

Simplifications of Target-Mediated Disposition Models

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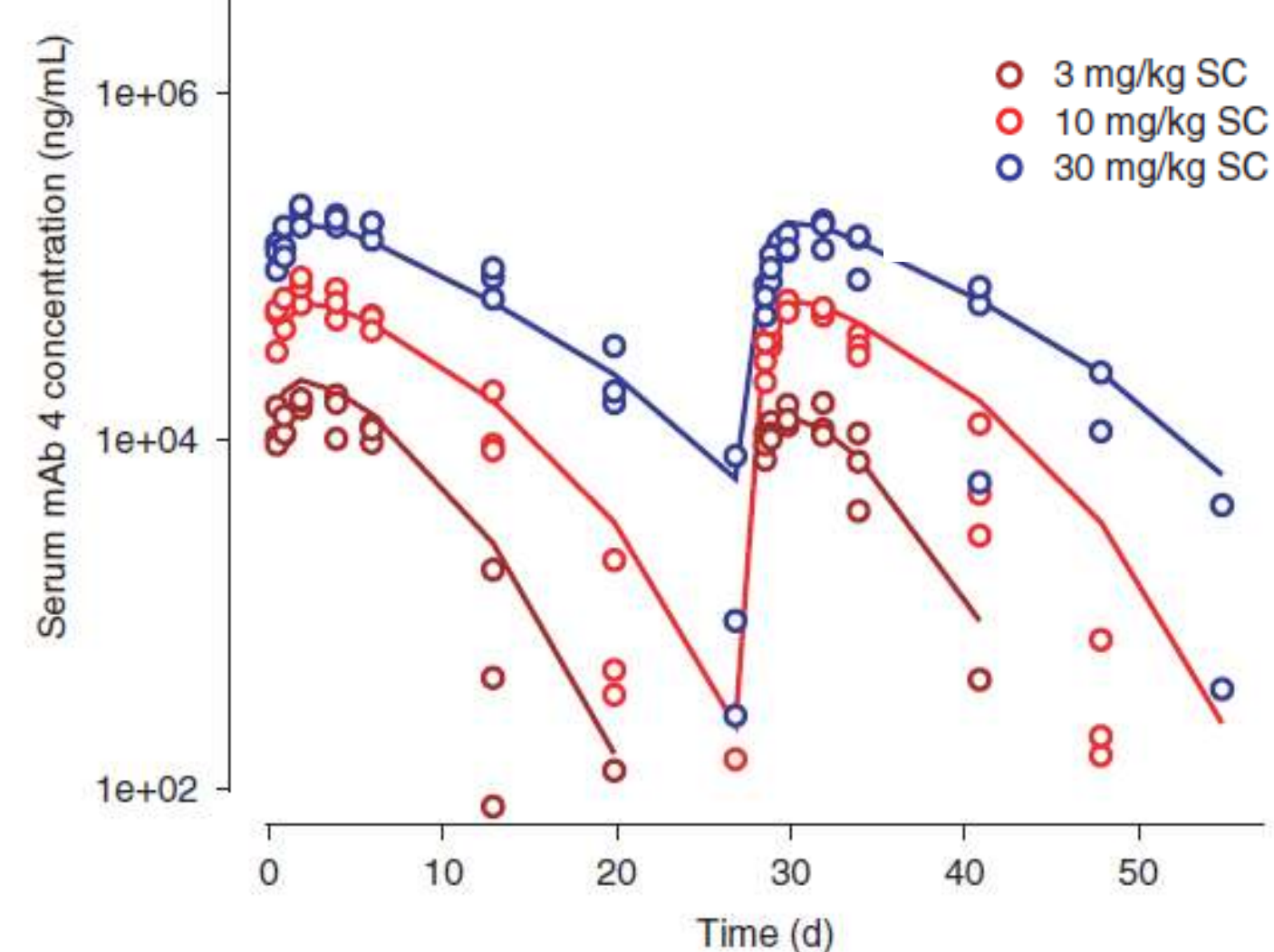
INTRODUCTION

Target-mediated disposition (TMD) describes the phenomenon that the interaction of the drug with its *in vivo* target (ligand or receptor) significantly influences the drug disposition.

