Target-Mediated Drug Disposition models

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Sationary state

- P: complex
- L: ligand (free drug)
- R: substrate (receptor/target)

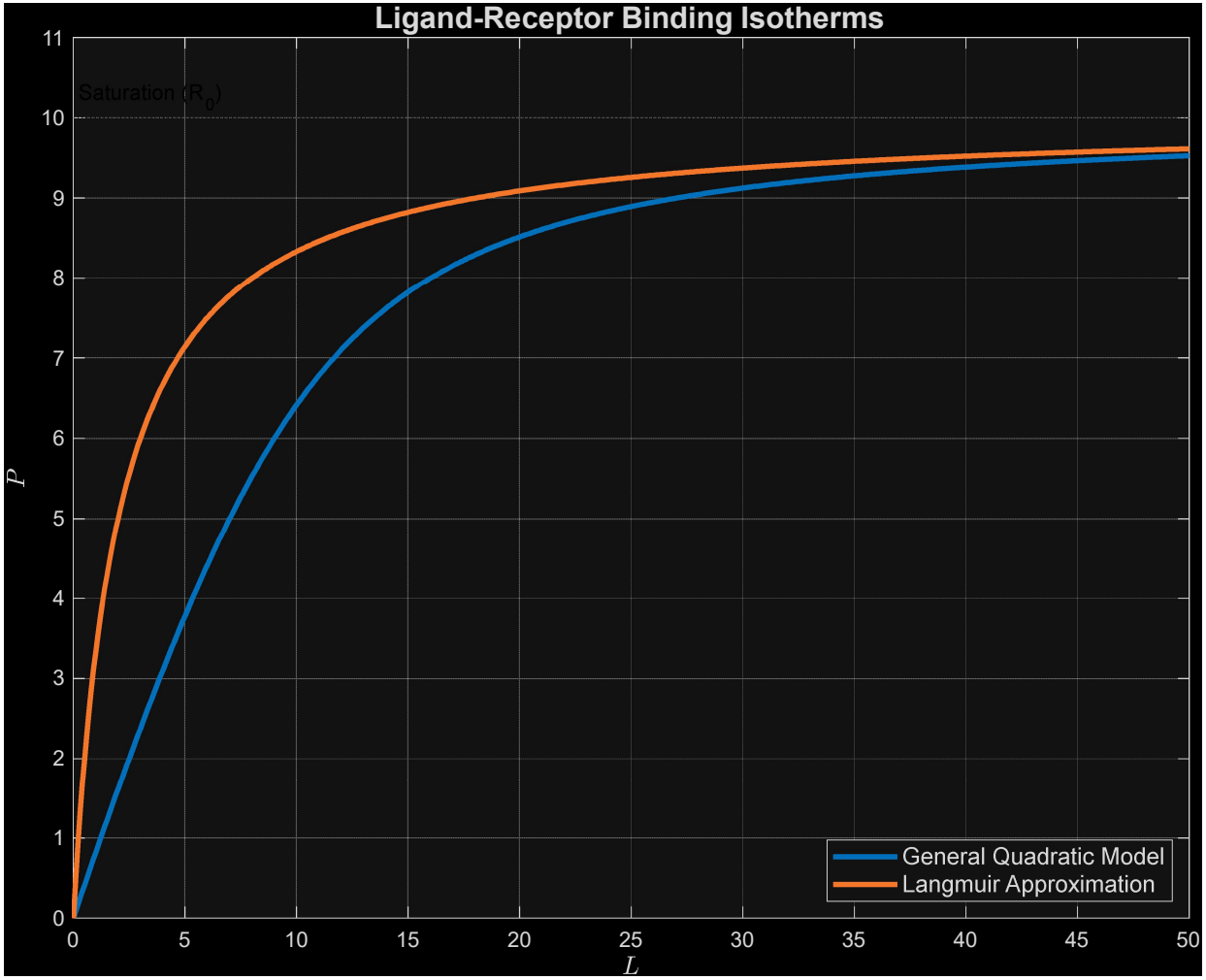
$$L + R \rightleftarrows P$$

Supposing $L >>> R$:

