kout : degradation of the drug receptor, In : injection rate of the drug

- Approximation methods have arisen from the increasing number of parameters in TMDD models, making it more feasible to develop simplified models for data fitting.

TMDD in cases when $R_{tot} > C_0$

- Previous studies on approximation methods have mainly focused on conditions with drug concentrations exceeding the target.
- Typically, TMDD is observed in high-affinity, low-capacity targets.
 - In low doses, most of the drug binds to the target, resulting in low systemic circulation.
 - In high doses, target saturation leads to higher systemic drug concentration.
- However, certain conditions like micro-dosing or significant non-specific protein binding also exhibit TMDD, even when drug concentration is lower than the target.
- This study is significant as it addresses these less common cases where drug concentration is lower than the target.

OBJECTIVES

This study aims to compare the full TMDD and three approximation methods

- Three TMDD approximation models were compared : the commonly used mTMDD and qTMDD models, and the newly proposed pTMDD approximation model by Byun *et al.*
- We classified three drug models into cases whether $C_0 \gg R_{tot}$ or $C_0 \ll R_{tot}$ and compared the estimation results in each cases.

METHODS

Validation criterion

- In the previous study by Byun *et al.* (to be published), the validity criterion of TMDD approximation methods, including Michaelis-Menten model (referred to as mTMDD), Quasi steady-state model (referred to as qTMDD), and first-order approximation of the total QSS (referred to as pTMDD), a new method suggested by the author, were presented.

	Equations
TMDD	$\frac{dC}{dt} = -k_{el}C - k_{on}C \cdot R_{tot} + (k_{on}C + k_{off})RC$ $\frac{dRC}{dt} = k_{on}C \cdot R_{tot} - (k_{on}C + k_{off} + k_{int})RC$
mTMDD	$\frac{dC}{dt} = -k_{el}C - k_{int} \frac{R_{tot} \cdot C}{k_m + C}$
qTMDD	$\frac{dC_{tot}}{dt} = -k_{el}C - k_{int} \frac{R_{tot} \cdot C(C_{tot})}{k_m + C(C_{tot})}$ $C(C_{tot}) = \frac{1}{2} [(C_{tot} - R_{tot} - k_m) + \sqrt{(C_{tot} - R_{tot} - k_m)^2 + 4k_m C_{tot}}]$
pTMDD	$\frac{dC_{tot}}{dt} = -k_{el}C_{tot} - (k_{int} - k_{el}) \frac{R_{tot} \cdot C_{tot}}{k_m + R_{tot} + C_{tot}}$

- Byun *et al.* demonstrated that when $C_0 + k_m \gg R_{tot}$, all three methods were accurate, whereas when $C_0 + k_m \ll R_{tot}$, mTMDD became inaccurate, while qTMDD and pTMDD remained accurate.

	mTMDD	qTMDD	pTMDD
$C_0 + k_m \gg R_{tot}$	O	O	O
$C_0 + k_m \ll R_{tot}$	X	O	O
Otherwise	X	O	X

Application on three antibody-drug conjugates (ADC) clinical trial studies

- Two anti-drug conjugates (ADC) clinical trial studies were selected.
 - Case 1** for *rhIL-1Ra-hyFc*, and **case 2** for *anakinra* (an active comparator of *rhIL-1Ra-hyFc*) from Ngo *et al.*
 - Case 3** for *rhIL-7-hyFc* from Lee *et al.*

	$C_0 > R_{tot}$		$R_{tot} > C_0$
	<i>rhIL-1Ra-hyFc</i> ($C_0/R_{tot} = 15.42$)	<i>Anakinra</i> ($C_0/R_{tot} = 19.27$)	<i>rhIL-7-hyFc</i> ($C_0/R_{tot} = 0.01$)
Mean drug concentration(C_0)	34.385 nM (29.140 nM)	29.672 nM (4.359 nM)	0.012 nM (0.012 pM)
Maximum drug concentration(C_0)	78.928 nM (70.965 nM)	55.041 nM (9.507 nM)	0.023 pM (0.023 pM)
Receptor concentration	2.23 nM	1.54 nM	1060 pM
FcRn concentration	749 nmol	-	40000 nM