TMD often results in non-linear PK behavior (Fig. 1). TMD Examples include:

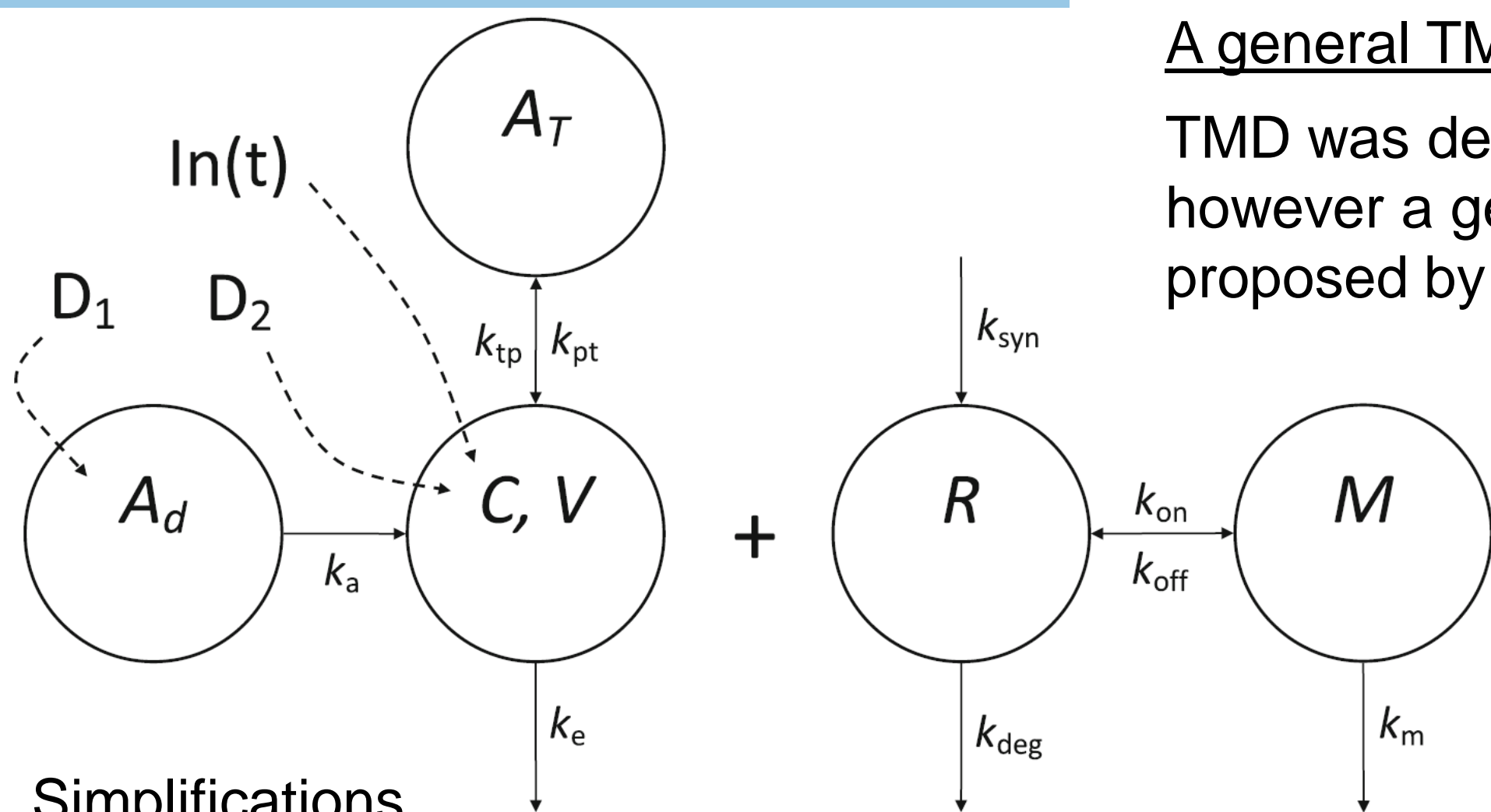
1. Recombinant protein products: erythropoietin, G-CSF, thrombopoietin, VEGF, IFN- β 1a
2. Erbitux® (cetuximab) and Vectibix® (panitumumab) for EGFR (cell membrane bound), Prolia® (denosumab) for RANKL (bound and soluble), Xolair® (omalizumab) for IgE (soluble).

Figure 1. Typical TMD model profiles (Dong *et al.* 2011)



METHODS

Figure 2. A general TMD model [2]



A general TMD model

TMD was described by Levy in 1994 [1]; however a general TMD model was first proposed by Mager and Jusko [2] (Fig. 2).

