Session 4b: PKPD Modeling of Antibody-Drug Conjugate (Symposium)

October 14, 2014, Las Vegas, NE

Approaches to Modeling Clinical PK of ADCs

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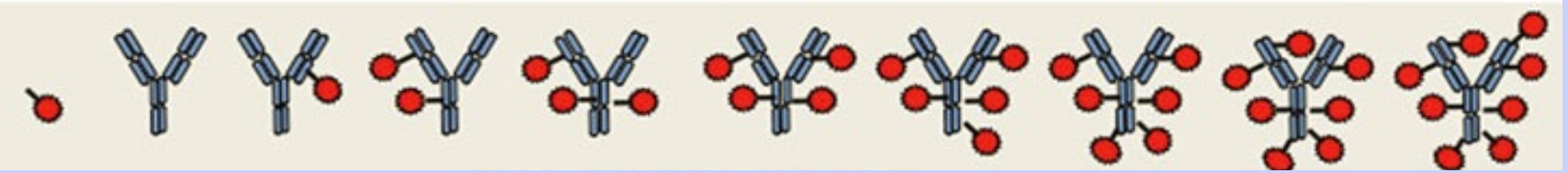
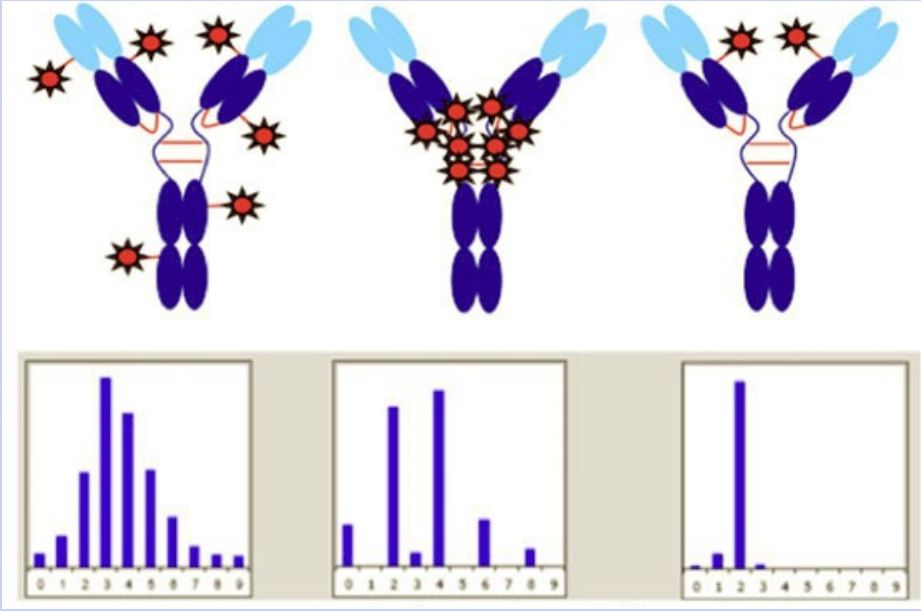
Antibody-Drug Conjugates

- Antibody (or antibody fragment) linked (through a chemical linker) to a payload (cytotoxic small molecule)
- Designed to:
  - Bind to its antigen on the surface of tumor cells
  - Be efficiently internalized through endocytosis
  - Release payload (toxin) in the lysosome and kill target cells

ADCs are mixtures with dynamically changing heterogeneity



- Heterogeneity due to conjugating through amino acid residues on the antibody
- Dynamic heterogeneity due to deconjugation