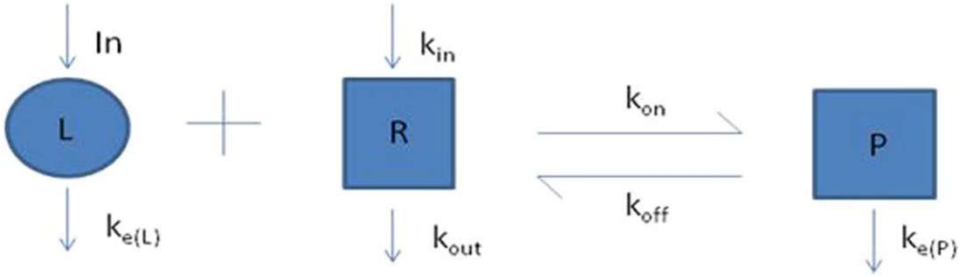
$$P = \frac{R_0 L}{K_D + L}$$

Otherwise, $L = L_0 - P$:

$$P = \frac{1}{2}\left[K_D + L_0 + R_0 - \sqrt{(K_D + L_0 + R_0)^2 - 4L_0R_0}\right]$$



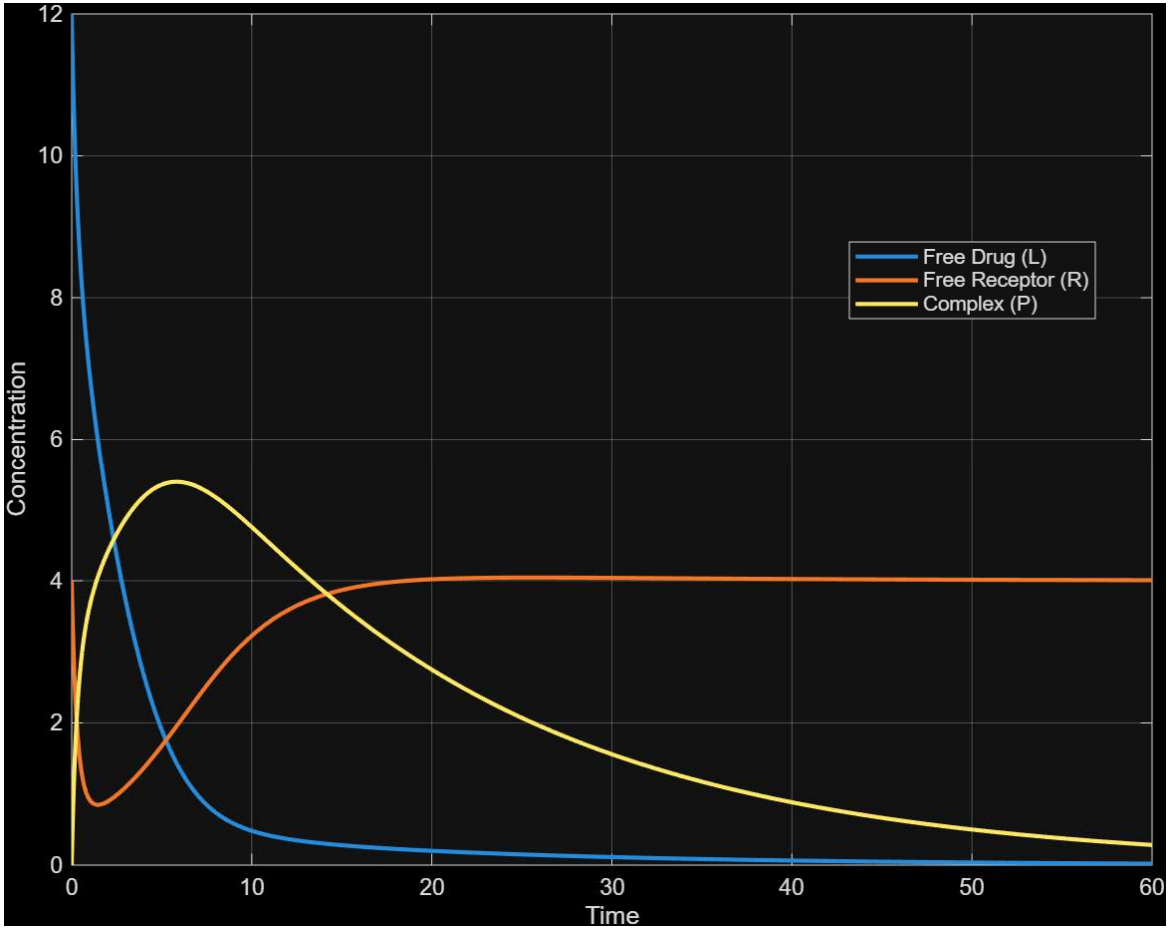
One-compartment model



$$\frac{dL}{dt} = -k_{e(L)}L - k_{on}LR + k_{off}P$$