Simplifications

In practice, not all data for modeling are quantifiable (e.g., target-related) or rich. The model in Fig. 2 is often over-parameterized and too complex to be supported by the available data. Various simplifications with fewer parameters have been proposed:

1. **Constant total target: $R_{tot} = \text{const.}$** [2],
2. **Rapid binding (RB): $k_{on} R \cdot C = k_{off} M$** [3], or
3. **Quasi-steady-state (Qss): $k_{on} R \cdot C = (k_{off} + k_m) M$** [4].

Here notations are shown in Fig. 2; e.g., M is the complex, k_m its degradation rate constant, etc. Combinations of 1 and 2 (or 3) lead to further simplifications.

Also, the Michaelis-Menten (MM) model, whose relationship with the general TMD model was unclear, was often used to describe TMD behavior.

Difficulties

Besides the above, not all were clear including even the derivations. Consider three of the differential equations (Fig. 3 below) that define the TMD model in Fig. 2.

Figure 3. Differential equations of the free drug C , the free target R , and the complex M for the general TMD model [5]

$$\frac{dC}{dt} = I(t) + k_a B_d - k_{on} R \cdot C + k_{off} M - (k_e + k_{pt})C + k_{tp} B_T,$$

$$\frac{dR}{dt} = k_{syn} - k_{deg} R - k_{on} R \cdot C + k_{off} M,$$

$$\frac{dM}{dt} = k_{on} R \cdot C - (k_{off} + k_m) M.$$

Note: Here $B_d = A_d/V$ and $B_T = A_T/V$.

When the RB assumption is applied, differential equations for free drug/target and the complex (C , R , and M) after cancelling the terms in boxes trivialize to be for a linear model with no binding. © In addition, how close a simplified model is to the general TMD model has not been answered.

Objectives

- To organize TMD types of models for a better understanding of their relationships,
- To discuss differences between a) MM and Qss models, and b) RB and Qss models,
- To present some criteria on assessing the closeness of MM and Qss models to the general TMD model.

RESULTS

A. From the Qss assumption, four simplified TMD models result from the general TMD model: the MM and Qss models, and Qss 2&3 listed in Fig. 5.

1. Qss model: using differential equations for $C_{tot} = C + M$ and $R_{tot} = R + M$.
2. MM model: using differential equations for C and R_{tot} .

B. In general, simplifications can be derived by an algebraic equation of the form $R \cdot C = \kappa M - \alpha R - \beta C + \gamma$ replacing one of the differential equations in Fig. 3.

As an example of B, a model with a nonlinear transfer from free drug to complex representing the nonlinear elimination component (Fig. 4) described in [2] can be obtained with $\kappa, \beta = 0, \alpha = K_m, \gamma = V_{max}/k_{on}$ from B.

The organization from A as a pictorial view is in Fig. 5.

RESULTS (continued)

Figure 4. A 2-compartment model with non-linear transfer from free drug C to complex M [2] (on the right)