Drug-to-antibody (DAR) ratio distribution

From Lin, Tibbitts. Pharm Res (2012) 29:2353-2366

ADC Assays

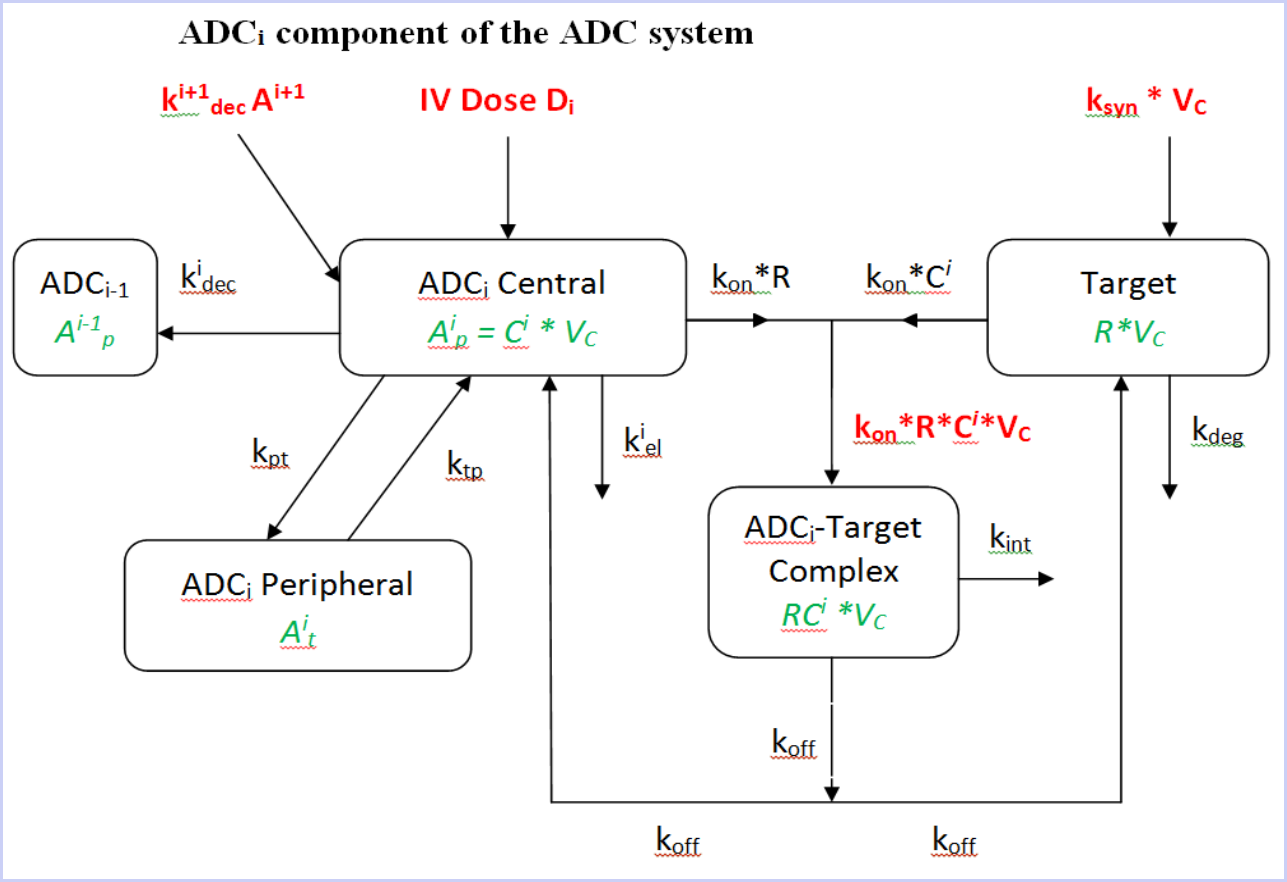
- Usually include concentrations of:
  - Total antibody (ADC + naked antibody) $C = \sum_{i=0}^{8} C^i = tAB$
  - Free toxin (unconjugated) T
- Also include one or more of :
  - Conjugated toxin (all toxin molecules on all antibodies) $acT = \sum_{i=0}^{8} i \cdot C^i$
  - ADC (conjugated antibody) $\sum_{i=1}^{8} C^i$
  - Naked antibody (unconjugated) C^0
- Rarely (at preclinical stage), but possibly more often in the future
  - Individual ADC species of different DARs C^i, i=1,…,8,…

What to Measure at Clinical Stage?