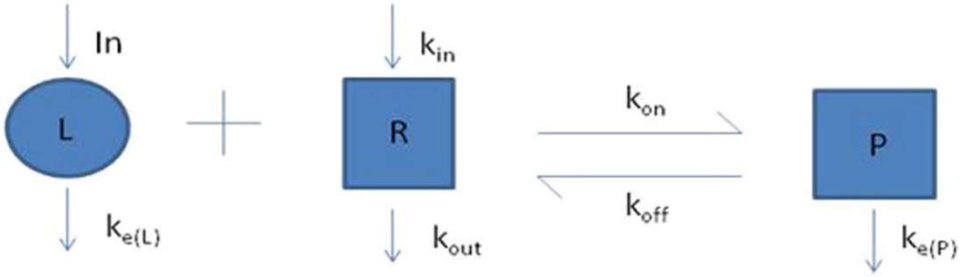
$$\frac{dR}{dt} = k_{in} - k_{out}R + k_{on}LR + k_{off}P$$

$$\frac{dP}{dt} = k_{on}LR - k_{off}P - k_{e(P)}P$$



$k_{e(L)} = 0.15 \quad k_{out} = 0.30 \quad k_{e(P)} = 0.05$

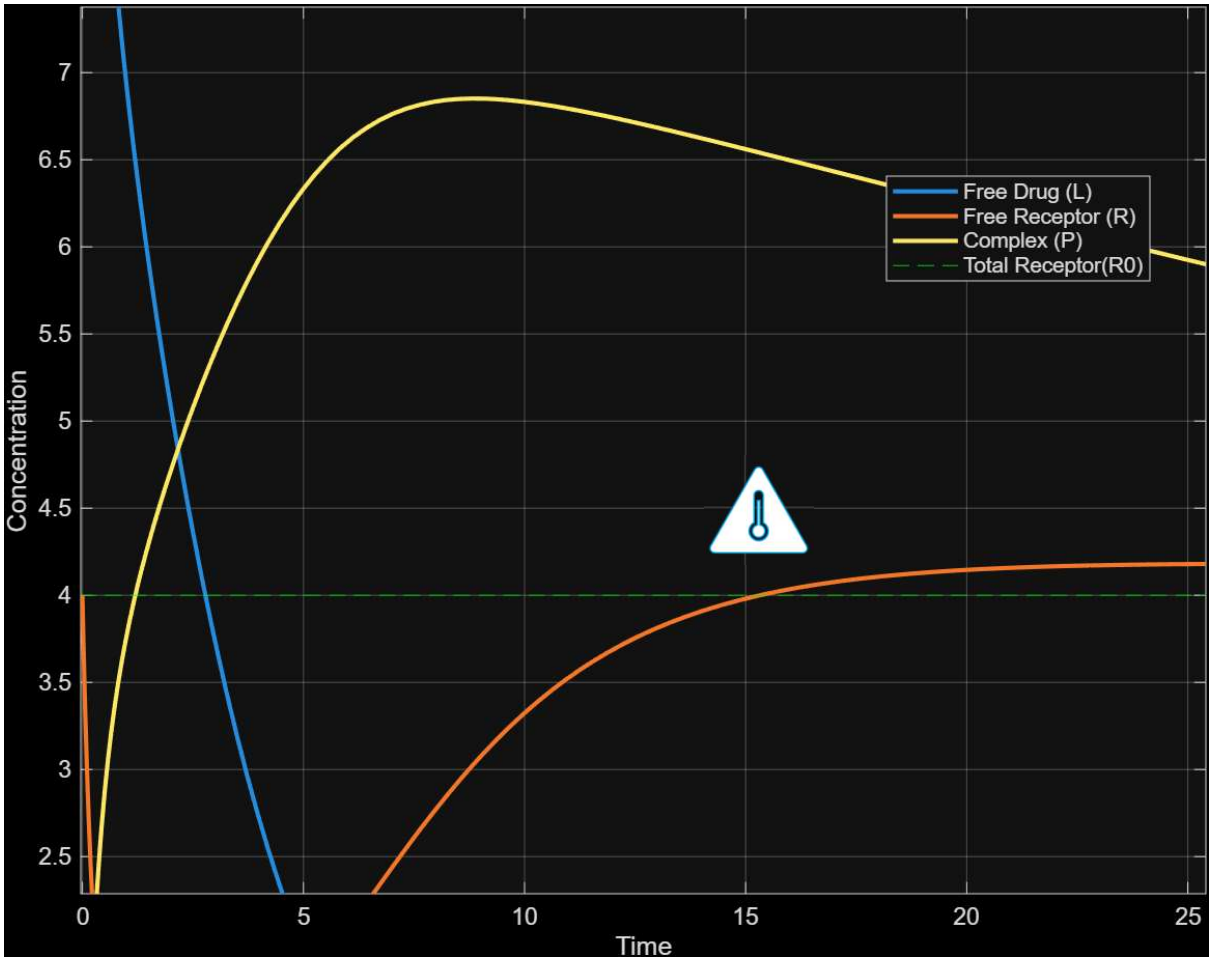
One-compartment model



Rebound effect:

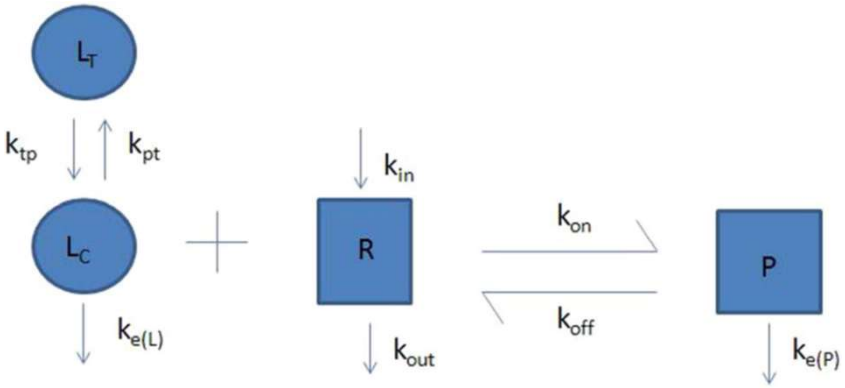
$k_{e(P)} < k_{e(L)} + k_{out}$

Gemtuzumab ozogamicin (LEUKEMIA)



$k_{e(L)} = 0.15 \quad k_{out} = 0.30 \quad k_{e(P)} = 0.001$

Two-compartment model

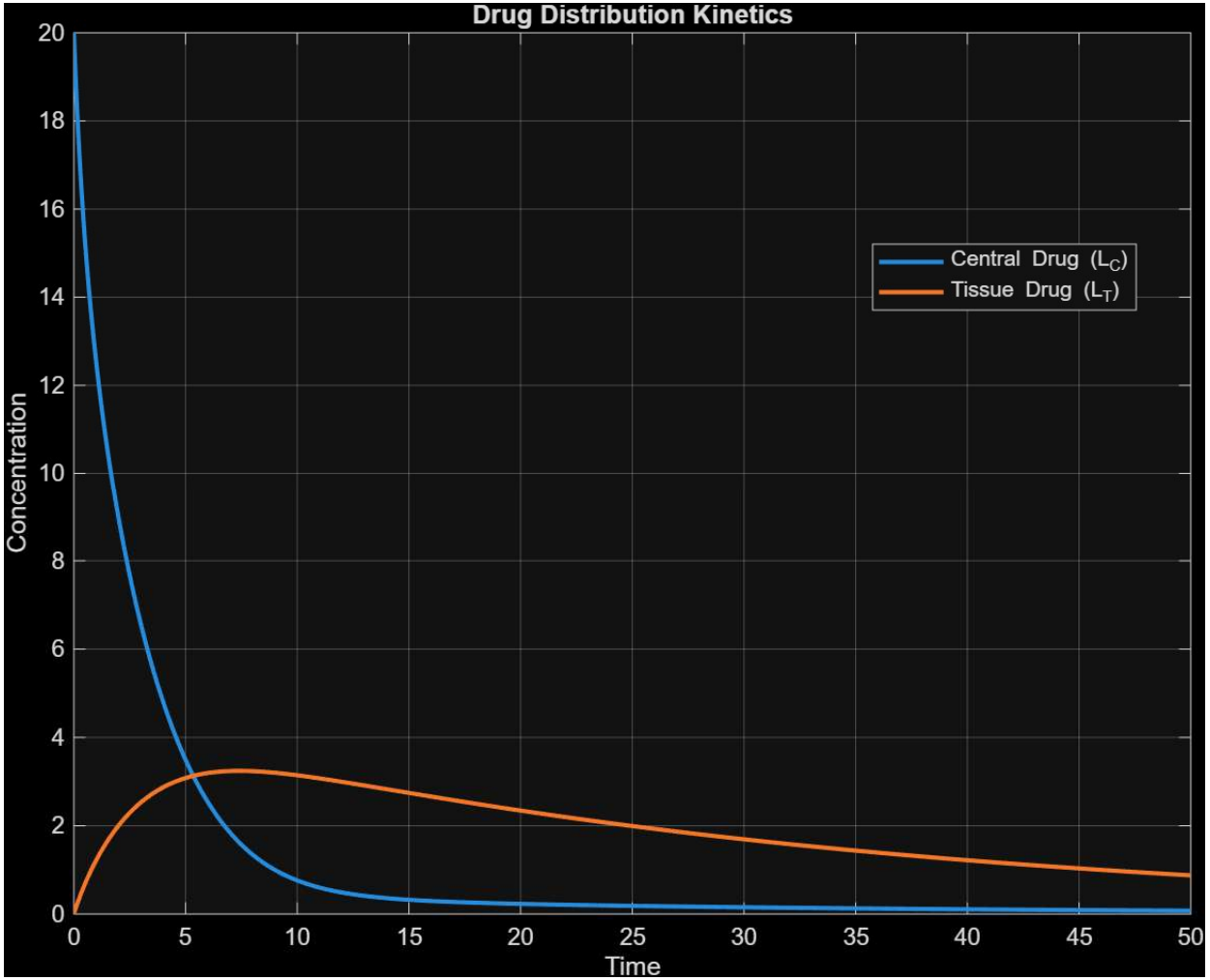


$$\frac{dL_T}{dt} = k_{pt}L_C - k_{tp}L_T$$

