Dynamics of Target-Mediated Drug Disposition
A Mathematical Analysis

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Outline

1. Analysis of data sets - Characteristic patterns
2. Simulations of the TMDD model
3. Identification of different phases of the dynamics
4. Obtaining quantitative results - Parameter estimates
5. Simplified models
Linear pharmacokinetics

One-compartment model:

\[ V_p \frac{dC_p}{dt} = \text{Input} - Cl \ C_p, \quad V_p = \text{Plasma volume}. \]

Two-compartment model:

\[
\begin{aligned}
  V_p \frac{dC_p}{dt} &= \text{Input} - Cl_p \ C_p - Cl_d (C_p - C_t), \\
  V_t \frac{dC_t}{dt} &= Cl_d (C_p - C_t),
\end{aligned}
\]

\((Cl_d \gg Cl_p)\)
Nonlinear pharmacokinetics

Data and fit of the concentration of the antibody hu1124 in humans with Psoriasis (a chronic skin disease) from Bauer et al. (1999), using:

\[
\begin{align*}
V_c \frac{dC_p}{dt} &= -Cl_{EH}C_p - Cl_d(C_p - C_t) - V_{max} \frac{C_p}{K_m + C_p} \\
V_t \frac{dC_t}{dt} &= Cl_d(C_p - C_t)
\end{align*}
\]

**Empirical evidence:** Saturable elimination: *Michaelis-Menten elimination*

**Find:** A mechanistic explanation
Another data set

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<th>Value 1</th>
<th>Value 2</th>
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Two points of inflection!
Target-Mediated Drug Disposition

Ligand and Receptor (Target) form active complex

\[ L + R \rightarrow RL \]

\[ k_{on} \quad k_{off} \quad k_{in} \quad k_{out} \quad k_{e(L)} \quad k_{e(RL)} \]

\[ R_0 = \frac{k_{in}}{k_{out}} \]

Parameter fit

<table>
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<th>Value 2</th>
<th>Value 3</th>
<th>Value 4</th>
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<td>( k_{off} )</td>
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<td>( k_{in} )</td>
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<td>( k_{e(L)} )</td>
<td>(mg/L) h^{-1}</td>
<td>(mg/L) h^{-1}</td>
<td>h^{-1}</td>
<td>h^{-1}</td>
<td>h^{-1}</td>
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<td>( k_{e(RL)} )</td>
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</tbody>
</table>

\[ K_d \overset{\text{def}}{=} \frac{k_{off}}{k_{on}} = 0.011 \text{ mg/L} \]

\[ K_m \overset{\text{def}}{=} \frac{k_{off} + k_{e(RL)}}{k_{on}} = 0.044 \text{ mg/L} \]
Questions

1. How to estimate the **six** parameters?

2. Which data do you need:
   - Is data about ligand $L$ enough?
   - Data about target $R$ and complex $RL$?
     
     *Often difficult, if not impossible, to get.*

3. Over what period do you need data? (Design of experiments)

4. How to distinguish between empirical Michaelis-Menten and TMDD?

5. Validity of *Rapid Binding* and *Quasi-Steady-State* models.
The equations

The dynamics is given by the system of nonlinear differential equations:

\[
\begin{align*}
\frac{dL}{dt} &= In_L - k_{on}L \cdot R + k_{off}RL - k_e(L)L \\
\frac{dR}{dt} &= k_{in} - k_{out}R - k_{on}L \cdot R + k_{off}RL \\
\frac{dRL}{dt} &= k_{on}L \cdot R - k_{off}RL - k_e(RL)RL
\end{align*}
\]

If $In_L = 0$, then the Baseline is given by

\[L = 0, \quad R = R_0 \overset{\text{def}}{=} \frac{k_{in}}{k_{out}}, \quad RL = 0.\]

The initial concentrations, right after a bolus dose, are given by

\[L(0) = L_0, \quad R(0) = R_0, \quad RL(0) = 0.\]
Simulations - Logarithmic scale

![Graphs showing ligand concentration over time with logarithmic scale.](image)

- Time (h) vs. Ligand (mg/L)
- Log(R₀ - R)
- Log(Rₐ₀ - R₀)

Parameters:
- L₀ = 30, 100, 300, 900; R₀ = 12

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Characteristics of the Ligand \textit{versus} time graph

Phase A: $L$, $R$ and $RL$ (quickly) reach quasi-equilibrium \quad (0 < t < T_1)