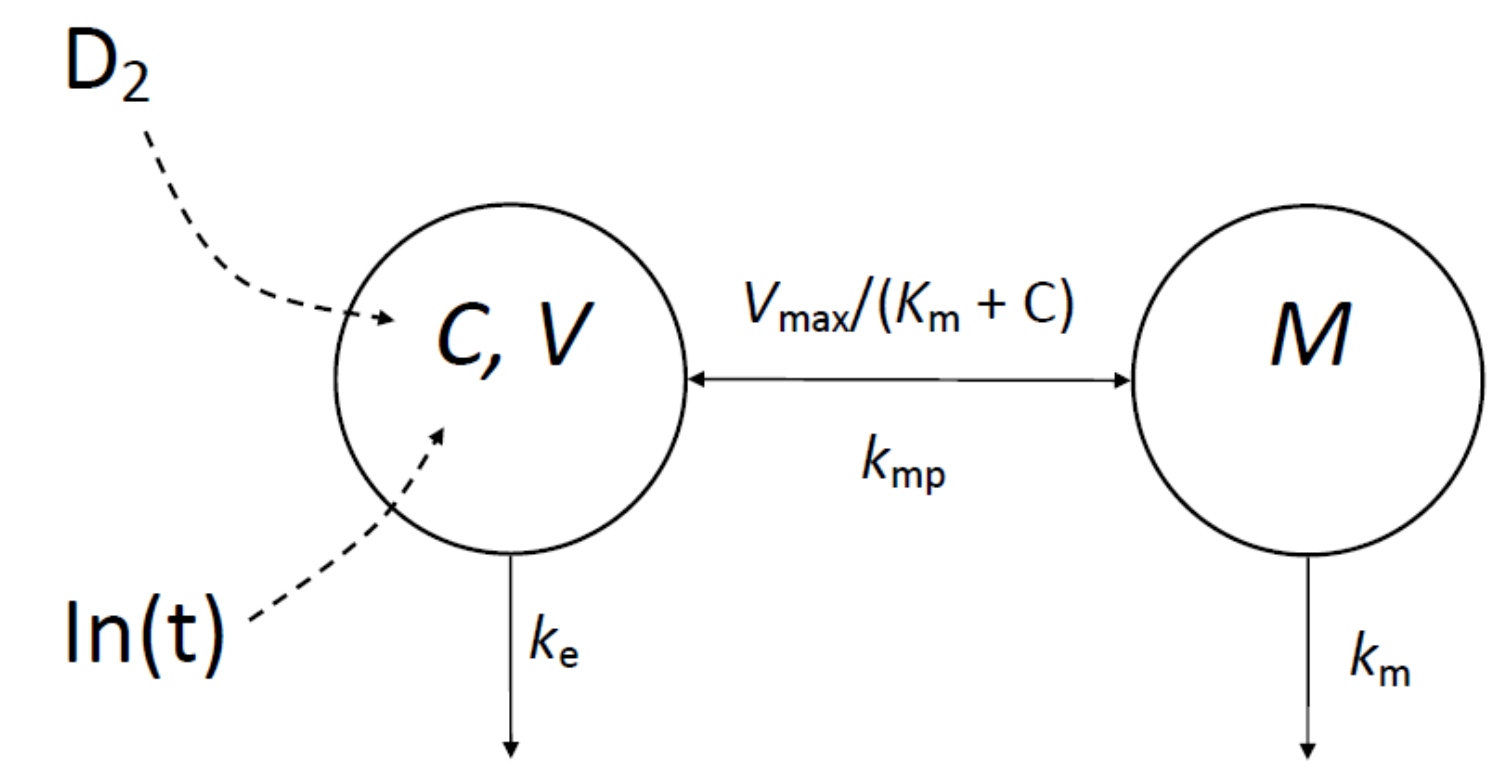
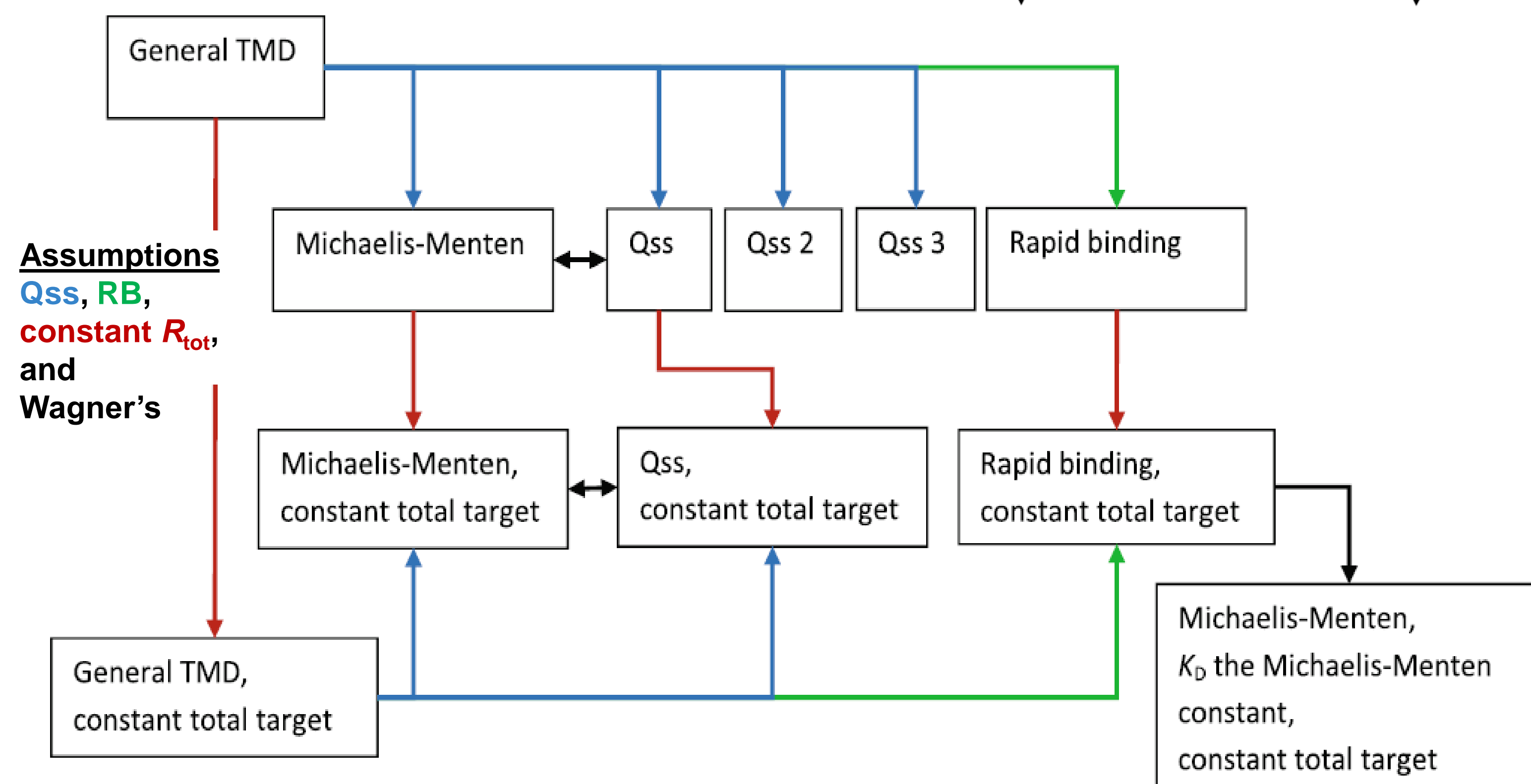