- The question is not completely settled;
- I am in favor of measuring these three analytes:
  - Total antibody (ADC + naked antibody) $C = \sum_{i=0}^{8} C^i = tAB$
  - Free toxin (unconjugated) T
  - Conjugated toxin (all toxin molecules on all antibodies) $acT = \sum_{i=0}^{8} i \cdot C^i$
- Why?
  - Total antibody may be needed to assess effects of the drug that are independent of the toxin;
  - Unconjugated toxin is needed to assess safety, as it is extremely toxic;
  - Conjugated toxin is most likely responsible for the ADC-induced efficacy.

ADC TMDD Model [1]

Red: input; Green: amount; Black: rate constants



ADC Assumptions

- For ADCs with different DARs, the same
  V_c, k_{pt}, k_{tp}, and k_{on}, k_{off}, k_{int}
- Deconjugation occurs in the central compartment
- Eliminated ADCs release toxin to the central compartment (not shown)

[1] L Gibiansky, E Gibiansky, J PKPD, 2014;41(1):35-47 doi: 10.1007/s10928-013-9344-y

Assumptions

In addition to the commonly used TMDD assumptions, the system assumes that:

- Different ADC^i species have the same volume of distribution and inter-compartment rate constants, but may differ by non-specific clearance and deconjugation rate;
- Different ADC^i species have the same binding and internalization constants k_{on}, k_{off} and k_{int};

Possible extensions of the equations such as deconjugation in the peripheral compartment, deconjugation in the ADC-target complex, delayed and/or incomplete release of the toxin load from the eliminated ADC^i species are straightforward but are not considered in this talk.

ADC Approximations

As with the general TMDD model, the drug-target association process is usually much faster than the processes of drug dissociation/distribution/elimination and of elimination of the target and the drug-target complex. Following the same scheme as for the TMDD model, the system of ADC TMDD equations can be simplified.

ADC Michaelis – Menten Equations

For mABs with fast internalization of the complex, like ADCs, TMDD elimination can be described by the Michaelis-Menten equations:

$$\frac{dC^i}{dt} = \frac{k_{tp}A^i{}_t}{V_c} - \left(k^i{}_{el} + k_{pt}\right)C^i - \frac{V_{\max}C^i}{K_{SS}+C} + k^{i+1}{}_{dec}C^{i+1} - k^i{}_{dec}C^i;$$