Phase B: Target is saturated - \textit{linear} \quad (T_1 < t < T_2)

Phase C: $L = O(K_m)$; target unsaturated - \textit{nonlinear} \quad (T_2 < t < T_3)

Phase D: Linear elimination. \quad (T_3 < t < \infty)
Phase A: Short time dynamics

Conservation laws for $L$ and $R$:

$$L_{\text{tot}} = L + RL$$
$$R_{\text{tot}} = R + RL$$

\[
\begin{align*}
\frac{dL_{\text{tot}}}{dt} &= -k_{e(L)}L - k_{e(RL)}RL \\
\frac{dR_{\text{tot}}}{dt} &= k_{\text{in}} - k_{\text{out}}R - k_{e(RL)}RL
\end{align*}
\]
Dimensionless variables

In order to compare the magnitude of the different terms in the system of differential equations we introduce dimensionless variables.

(1) Scale the concentrations with appropriate reference values:

\[ x = \frac{L}{L_0}, \quad y = \frac{R}{R_0}, \quad z = \frac{RL}{R_0} \]

(2) Scale the time with an appropriate time scale. Consider the equation:

\[ \frac{dL}{dt} = -k_{on} L \cdot R \quad \implies \quad \frac{dx}{dt} = -k_{on} R_0 x \cdot y \]

This suggests for dimensionless time \( \tau \):

\[ \tau = k_{on} R_0 t \quad (or \quad \tau = k_{on} L_0 t) \]
Dimensionless equations

Introducing the dimensionless variables leads to the equations

\[
\begin{align*}
\frac{dx}{d\tau} &= -x \cdot y + \mu \frac{K_d}{R_0} z - \frac{k_{el}}{k_{on R_0}} x \\
\frac{dy}{d\tau} &= \frac{k_{out}}{k_{on R_0}} (1 - y) - \frac{1}{\mu} x \cdot y + \frac{K_d}{R_0} z \\
\frac{dz}{d\tau} &= \frac{1}{\mu} x \cdot y - \frac{K_d}{R_0} z - \frac{k_{e(RL)}}{k_{on R_0}} z
\end{align*}
\]

For the conservation laws we obtain:

\[
\begin{align*}
\frac{d}{d\tau} (x + \mu z) &= -\varepsilon \left( \frac{k_{el}}{k_{off}} x + \mu \frac{k_{e(RL)}}{k_{off}} z \right) \\
\frac{d}{d\tau} (y + z) &= \varepsilon \left( \frac{k_{out}}{k_{off}} (1 - y) - \frac{k_{e(RL)}}{k_{off}} z \right)
\end{align*}
\]

Because $\varepsilon \ll 1$ we conclude that

\[x(\tau) + \mu z(\tau) \approx 1, \quad y(\tau) + z(\tau) \approx 1\]
Phase A: Short-time dynamics

Elimination of $x$ and $y$ yields:

$$\mu \frac{dz}{d\tau} = f(z) \overset{\text{def}}{=} (1 - \mu z)(1 - z) \left\{ -\mu \frac{K_m}{R_0} \right\}$$

Note that $\mu \frac{K_m}{R_0} = O(\mu \cdot \varepsilon)$ and may be omitted.

**Exercise 1:** The function $f(\bar{z})$ has a unique zero $\bar{z} = 1$ in the interval $[0, 1]$, and that

(a) $z(\tau) \to \bar{z}$ as $\tau \to \infty$;

(b) $\tau_{1/2} = O\left(\frac{1}{\mu}\right)$, $t_{1/2} = O\left(\frac{1}{k_{\text{on}}L_0}\right)$ (if $\mu \ll 1$)

**Exercise 2:** Show that

$L(t) \to \bar{L} = L_0 - R_0$, $R(t) \to 0$, $RL(t) \to R_0$ as $t \to T_1$
Receptor dynamics

Recall that
\[
\frac{dR_{\text{tot}}}{dt} = k_{\text{in}} - k_{\text{out}}R - k_{e(RL)}RL
\]
and initially
\[
R_{\text{tot}} = R + RL
\]
\[
R(0) = R_0 \quad \text{and} \quad RL(0) = 0
\]

Then the following uniform upper bound holds:

**Theorem 1:** Let \( R, RL \) and \( R_{\text{tot}} \) satisfy the above equations. Then
\[
R_{\text{tot}}(t) \leq \max \left\{ \frac{k_{\text{in}}}{k_{\text{out}}}, \frac{k_{\text{in}}}{k_{e(RL)}} \right\} \quad \text{for all} \quad t \geq 0
\]

These bounds are valid for all \( L_0 > 0 \), and all parameter values.