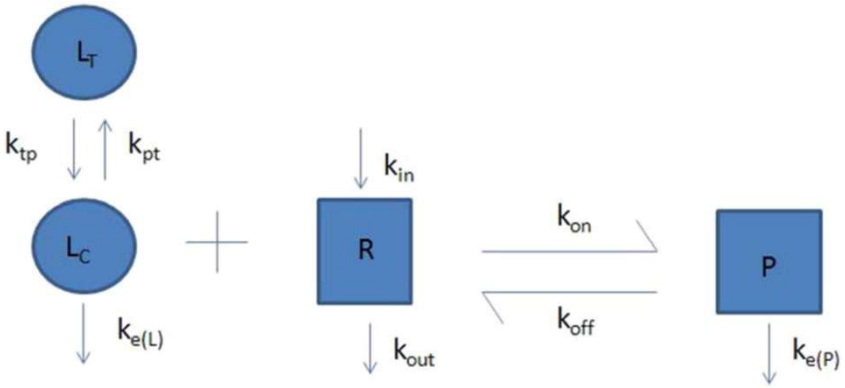
$$\frac{dL_C}{dt} = -k_{e(L)}L_C - k_{on}L_C R + k_{off}P - k_{pt}L_C + k_{tp}L_T$$

$$\frac{dR}{dt} = k_{in} - k_{out}R + k_{on}L_C R + k_{off}P$$

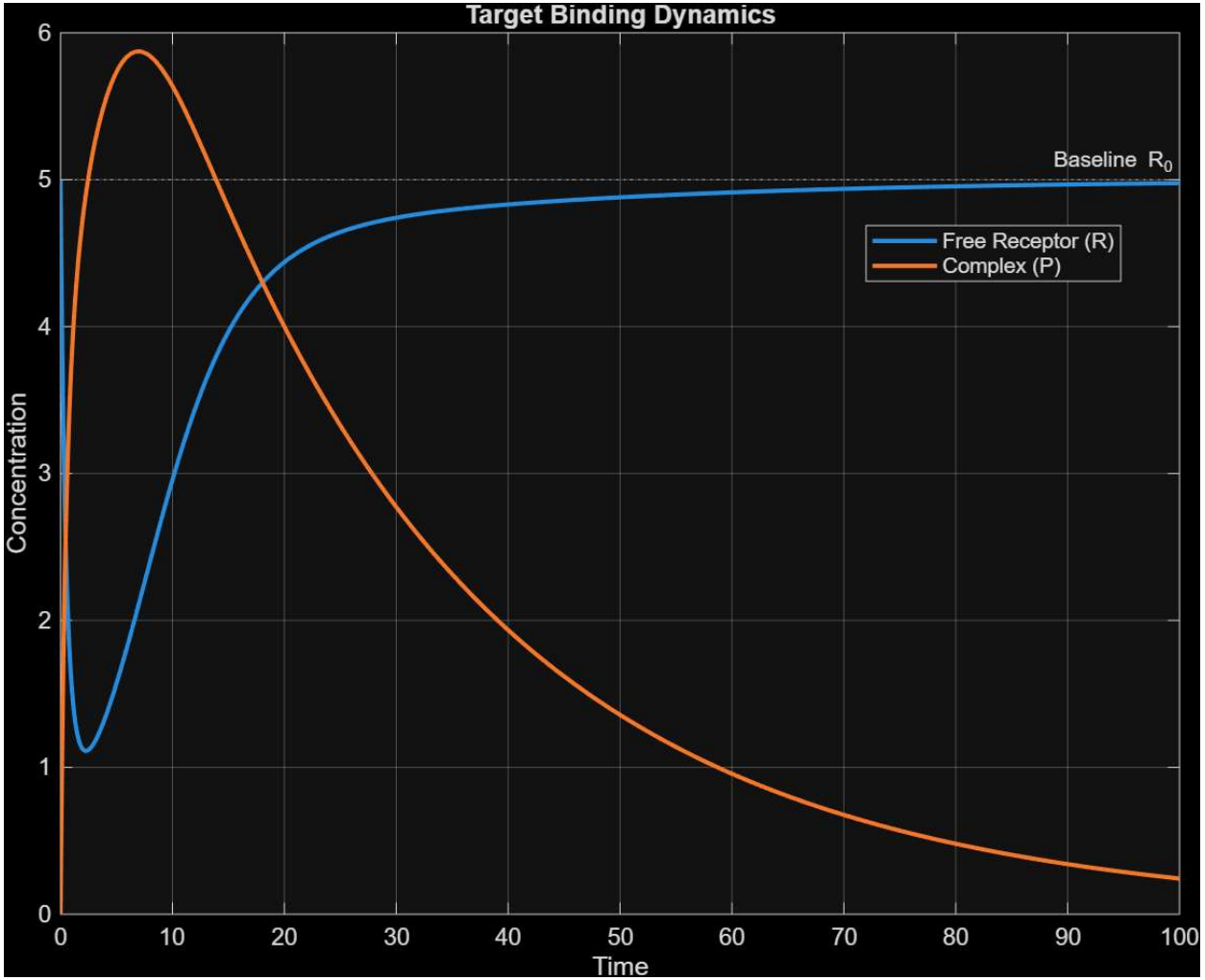
$$\frac{dP}{dt} = k_{on}L_C R - k_{off}P - k_{e(P)}P$$