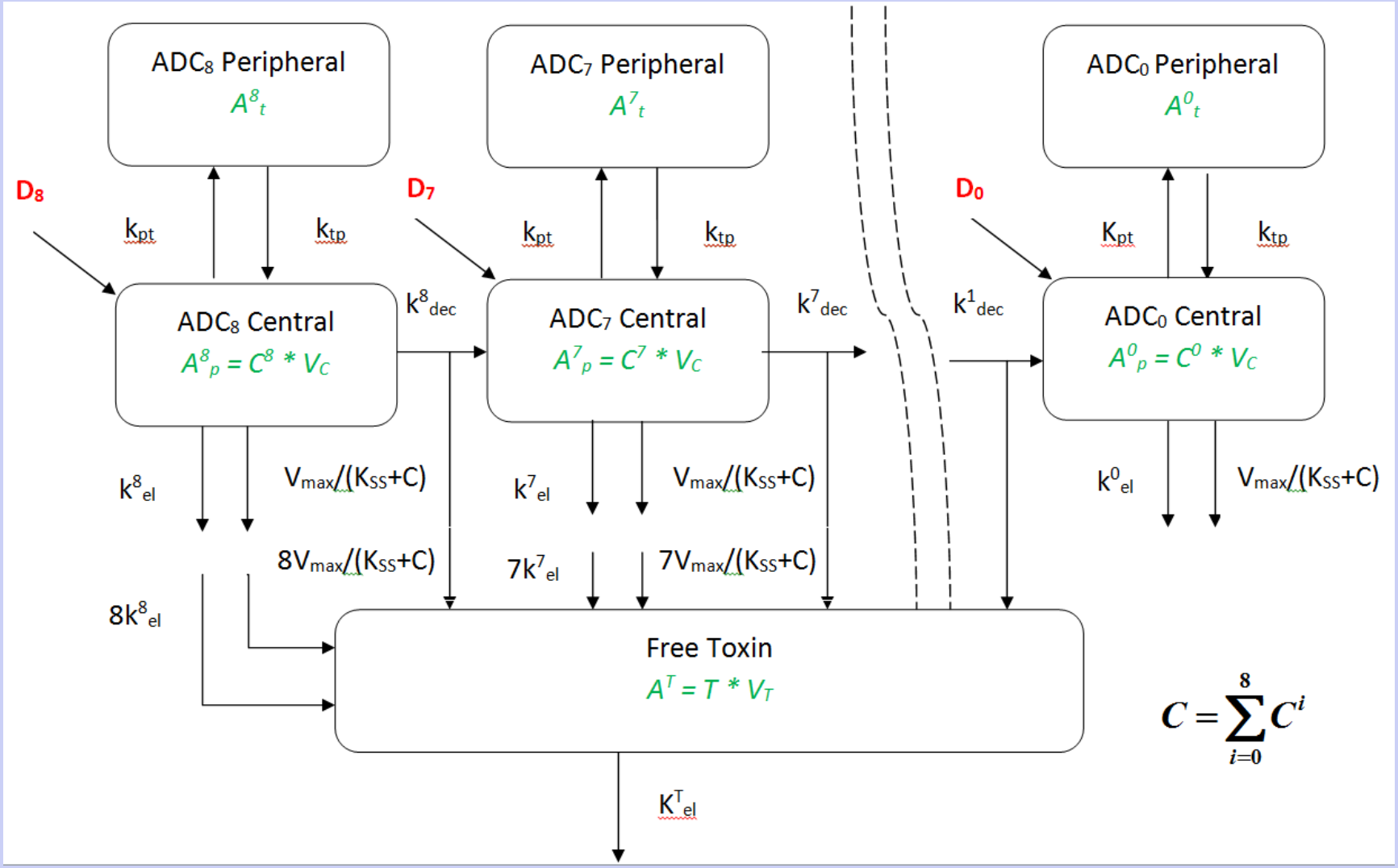
$$\frac{dA^i{}_t}{dt} = k_{pt}C^iV_c - k_{tp}A^i{}_t; \qquad (k^0{}_{dec} = 0; \quad k^9{}_{dec} = 0);$$

$$\frac{dA_T}{dt} = V_c\sum_{i=1}^{8}\left(k^i{}_{dec}C^i + i\cdot k^i{}_{el}C^i + \frac{i\cdot V_{\max}C^i}{K_{SS}+C}\right) - k^T{}_{el}A_T; \qquad A_T(0) = 0;$$

$$C^i(0) = D^i/V_c; \qquad C = \sum_{i=0}^{8}C^i; \qquad i = 0,\ldots,8.$$

If concentrations of individual ADC^i species are not available, the system is not likely to be identifiable. Additional assumptions (for $k^i{}_{el}$ and $k^i{}_{dec}$) are needed.

ADC MM Model


ADC8 Peripheral
A8t
ADC7 Peripheral
A7t
ADC0 Peripheral
A0t
D8
D7
D0
kpt
ktp
kpt
ktp
Kpt
ktp
ADC8 Central
A8p = C8 * VC
k8dec
ADC7 Central
A7p = C7 * VC
k7dec
k1dec
ADC0 Central
A0p = C0 * VC
k8el
Vmax/(KSS+C)
k7el
Vmax/(KSS+C)
k0el
Vmax/(KSS+C)
8Vmax/(KSS+C)
7k7el
7Vmax/(KSS+C)
8k8el
Free Toxin
AT = T * VT
KTel
C = Σ Ci

ADC with Load-Independent Properties

Earlier assumptions: different ADC^i have the same volume of distribution, inter-compartment rate constants and binding parameters.

Additional assumptions:

- Elimination rate is independent of the toxin load: $k^i_{el} = k_{el}$;
- Deconjugation rate of each toxin molecule is independent of the position and the number and positions of other toxins attached to the same ADC^i.

ADC with LIP : $\mathbf{k^i_{el} = k_{el}}$, $\mathbf{k^i_{dec} = i \cdot k_{dec}}$

Assumptions may or may not hold but they allow a significant simplification of the model equations for ADC.

