Enzyme Kinetics Equations

**TMD Model:**
\[
\frac{dC_{\text{complex}}}{dt} = \frac{K_{ON} C_{\text{FreeDrug}} C_{\text{Target}}}{K_{OFF} + K_{ON} C_{\text{complex}}} - (K_{\text{int}} + K_{OFF}) C_{\text{complex}}
\]

**QE Approximation:**
\[
K_{ON} C_{\text{FreeDrug}} C_{\text{Target}} - (K_{\text{int}} + K_{OFF}) C_{\text{complex}} = 0
\]

**QSS Approximation:**
\[
K_{ON} C_{\text{FreeDrug}} C_{\text{Target}} - (K_{\text{int}} + K_{OFF}) C_{\text{complex}} = 0
\]

**Quasi-Equilibrium or Quasi-Steady-State:**
\[
\frac{dC_{\text{total}}}{dt} = \frac{R_{\text{Total}} K_{\text{INT}}}{K_{\text{ON}} K_{\text{OFF}}} - (K_{\text{INT}} + K_{\text{OFF}}) C_{\text{total}}
\]

**Quasi-Equilibrium:**
\[
C_{\text{complex}}^{\text{QSS}} = \frac{K_{\text{INT}}}{K_{\text{ON}}}
\]

**Quasi-Steady-State:**
\[
C_{\text{complex}}^{\text{QSS}} = \frac{K_{\text{INT}}}{K_{\text{ON}}}
\]

**Michaelis-Menten Approximation:**
\[
C_{\text{complex}}^{\text{MM}} = \frac{K_{\text{MM}}}{R_{\text{MM}}}
\]

**Parameters used for simulations (Figures 1-4):**
- It was assumed that the total target concentration $R_{\text{Total}}$ is constant, and $V=1$

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<tr>
<th>Case</th>
<th>$K_{\text{OFF}}$</th>
<th>$K_{\text{INT}}$</th>
<th>$K_{\text{ON}}$</th>
<th>$K_{\text{MM}}$</th>
<th>$R_{\text{MM}}$</th>
<th>$V_{\text{MAX}}$</th>
<th>$R_{\text{Total}}$</th>
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**Discussion of simulation results:**
- The QE/QSS model provides better description of the TMDD data (relative to the QE/QE model) when $K_{\text{OFF}} > K_{\text{INT}}$
- The TMDD model provide adequate description of the TMDD data when $R_{\text{MM}}$ is small when compared to the characteristic concentration range (Figure 1 and Figure 3, high concentrations);
- The MM predictions may diverge from the true concentrations when the drug concentrations fall below $R_{\text{Total}}$ (Figure 2 and Figure 4).

**Implications for modeling of drugs with the TMDD:**
- Investigation of identifiability of the TMDD model parameters for each specific data set: only parameters of the parsimonious model should not be trusted;
- Simulations can identify dosing regimens and concentration ranges that need to be explored to identify all TMDD parameters: regions where predictions of the simpler models diverge from the TMDD model predictions are of interest;
- Results allow selecting the parsimonious model that is sufficient to describe the data for the therapeutic dosing regimens. Even if the TMDD model is necessary to describe the entire range of tested doses, only simpler model might be necessary to describe the pharmacokinetic of the drug in the therapeutic range of concentrations and for the clinically relevant dosing regimens;
- The proposed method was tested on the example of the simulated dataset as described in Poster # 1271.