Figure 5. Model organization diagram [5] (below)



Examples of TMD models in applications

- AMG 317, an anti-interleukin-4 receptor antibody (Kakkar *et al.* 2011, Qss model)
- Prolia, an antibody to RANKL, for osteoporosis (Marathe *et al.* 2008, RB model; Gibiansky *et al.* 2011, Qss model)
- Raptiva® (efalizumab), an antibody to CD11a (Bauer *et al.* 1999, MM model)
- An antibody to CD11b (Jonsson *et al.* 2005, a simplified TMD model using C and R , equivalent to irreversible binding and consistent with Qss 2)

Model comparison

- Neither MM nor Qss model is always better as an approximation to the model in Fig. 2.
- In practice Qss model appears to fit data well more often than MM model.
- For MM model to be a good approximation, it doesn't have to be that $C \gg R$ (e.g., when K_M is large relative to C).
- For data fitting purpose, RB and Qss models are equivalent. Thus, one needs to ask: does model-derived "potency parameter" resemble more of $K_D = k_{off}/k_{on}$ or $K_M (> K_D)$?

Approximations

Using some techniques from singular perturbation theory, one can generate expressions ϵ , shown in Fig. 6, defined as the ratio of slow and fast time scales (T_f and T_s) under the assumption that R_{tot} is constant. When ϵ is small, the corresponding simplified model is appropriate as an approximation to the general TMD model.

Figure 6. Criteria to assess closeness of Qss/MM models to general TMD model [5]

| ϵ | One Compartment | Two Compartments |
|------------|--|---|
| MM | $\frac{k_e/k_{on} + R_{tot}}{K_m + C_0}$ | $\frac{\max\{k_{on}R_{tot} + k_e + k_{pt}, k_{tp}\}}{k_{on}(K_m + C_0)}$ |
| Qss | $\frac{\max\{k_e, k_m - k_e\}}{k_{on}(K_m + C_0 + R_{tot})}$ | $\frac{\max\{k_e + k_{pt}, k_m - k_e - k_{pt}, k_{tp} + k_{pt}\}}{k_{on}(K_m + C_0 + R_{tot})}$ |

In the table C_0 represents the initial free drug concentration. It follows from the criteria that the MM model can be a good approximation, if the free drug concentration is much larger than the target. This doesn't have to be the case for Qss model.

CONCLUSIONS

- Organization of TMD models facilitates model selection and provides more rigorous basis for theoretical/practical research in the area, important for investigating PK-PD relationships of many biologics.
- Closeness of a simplification to the general TMD model should be considered in applications.

Acknowledgement

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