Two-compartment model



Vildagliptin (DIABETES)



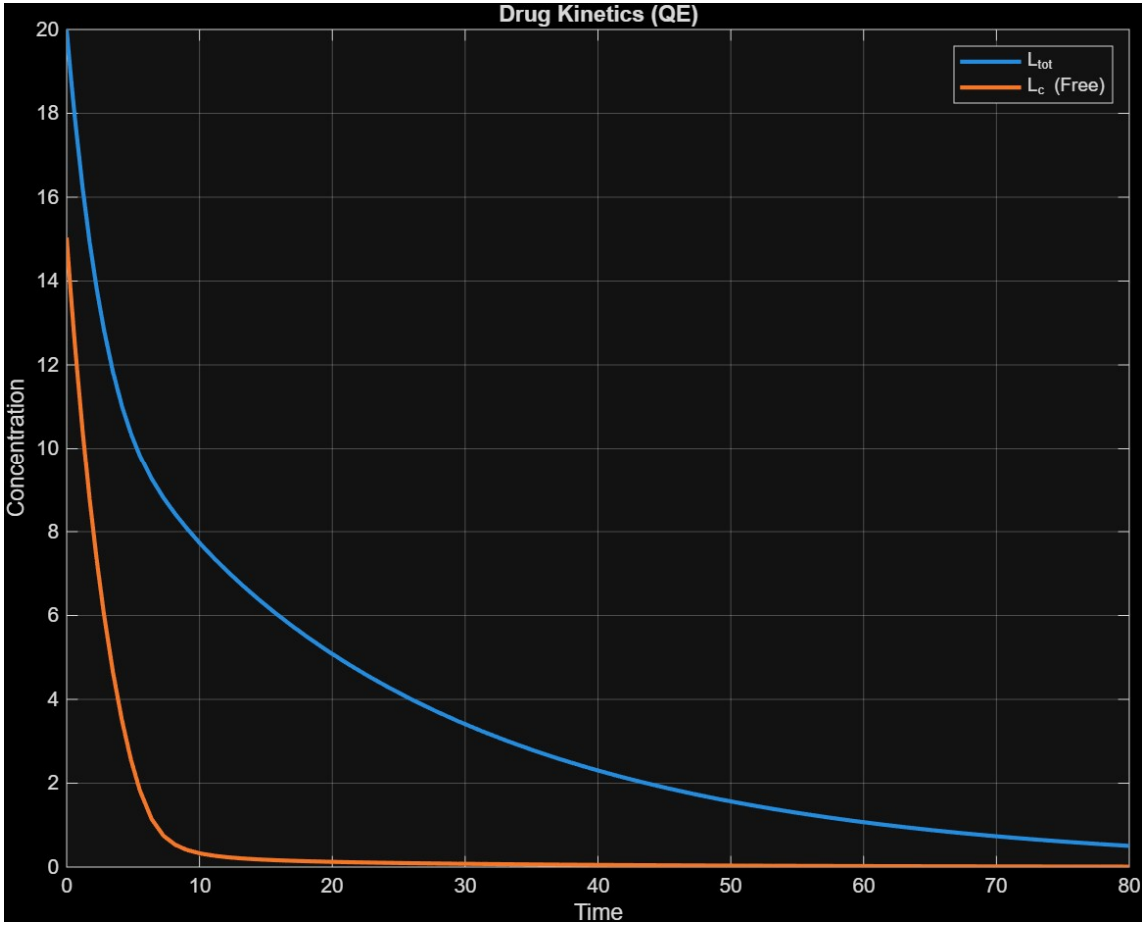
Quasi-Equilibrium approximation

$$\frac{dL_T}{dt} = k_{pt}L_C - k_{pt}L_T$$

$$\frac{dL_{tot}}{dt} = -\left(k_{e(L)} + k_{pt}\right)L_C - \frac{R_{tot}k_{e(P)}L_C}{K_D + L_C} + k_{pt}L_T$$

$$\frac{dR_{tot}}{dt} = k_{in} - k_{out}R_{tot} - \left(k_{e(P)} - k_{out}\right)\frac{R_{tot}L_C}{K_D + L_C}$$

$$L_C = \frac{1}{2}\left[L_{tot} - R_{tot} - K_D + \sqrt{(L_{tot} - R_{tot} - K_D)^2 + 4K_D tot}\right]$$