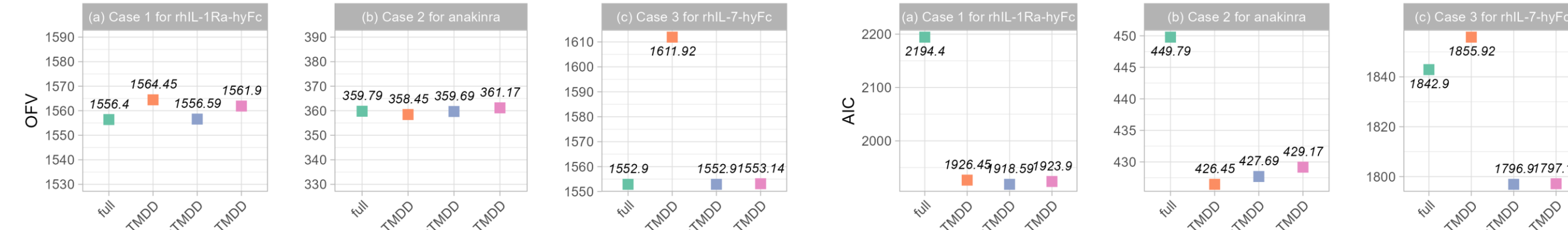
- All studies were a semi-mechanistic model with TMDD and FcRn-mediated recycling, except for *Anakinra*.
 - Although FcRn is not a therapeutic target of the drug, the interaction between the drug and FcRn follows the kinetics of a TMDD process in which the recycling rate constant(K_{rec}) is related to the degradation rate constant of a complex(K_{in}).
- The models underwent parameter optimization using the first-order conditional estimation with interaction (FOCE-I) method using NONMEM 7.5 and PsN 5.3.1 software.
- The performance of the models was assessed based on **Objective Function Value (OFV)**, **pharmacokinetic parameters**, and **Visual Predictive Check (VPC)**.

RESULTS

1. Numerical assessment

1.1. Objective Function Value(OFV), Akaike Information Criterion(AIC)

- In both the **Case 1** for *rhIL-1Ra-hyFc* ($C_0/R_{tot} = 15.42$) and **Case 2** for *anakinra* ($C_0/R_{tot} = 19.27$), **OFV** were also similar across all models. Except for the full TMDD with a large number of parameters, the **AIC** were all similar.
- In **Case 3** for *rhIL-7-hyFc* ($C_0/R_{tot} = 0.01$), the mTMDD model had the highest **OFV** and showed **AIC** values similar to the full TMDD model.



1.2. Parameter estimates

- In both the **case 1** for *rhIL-1Ra-hyFc* ($C_0/R_{tot} = 15.42$) and **case 2** for *anakinra* ($C_0/R_{tot} = 19.27$), all the models generally provided similar **PK parameter** estimate results. The confidence intervals of the parameters generally overlapped.
- In **case 3** for *rhIL-7-hyFc* ($C_0/R_{tot} = 0.01$), the PK models with qTMDD and pTMDD, but not the mTMDD model, provided a similar estimation of **PK parameters** with the PK model with TMDD. In the mTMDD model, the confidence intervals were either excessively wide compared to other models, or the parameter estimates fell outside the confidence intervals of other models.

