PK model development guidance for biologics and case study on crizanlizumab PK

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Jaeyeon Kim[1], Andrew M Stein[1], Sherwin Sy[2] and Kai Grosch[3]

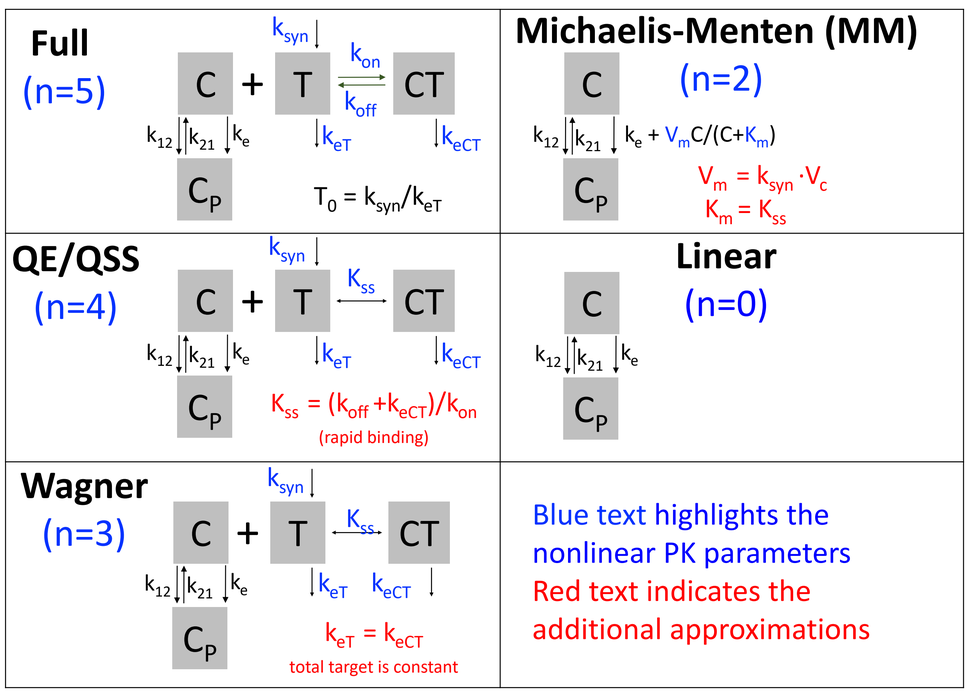
[1]Novartis Pharmacueticals Inc., 250 Massachusetts Ave, Cambridge, MA 02139, USA
[2]Novartis Pharmacueticals Inc., One Health Plaza, East Hanover, NJ 07936, USA
[3]Novartis Pharma AG, Forum 1, 4056, Basel, Switzerland

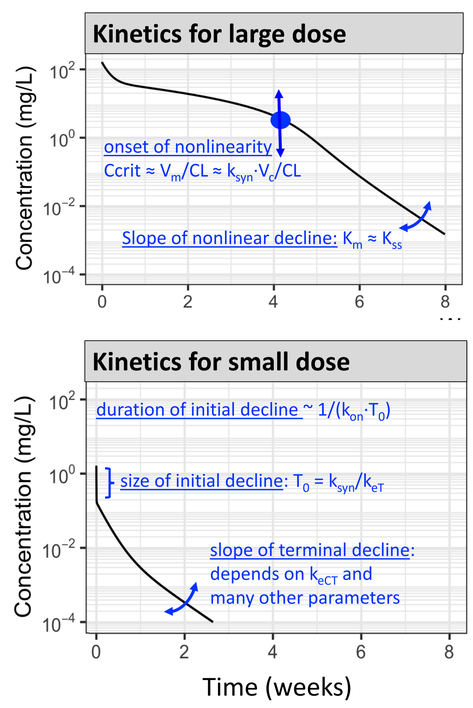
Objectives

For biologics (e.g. mAbs), non-linear PK is often observed at lower doses and the Michaelis-Menten equation is frequently used to describe non-linear elimination of mAb drug. A more mechanistic target mediated drug disposition (TMDD) model can also be used, but not all model parameters are identifiable when only PK data is available. While tutorials provide an overview of the various model approximations [1], there does not exist a simple guide for selecting which approximation to use. Modelers often lack the intuition in understanding which models to explore and spend a lot of time trying to fit unidentifiable models. Here, we propose a guidance for selecting a suitable model for a given PK data set.

Methods

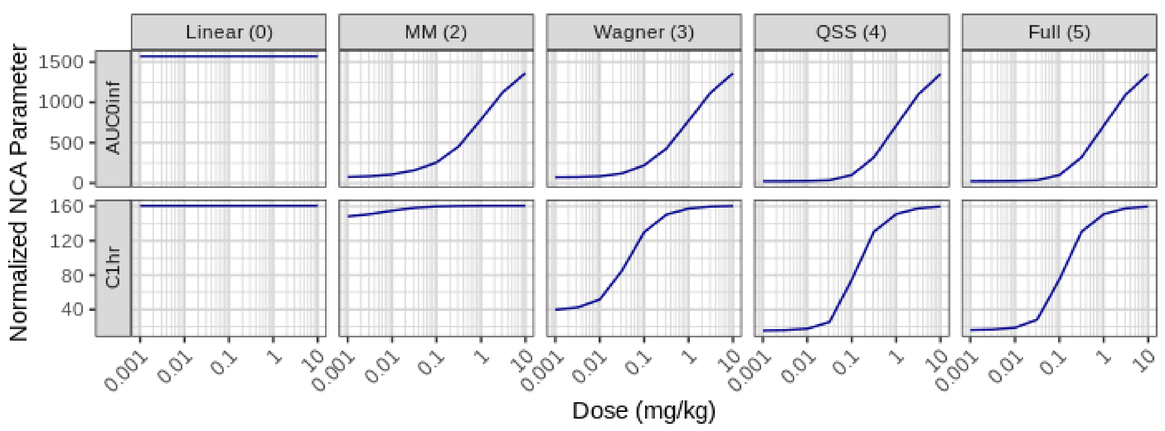
- Five standard target mediated drug disposition models [1] were simulated and fit to crizanlizumab PK data
- The five TMDD models are summarized in the table below, where C = drug concentration, T = target concentration, and CT = complex
- The number in blue shows the number of parameters that describe nonlinear aspects of the PK profile