Validity of LIP Assumption $k^i_{el} = k_{el}$

Pro	Con
Each toxin is small (< 1 kDa) and unlikely to change the properties of 150 kDa mAB;	Conjugation may change configuration and/ or other mAB properties resulting in increase of non-specific clearance;
ADC equations with different CL^i are un-identifiable given the typically available clinical data; DAR-independence of CL is the simplest assumption that stabilizes the model;	Pre-clinical experimental data in mice suggest increase of CL with DAR [3, 4], especially for high-DAR species;
Comparison of models with DAR-proportional and DAR-independent CL indicated similar fit of clinical data [2]	Modeling of preclinical data in monkey suggests increase of CL with DAR [5].

[2] Lu D et al., ACoP 2014, Poster T-011.

[3] Hamblett KJ et al., (2004) Clin. Cancer Res, 10, 7063-7070

[4] McDonagh CF et al., (2006) Protein Eng Des Sel., 19(7), 299-307.

[5] Bender B et al.,AAPS J. 2014 Sep;16(5):994-1008. doi: 10.1208/s12248-014-9618-3

Validity of LIP Assumption $k^i_{dec} = i \cdot k_{dec}$

Pro	Con
If probability of deconjugation is independent of the conjugation site, this relation can be easily derived rigorously	If deconjugation probability depends on the conjugation site, k^i_{dec} should increase with DAR faster than DAP-proportional;
ADC equations with different k^i_{dec} are un-identifiable given the typically available clinical data	Pre-clinical and clinical experimental data suggest position-dependent deconjugation rate for some types of ADCs.
DAR-independent k^i_{dec} is hard to justify, as this leads to decreased deconjugation probability of each toxin in high-DAR species	Modeling of preclinical data in monkey suggests DAR-independent k^i_{dec} for DAR >= 3 [5]
Modeling of preclinical data in monkey suggests DAR-proportional increase of k^i_{dec} for DAR <= 3 [5]	

Modeling based on LIP assumptions resulted in a stable model with good fit of all observed total antibody, conjugated toxin, and unconjugated toxin data [2]. The run time of simplified models based on LIP assumptions was 10-fold smaller than for the same models in the original form.

Simplified ADC Equations

LIP assumptions: $k^i_{el} = k_{el}$ and $k^i_{dec} = i \cdot k_{dec}$

$$\frac{dC^i}{dt} = \frac{k_{tp} A^i{}_t}{V_c} - \left(k_{el} + k_{pt}\right) C^i - \frac{V_{\max} C^i}{K_{SS} + C} + (i+1) k_{dec} C^{i+1} - i \cdot k_{dec} C^i$$

$$\frac{dA^i{}_t}{dt} = k_{pt} C^i V_c - k_{tp} A^i{}_t \qquad i = 0,\ldots,8; \quad C^9 = 0$$