**Exercise 3:** Prove this theorem.
Receptor dynamics in Phase B \((L \gg K_m)\)

In **Phase B**: \(L, R\) and \(RL\) are approximately in quasi-equilibrium:

\[
RL \approx R_{\text{tot}} \frac{L}{L + K_m} \quad \text{and} \quad R \approx R_{\text{tot}} \frac{K_m}{L + K_m}
\]

Hence, since in Phase B we have \(L \gg K_m\), it follows that

\[
RL \approx R_{\text{tot}} \quad \text{and} \quad R \approx 0
\]

Therefore

\[
\frac{dR_{\text{tot}}}{dt} = k_{\text{in}} - k_{e(RL)}R_{\text{tot}}, \quad T_1 < t < T_2
\]

Since \(T_1 \approx 0 \implies R_{\text{tot}}(T_1) \approx R_0\), we obtain for \(0 < t < T_1\),

\[
R_{\text{tot}}(t) \approx R_* + (R_0 - R_*) e^{-k_{e(RL)}t}, \quad R_* = \frac{k_{\text{in}}}{k_{e(RL)}}
\]
Receptor curve in Phase B - theory and simulation

\[ R_{\text{tot}}(t) \approx R_* + (R_0 - R_*)e^{-k_{e(RL)}t}, \quad 0 < t < T_2 \]

\[ t_{1/2} = \frac{\ln(2)}{k_{e(RL)}} = 231 \text{ h} \]
Ligand curves in Phase B

We have

\[
\frac{dL_{\text{tot}}}{dt} = \frac{d}{dt} (L + RL) = -ke(L)L - ke(RL)RL
\]

In Phase B, \( L \gg K_m \), so that \( RL \approx R_{\text{tot}} \) and

\[
\begin{align*}
\frac{d}{dt} (L + R_{\text{tot}}) &= -ke(L)L - ke(RL)R_{\text{tot}} \\
\frac{dR_{\text{tot}}}{dt} &= k_{\text{in}} - ke(RL)R_{\text{tot}}
\end{align*}
\]

Subtraction yields

\[
\frac{dL}{dt} = -ke(L)L - k_{\text{in}}; \quad L(T_1) = \bar{L} = L_0 - R_0
\]

Hence

\[
L(t) = \left( \frac{\bar{L}}{ke(L)} + \frac{k_{\text{in}}}{ke(L)} \right) e^{-ke(L)t} - \frac{k_{\text{in}}}{ke(L)}
\]
Ligand curve in Phase B - simulation

\[ L(t) = \left( \bar{L} + \frac{k_{\text{in}}}{k_{e(L)}} \right) e^{-k_e(L)t} - \frac{k_{\text{in}}}{k_e(L)}, \quad \bar{L} = L_0 - R_0 \]
Dynamics in Phase C and D - a different scaling

Dimensionless variables

\[ u = \frac{L}{K_d}, \quad v = \frac{R}{R_0}, \quad w = \frac{RL}{R_0}, \quad \tau = k_{\text{off}} t \]

Transformed equations:

\[
\begin{align*}
\frac{\varepsilon du}{d\tau} &= -u \cdot v + w - \varepsilon \alpha u \\
\frac{dv}{d\tau} &= \beta (1 - v) - (u \cdot v - w) \\
\frac{dw}{d\tau} &= u \cdot v - (1 + \gamma)w
\end{align*}
\]

\[ \varepsilon = \frac{K_d}{R_0}, \quad \alpha = \frac{k_e(L)}{k_{\text{off}}}, \quad \beta = \frac{k_{\text{out}}}{k_{\text{off}}}, \quad \gamma = \frac{k_e(RL)}{k_{\text{off}}}, \]

\[ \varepsilon = 0.0009, \quad \alpha = 1.5, \quad \beta = 9, \quad \gamma = 3 \]
Receptor dynamics in Phases C \((L = O(K_d))\) and D