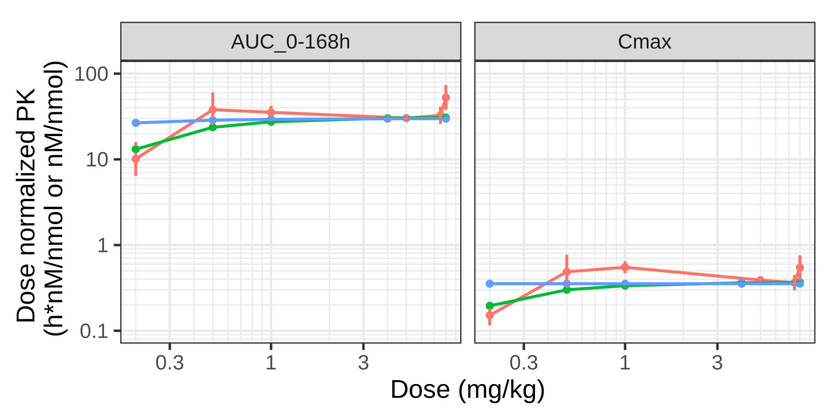
Parameter	Identifiability	Reason
$V_m \approx k_{syn} \cdot V_c$	Yes	Governs Ccrit, the concentration of the onset of the PK nonlinearity [2]
$K_m \approx K_{ss}$	Sometimes	Governs the slope of the nonlinearity at large doses [2]
$T_0 = k_{syn}/k_{eT}$	Sometimes	Governs rapid initial drop at low doses (due to drug-target binding). It is difficult to observe at high doses due to assay error [3]
k_{eCT} different from k_{eT}	Almost Never	Can impact the long-term terminal slope [3]; it is usually clinically irrelevant
k_{off} and k_{on}	Almost Never	Governs the rate of this rapid initial drop [3]; almost impossible to observe.

Simulated Dose Normalized NCA parameters vs dose

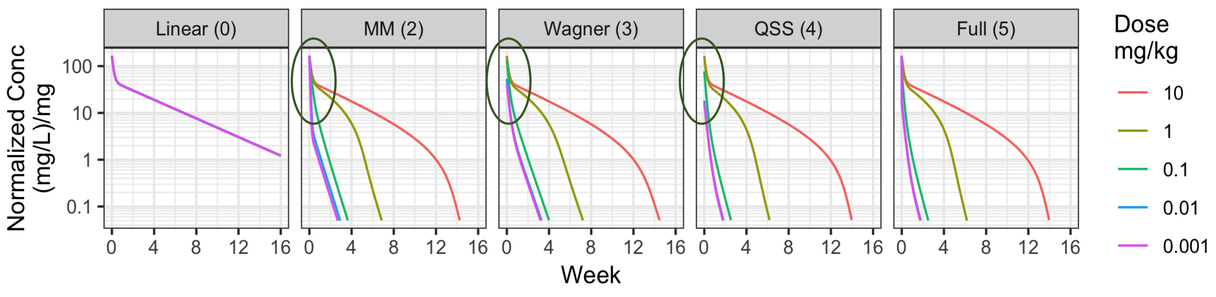


Application to crizanlizumab PK model development

Comparison of dose-normalized NCA parameters reveals that **Wagner** model better characterizes NCA nonlinearity than **MM** model for crizanlizumab PK data



Simulated Dose Normalized PK Profiles



The above theory and simulations confirm there is almost no difference between Wagner, QSS, and Full model PK profiles.

Main difference between MM and Wagner: At small doses, when drug rapidly binds target, the dose-normalized Cmax is constant with MM, but decreases with dose for Wagner.

Conclusion and Guidance for Nonlinear PK

- If PK is nonlinear, start with Michaelis-Menten
- If the Michaelis-Menten fails to capture the dose vs Cmax relationship, consider the Wagner model
- The QE/QSS and Full model are usually not useful for fitting just PK data, they are applicable when target data is available for fitting as well
- More complex models sometimes better describe very low concentration data, but this data is usually not clinically relevant

References

1. Dua, P., et al. "A tutorial on target-mediated drug disposition (TMDD) models." CPT:PSP 4.6 (2015): 324-337
2. Stein, AM., and Peletier LA. "Predicting the Onset of Nonlinear Pharmacokinetics." CPT:PSP 7.10 (2018): 670-677
3. Peletier, LA. and Gabrielsson J. "Dynamics of target-mediated drug disposition: characteristic profiles and parameter identification." J PKPD 39.5 (2012): 429-451

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