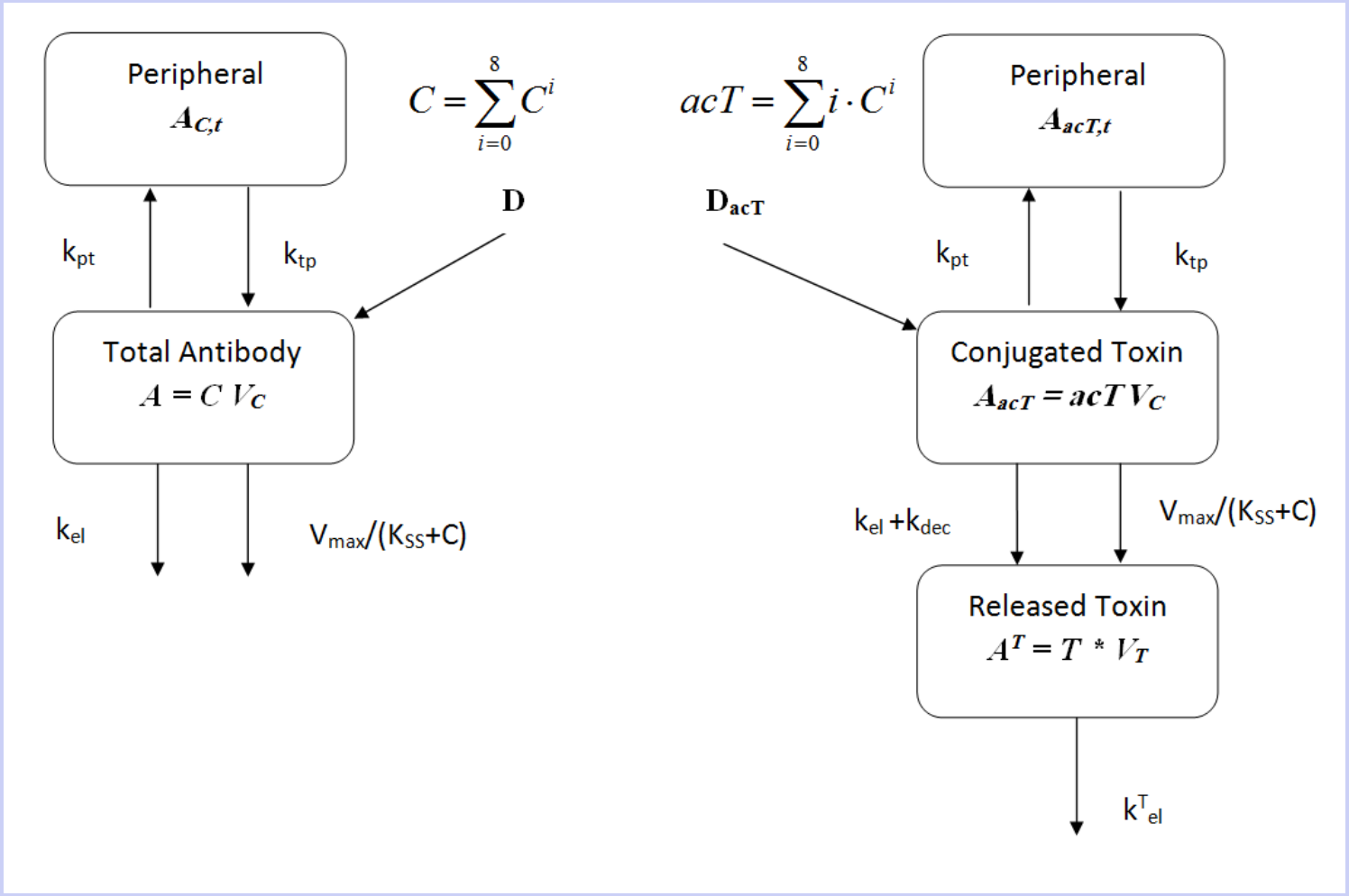
$$\frac{dA_T}{dt} = V_c \sum_{i=1}^{8} i \cdot (k_{dec} + k_{el} + \frac{V_{\max}}{K_{SS} + C}) C^i - k^T{}_{el} A_T$$

Model includes 19 differential equations (if $i \leq 8$)

If $C = \sum_{i=0}^{8} C^i$ and $acT = \sum_{i=0}^{8} i \cdot C^i$ are measured, the system can be further reduced

Reduced ADC model

Assumptions: $k^i_{el} = k_{el}$ and $k^i_{dec} = i \cdot k_{dec}$



MM term is the same for 2 systems:

$$\frac{V_{max}}{K_{SS} + C}$$

All parameters are shared between C and acT systems, except k_{dec}

Reduced ADC equations

$$\frac{dC}{dt} = \frac{k_{tp} A_{C,t}}{V_c} - \left(k_{el} + k_{pt}\right) C - \frac{V_{\max} C}{K_{SS} + C};$$

$$\frac{dA_{C,t}}{dt} = k_{pt} C \cdot V_c - k_{tp} A_{C,t};$$

$$\frac{dacT}{dt} = \frac{k_{tp} A_{acT,t}}{V_c} - \left(k_{el} + k_{pt} + k_{dec}\right) acT - \frac{V_{\max} acT}{K_{SS} + C};$$

$$\frac{dA_{acT,t}}{dt} = k_{pt} acT \cdot V_c - k_{tp} A_{acT,t}$$

$$\frac{dA_T}{dt} = V_c \left(k_{dec} + k_{el} + \frac{V_{\max}}{K_{SS} + C} \right) acT - k^T{}_{el}\, A_T; \qquad A_T(0) = 0;$$

$$C(0) = \frac{D_C}{V_c}; \qquad acT(0) = \frac{D_{acT}}{V_c}; \quad C = \sum_{i=0}^{8} C^i; \quad acT = \sum_{i=0}^{8} i \cdot C^i$$