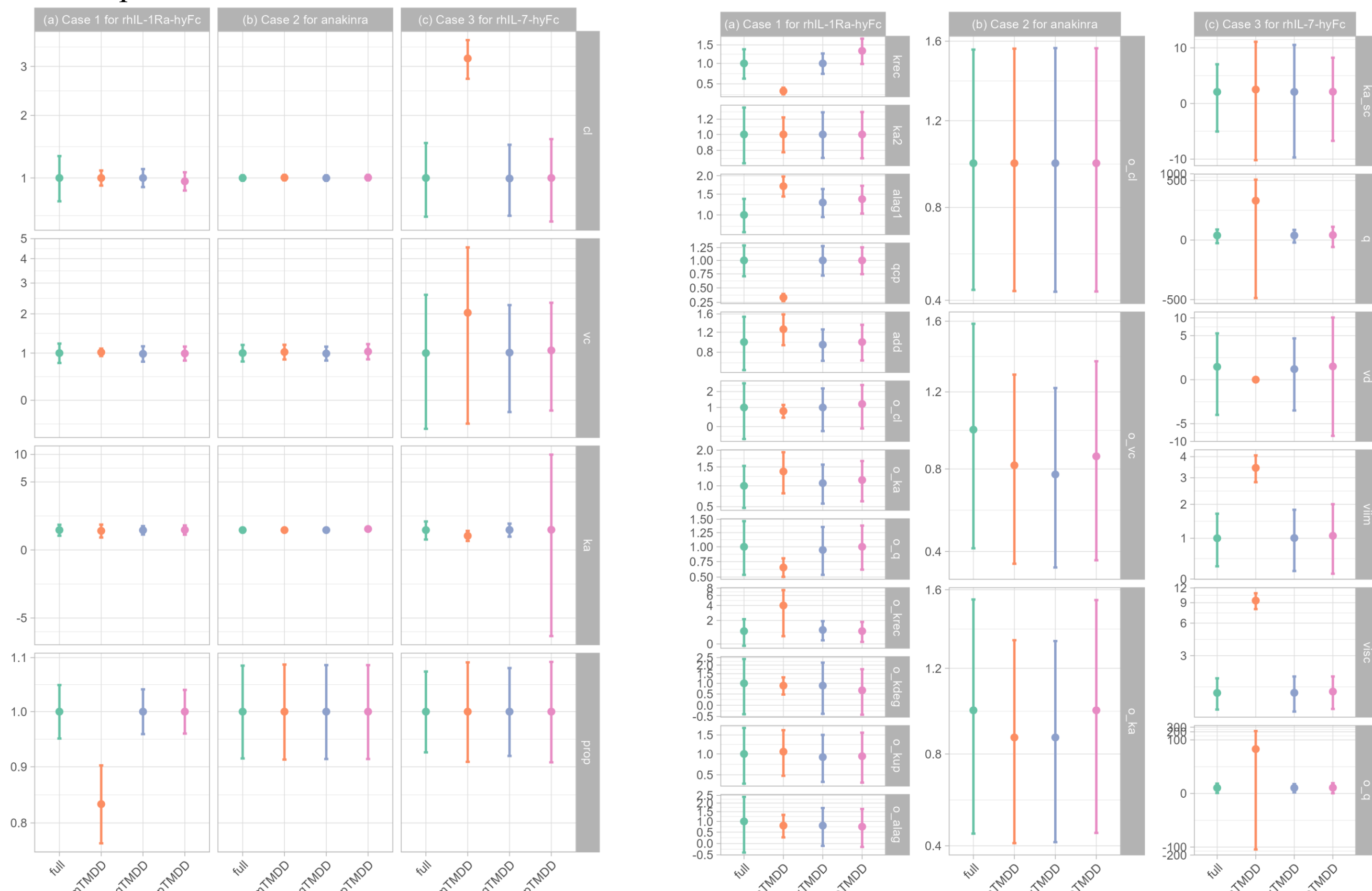


Figure. Parameter estimate results (Left : common parameters, Right : non-common parameters)

The y-axis represents the pseudo-log-transformed values of each model's parameters normalized to those from the full TMDD model.