Reduced equations

\[
\begin{align*}
u \cdot v - w &= 0, \\
\frac{dv}{d\tau} &= \beta(1 - v), \\
\frac{dw}{d\tau} &= -\gamma w
\end{align*}
\]

or, in the original variables:

\[
\begin{align*}
L \cdot R &= K_d \cdot RL, \\
\frac{dR}{dt} &= k_{out}(R_0 - R), \\
\frac{dRL}{dt} &= -k_{e(RL)}RL
\end{align*}
\]

\[
\text{Log(R)}_0 = 30, 100, 300, 900; \quad R_0 = 12
\]

\[
\text{Log(RL)}_0 = 30, 100, 300, 900; \quad R_0 = 12
\]

**Note:** The RB approximation, \(L \cdot R = K_d \cdot RL\), is satisfied here
Parameter estimates

Suppose that the volume of the compartment $V_c$ is known

**Phase A:**

$$L_0, R_0 \quad \text{and} \quad T_1 = O(1/(k_{on}L_0)) \implies k_{on}$$

**Phase B:**

$$k_{e(L)} \quad \text{and} \quad T_2(k_{e(L)}, k_{in}) \implies k_{in} \quad \& \quad k_{out} = k_{in}/R_0$$

**Phase C:**

$$K_d \implies k_{off} = K_d k_{on}$$

**Phase D:**

$$k_{e(RL)}$$

**Conclusion:** The ligand graph yields all six parameters of the TMDD model (Provided one has rich data)
Simplified models

The TMDD model has been simplified on the basis of certain assumptions

1. The Quasi-Steady State (QSS) assumption:

   \[ L \cdot R = K_m RL \]

2. The Rapid-Binding (RB) assumption:

   \[ L \cdot R = K_d RL \]

3. The constant-receptor assumption:

   \[ R_{\text{tot}} = R + RL = \text{constant} = R_0 \]

4. The Michaelis-Menten model
   
   *Ligand curves are concave for larger times.* (cf. Bauer).

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The QSS assumption

\[ L \cdot R = K_m RL = \frac{k_{\text{off}} + k_{e(RL)}}{k_{\text{on}}} RL \]

Recall:

\[ \frac{dRL}{dt} = k_{\text{on}} L \cdot R - (k_{\text{off}} + k_{e(RL)}) RL = 0 \]

We have

\[ \frac{d}{dt}(L + RL) = -k_{e(L)} L - k_{e(RL)} RL \]

and hence

\[ \frac{dL}{dt} = -k_{e(L)} L - k_{e(RL)} RL \]

However,

\[ RL = R_{\text{tot}} \frac{L}{L + K_m} \quad \text{(QSS assumption)} \]

Therefore,

\[ \begin{cases} \frac{dL}{dt} = -k_{e(L)} L - k_{e(RL)} R_{\text{tot}} \frac{L}{L + K_m} \\ \frac{dR_{\text{tot}}}{dt} = k_{\text{in}} - k_{e(RL)} R_{\text{tot}} \quad \text{as long as } R \approx 0 \end{cases} \]
The constant receptor assumption

\[ k_{\text{out}} = k_{e(RL)} \implies R + RL \equiv R_0 \]

The QSS model now simplifies to the MM model:

\[
\frac{dL}{dt} = -k_{e(L)} L - k_{e(RL)} R_0 \frac{L}{L + K_m}
\]

The Full model simplifies to

\[
\begin{align*}
\frac{dL}{dt} &= -(k_{\text{on}} R_0 + k_{e(L)}) L + (k_{\text{on}} L + k_{\text{off}}) RL \\
\frac{dRL}{dt} &= k_{\text{on}} R_0 L - (k_{\text{on}} L + k_{\text{off}} + k_{e(RL)}) RL
\end{align*}
\]

The dashed lines are the Null clines on which \( dRL/dt = 0 \) and \( dL/dt = 0 \):

\[
\begin{align*}
RL &= R_0 \frac{L}{L + K_m}, & RL &= R_0 \frac{L + \kappa_{e(L)}}{L + K_d}, & \kappa_{e(L)} &= \frac{k_{e(L)}}{k_{\text{on}}}
\end{align*}
\]
Conclusions

1. It is possible to extract the following information from ligand-versus time curves over a sufficiently long time span:

   (a) Estimates for many parameters.

   (b) Analytical approximations over the time span when \( L \gg K_m \).

   (c) Estimates for the Area Under the ligand-versus-time curve and Clearance when \( L_0 \gg K_m \).

2. Verifying the assumptions under which simplified models are valid is a challenge.

3. The Michaelis-Menten model cannot fit ligand-versus-time curves with more than 1 inflection point.
References