Unobserved C^i concentrations can be computed from the MM equations

Modeling of Unconjugated Toxin Data

- Three routes for unconjugated toxin to appear in the systemic circulation:
  - ✓ Deconjugation (k_{dec}·acT);
  - ✓ Elimination of the ADC via non-specific clearance (k_{el}·acT);
  - ✓ Target-mediated elimination (V_{max}·acT/(K_{SS}+C));
- Each route may have it's own efficiency ("bioavalability") and time delay;

$$\frac{d\,A_{d1}}{dt} = k_{dec}\,acT \cdot V_c - k_{d1-T} A_{d1}; \qquad acT = \sum_{i=0}^{8} i \cdot C^i;$$

$$\frac{d\,A_{d2}}{dt} = k_{el}\,acT \cdot V_c - k_{d2-T} A_{d2}; \qquad C = \sum_{i=0}^{8} C^i;$$

$$\frac{d\,A_{d3}}{dt} = \frac{V_{\max} acT \cdot V_c}{K_{SS} + C} - k_{d3-T} A_{d3};$$

$$\frac{dA_T}{dt} = f_1 \cdot k_{d1-T} A_{d1} + f_2 \cdot k_{d2-T} A_{d1} + f_3 \cdot k_{d3-T} A_{d3} - k^T{}_{el}\, A_T; \qquad A_T(0) = 0;$$

Modeling of Unconjugated Toxin Data

- Toxin clearance is much higher than ADC clearance: formation-limited kinetics;

$$A_T = \frac{f_1 \cdot k_{d1-T} A_{d1} + f_2 \cdot k_{d2-T} A_{d1} + f_3 \cdot k_{d3-T} A_{d3}}{k^T{}_{el}};$$

$$T = \frac{f_1 \cdot k_{d1-T} A_{d1} + f_2 \cdot k_{d2-T} A_{d1} + f_3 \cdot k_{d3-T} A_{d3}}{CL_T}.$$

- "Bioavailability" parameters f_i and delay rates $k_{di\text{-}T}$ may not be identifiable;
- Delay process may be non-linear and concentration-dependent;
- Appropriate simplified or more complex models could be developed based on the observed data, see example of implementation in ACoP-2014 poster T-11 [2].

Implication of the Integrated Model

- The integrated ADC PK model (total antibody + conjugated toxin + unconjugated toxin) provides a mechanistic framework for the description of observed ADC PK data;
- Under LIP assumptions, equations that describe PK properties of the total antibody and of the conjugated toxin are very similar; in fact, they differ by just one constant, k_{dec};
- For ADC with LIP, similarity of equations allows to predict total antibody PK from conjugated toxin measurements, and vise versa, see example in ACoP poster T-011 [2].

Conclusions

- Mechanistic (TMDD) framework for description of ADC PK was developed;
- The Michaelis-Menten approximation of the ADC-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^i parameters on drug load are necessary to make the system identifiable;
- For ADC with load-independent properties (LIP) $k^i_{el} = k_{el}$ and $k^i_{dec} = i \cdot k_{dec}$;
- Under LIP assumptions, ADC PK can be described by two coupled two-compartment systems with parallel linear and Michaelis-Menten elimination;
- When Michaelis-Menten term is negligible and the systems are linear, the two systems decouple allowing for independent fit;
- Proposed models can be used to describe the observed clinical ADC PK data, including total antibody, conjugated toxin, and unconjugated toxin data;
- The presented model was successfully used for the clinical development of a real-life ADC, see ACoP Poster T-011 [2].

Any questions?