2. Elapsed time

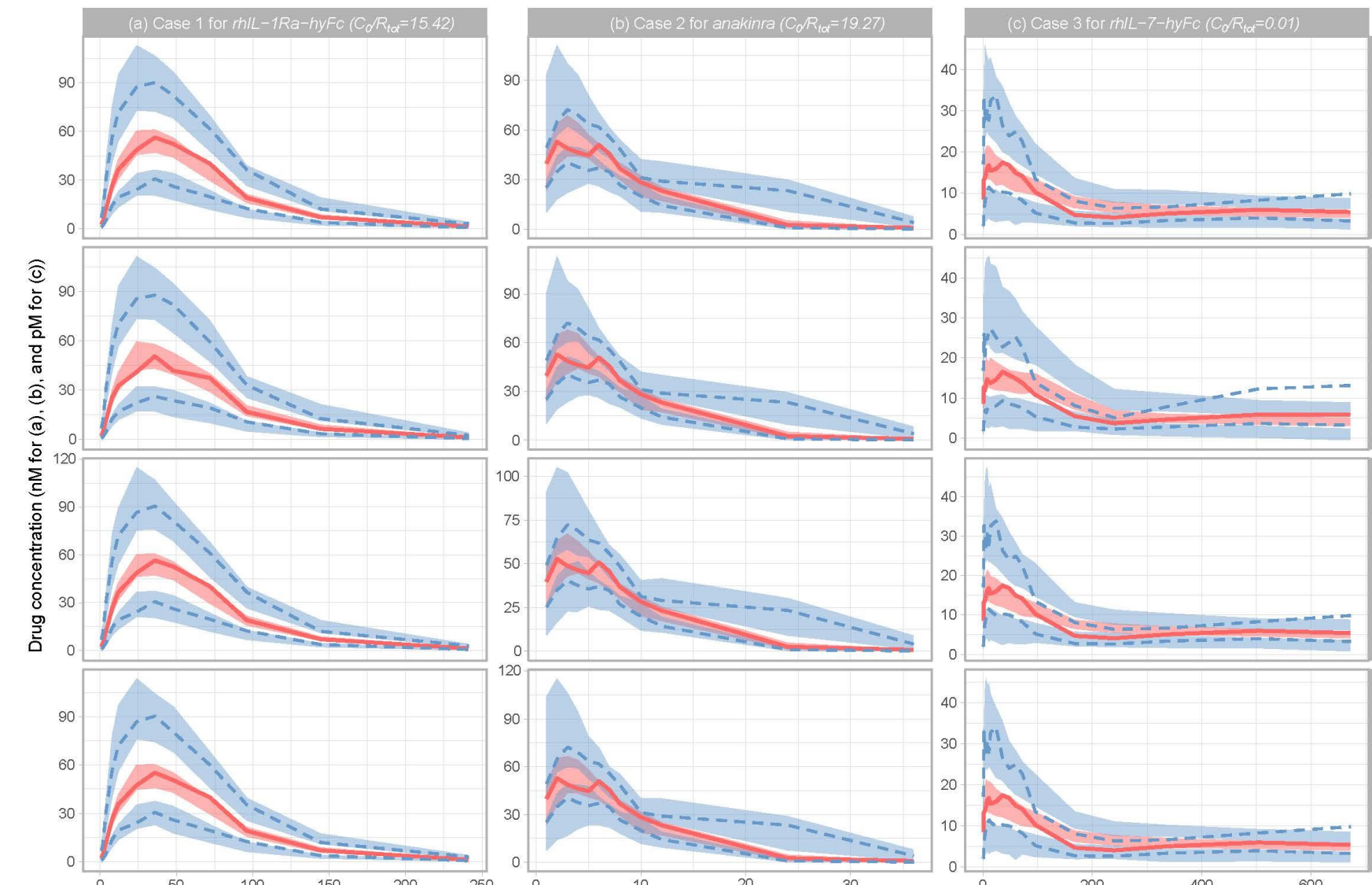
- We measured the seconds it took to proceed with the estimation using the final model. Measurements were made five times and calculated as means, with values in bracket indicating standard deviation.

	full TMDD	mTMDD	qTMDD	pTMDD
<i>rhIL-1Ra-hyFc</i>	5345.3 (184.1)	403.3 (59.7)	1113.5 (95.1)	556.0 (59.6)
<i>anakinra</i>	21.08 (3.83)	4.13 (0.39)	2.70 (0.34)	2.90 (0.40)
<i>rhIL-7-hyFc</i>	136.1 (11.9)	44.4 (7.9)	65.3 (9.5)	39.1 (4.5)

- In the case of the tTMDD model, the **elapsed time** was as short as the mTMDD model.

3. Visual assessment

- In both the **case 1** for *rhIL-1Ra-hyFc* ($C_0/R_{tot} = 15.42$) and **case 2** for *anakinra* ($C_0/R_{tot} = 19.27$), the **Visual Predictive Check (VPC)** plots showed that all the approximation models could predict appropriately,
- In **case 3** for *rhIL-7-hyFc* ($C_0/R_{tot} = 0.01$), **Visual Predictive Check (VPC)** plots showed that the mTMDD model could not predict appropriately, whereas the qTMDD and pTMDD model could appropriately describe the observation.



CONCLUSION & DISCUSSION

- When $C_0 + k_m \gg R_{tot}$, mTMDD, qTMDD, and pTMDD were all accurate in clinical cases.
- When $C_0 + k_m \ll R_{tot}$, mTMDD became inaccurate while qTMDD and pTMDD remained accurate.
- Elapsed time in pTMDD was as short as in mTMDD.
- In both cases where the concentration of the target markedly exceeds that of the drug or vice versa, the pTMDD approximation is a viable option, delivering both precision and computational efficiency.

ACKNOWLEDGEMENT

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