# Monoclonal Antibody-Drug Conjugates: TMDD Equations, Approximations, and Identifiability of Model Parameters

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## OBJECTIVES

- To derive equations that describe antibody-drug conjugates (ADC); their distribution, deconjugation, elimination and interaction with the target;
- To derive Michaelis-Menten approximation of these equations;
- To investigate identifiability of model parameters given typically available measurements and clinically feasible sampling schemes.

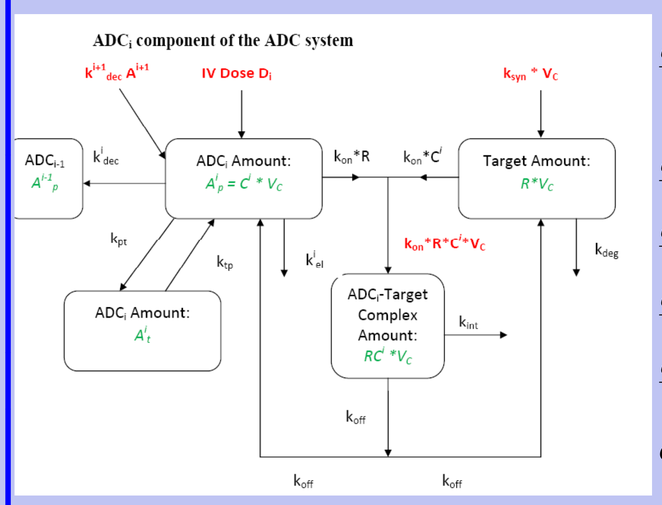
## METHODS

ADC - target system includes the naked antibody ($ADC^0$), ADCs with various loads ($ADC^i$, i=1,8), released drug (L), free target (R), and various antibody ADC-target complexes ($RC^i$, i=0,8). TMDD equations to describe concentration-time course of the ADC - target system were derived.

### General TMDD Equations for ADC

**Red:** input; ***Green***: amounts; **Black**: rate constants. **Flux** = **rate** x **amount**

$ADC_i$ with *i* drug molecules is shown. Released drug compartment (L) is not shown.




$$\frac{dC^i}{dt} = \frac{k_{tp}A^i{}_t}{V_c} - (k^i{}_{el} + k_{pt})C^i - k_{on}C^i \cdot R + k_{off}RC^i;$$
$$+ k^{i+1}{}_{dec}C^{i+1} - k^i{}_{dec}C^i; \quad (k^0{}_{dec} = 0; \quad k^9{}_{dec} = 0);$$
$$\frac{dA^i{}_t}{dt} = k_{pt}C^iV_c - k_{tp}A^i{}_T; \quad C^i(0) = D^i/V_c; \quad A^i{}_t(0) = 0;$$
$$\frac{dR}{dt} = k_{syn} - k_{deg}R - k_{on}C \cdot R + k_{off}RC; \quad R(0) = k_{syn}/k_{deg};$$
$$\frac{dRC^i}{dt} = k_{on}C^i \cdot R - (k_{int} + k_{off})RC^i; \quad RC^i(0) = 0;$$
$$\frac{dL}{dt} = V_c\sum_{i=1}^{8}(k^i{}_{dec}C^i + i \cdot k^i{}_{el}C^i + i \cdot k_{int}RC^i) - k^L{}_{el}L; \quad L(0) = 0;$$
$$C = \sum_{i=0}^{8}C^i; \quad RC = \sum_{i=0}^{8}RC^i; \quad i = 0,...,8.$$

**Assumptions (in addition to the commonly used TMDD assumptions):**

- ADC species with different DAR values (drug antibody ratio) have the same volume of distribution and inter-compartment rate constants, but may differ by non-specific clearance;
- ADC species with different DARs have the same target properties $k_{on}$, $k_{off}$ and $k_{int}$;
- Released drug can be described by a one-compartment model;
- Deconjugation can occur only in the central compartment;
- Eliminated ADC releases the drug load to the central compartment.

### Quasi-Steady-State and Rapid Binding Approximations

From $$k_{on}C^i \cdot R - (k_{off} + k_{int})RC^i = 0; \quad i = 0,...,8$$

we derive $$k_{on}C \cdot R - (k_{off} + k_{int})RC = 0.$$

Therefore $$\frac{C \cdot R}{RC} = K_D + \frac{k_{int}}{k_{on}} = K_{SS}; \quad RC = \frac{R_{tot}C}{K_{SS} + C}; \quad R = \frac{R_{tot}K_{SS}}{K_{SS} + C}$$

$$\frac{C^i \cdot R}{RC^i} = K_{SS}; \quad RC^i = \frac{R_{tot}C^i}{K_{SS} + C}, \quad i = 0,...,8$$

Then unbounded ADC concentrations $C^i$ can be found as a solution of the system of equations:

$$C^i{}_{tot} = C^i + \frac{R_{tot}C^i}{K_{SS} + C}; \quad i = 0,...,8 \quad C = \sum_{i=0}^{8}C^i$$

Then QSS Approximation is given by:

$$\frac{dC^i{}_{tot}}{dt} = \frac{k_{tp}A^i{}_t}{V_c} - (k^i{}_{el} + k_{pt})C^i - \frac{R_{tot}k_{int}C^i}{K_{SS} + C} + k^{i+1}{}_{dec}C^{i+1} - k^i{}_{dec}C^i;$$
$$\frac{dA^i{}_t}{dt} = k_{pt}C^iV_c - k_{tp}A^i{}_t; \quad A^i{}_t(0) = 0; \quad (k^0{}_{dec} = 0; \quad k^9{}_{dec} = 0);$$
$$\frac{dR_{tot}}{dt} = k_{syn} - k_{deg}R_{tot} - (k_{int} - k_{deg})\frac{R_{tot}C}{K_{SS} + C}; \quad R_{tot}(0) = R_0 = \frac{k_{syn}}{k_{deg}};$$
$$\frac{dL}{dt} = V_c\sum_{i=1}^{8}(k^i{}_{dec}C^i + i \cdot k^i{}_{el}C^i + i \cdot k_{int}RC^i) - k^L{}_{el}L; \quad L(0) = 0.$$

**Assumptions: Same as QSS (RB) assumptions of conventional TMDD.**

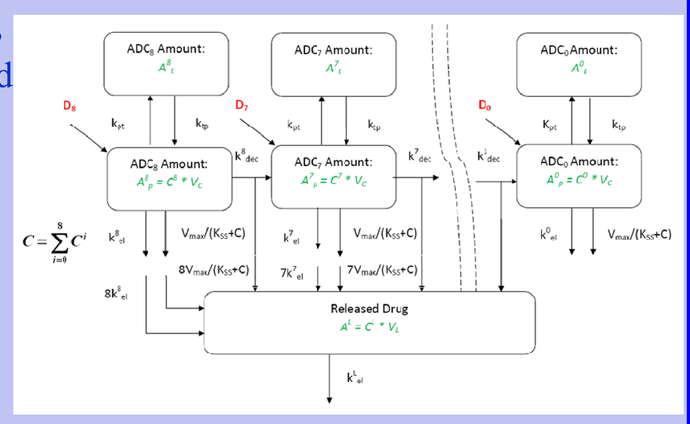
**Limitations: Cannot be resolved analytically; needs further simplification.**

### Michaelis-Menten Approximations

**Assumptions (same as MM assumptions of conventional TMDD):** Total target concentration is small, for example, when internalization rate is high.

$$\frac{dC^i}{dt} = \frac{k_{tp}A^i{}_t}{V_c} - (k^i{}_{el} + k_{pt})C^i - \frac{R_{tot}k_{int}C^i}{K_{SS} + C} + k^{i+1}{}_{dec}C^{i+1} - k^i{}_{dec}C^i;$$
$$\frac{dA^i{}_t}{dt} = k_{pt}C^iV_c - k_{tp}A^i{}_t; \quad (k^0{}_{dec} = 0; \quad k^9{}_{dec} = 0);$$
$$\frac{dR_{tot}}{dt} = k_{syn} - k_{deg}R_{tot} - (k_{int} - k_{deg})\frac{R_{tot}C}{K_{SS} + C}; \quad R_{tot}(0) = k_{syn}/k_{deg};$$
$$\frac{dL}{dt} = V_c\sum_{i=1}^{8}(k^i{}_{dec}C^i + i \cdot k^i{}_{el}C^i + i \cdot k_{int}RC^i) - k^L{}_{el}L; \quad L(0) = 0;$$
$$C^i(0) = D_i/V_c; \quad C = \sum_{i=0}^{8}C^i; \quad i = 0,...,8.$$

When $k_{int}$=$k_{deg}$, $R_{tot}$ is constant, TMDD elimination is described by the Michaelis-Menten term with $V_{max}$=$R_{tot}k_{int}$, $K_M$=$K_{SS}$.




ADC parameters assumed to be independent of DAR: $V_c$, $k_{pt}$, $k_{tp}$.

ADC parameters that may depend on DAR: $CL_i$, i = 0,…,8; $k^i{}_{dec}$; i = 1,…,8.

**Possible generalizations**: deconjugation in the peripheral compartments; delayed and/or incomplete release of the drug load by the eliminated ADC species; two-compartment PK of the released drug.

**Possible simplifications**: decrease the number of ADC species; use linear model ($V_{max}$=0).

**Identifiability of model parameters was investigated using PFIM 3.2 [1]**

Measurable quantities: $$C = \sum_{i=0}^{8}C^i; \quad L_C = \sum_{i=1}^{8}i \cdot C^i; \quad C^L = L/V_L.$$

## RESULTS

- The ADC system can be described using the general TMDD framework with an additional element that accounts for the deconjugation process.
- Given the typically available measurements, parameters of the individual ADC species (ADCs with specific DARs) are not identifiable.
- Assumptions that relate ADC and ADC-target parameters with different DARs are required.
- In particular, the system where ADC model parameters do not depend on DAR is identifiable.
- The system where parameters linearly depend on DAR is identifiable.
- Deconjugation rate of individual ADC species can be identifiable only under specific assumptions on how deconjugation rate depends on DAR; the individual ADC deconjugation rates cannot be estimated from the typically available data.

## CONCLUSIONS

- Michaelis-Menten approximation of the TMDD model can be used to describe the interaction of ADC with the target when internalization rate is fast.
- Assumptions that describe dependence of the ADC parameters on drug load are necessary to make the system identifiable.
- In particular, the system with ADC parameters linearly dependent on DAR is identifiable.

**References:** [1] Bazzoli C, Retout S, Mentré F. Design evaluation and optimisation in multiple response nonlinear mixed effect models: PFIM 3.0. Computer Methods and Programs in Biomedicine, 2010, 98: 55-65; http://www.pfim.biostat.fr