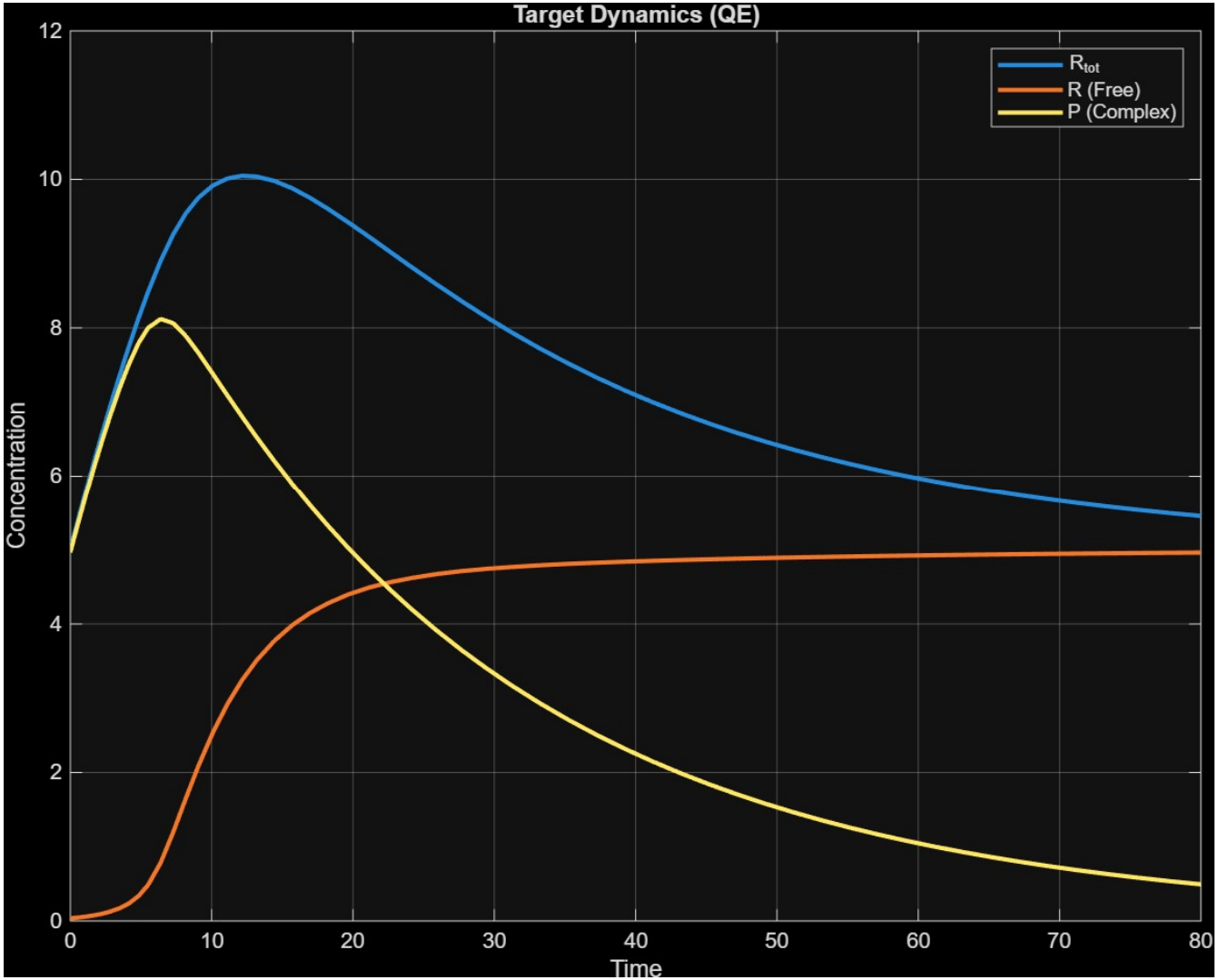
Quasi-Equilibrium approximation

Assumes that the binding is much faster than the elimination, therefore it is considered to be in equilibrium:

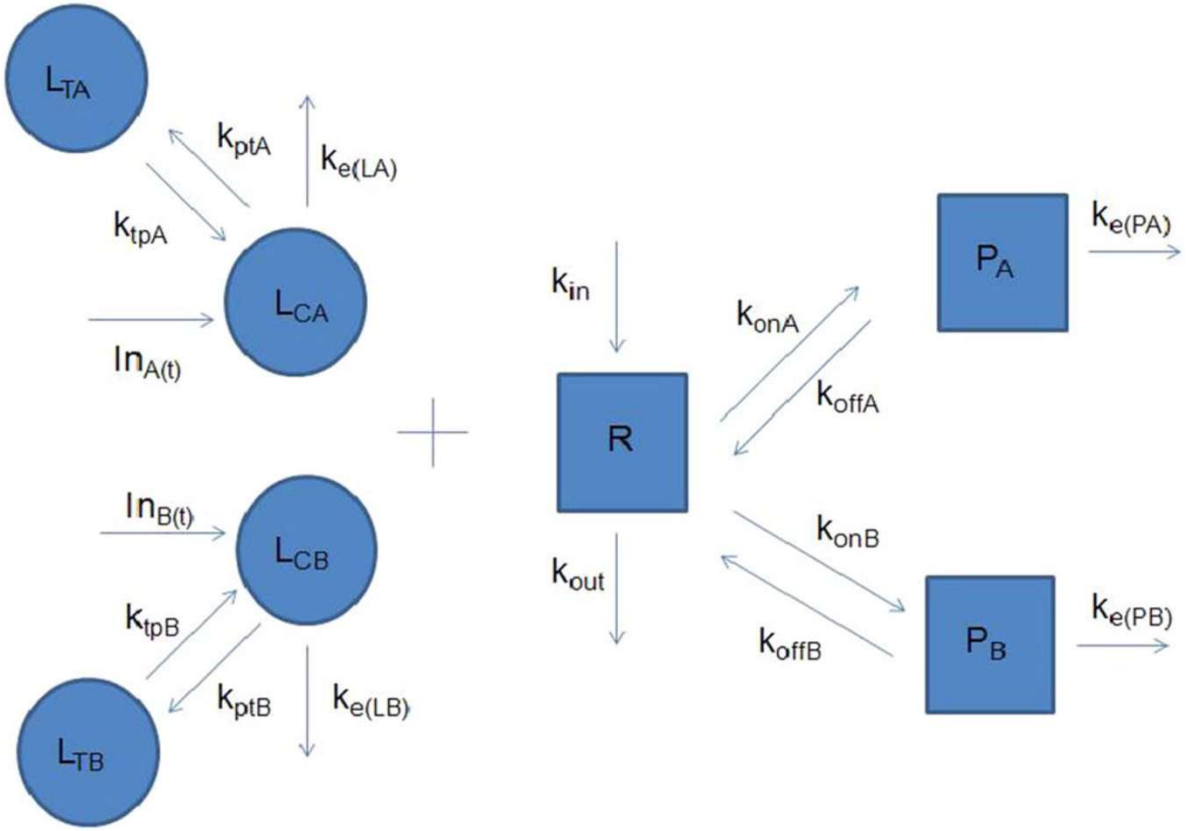
$$K_D = \frac{k_{off}}{k_{on}}$$

Predicts accurately **terminal half-life** and **clearance** at high doses of the drug.

Romiplostim (COAGULANT AGENT)

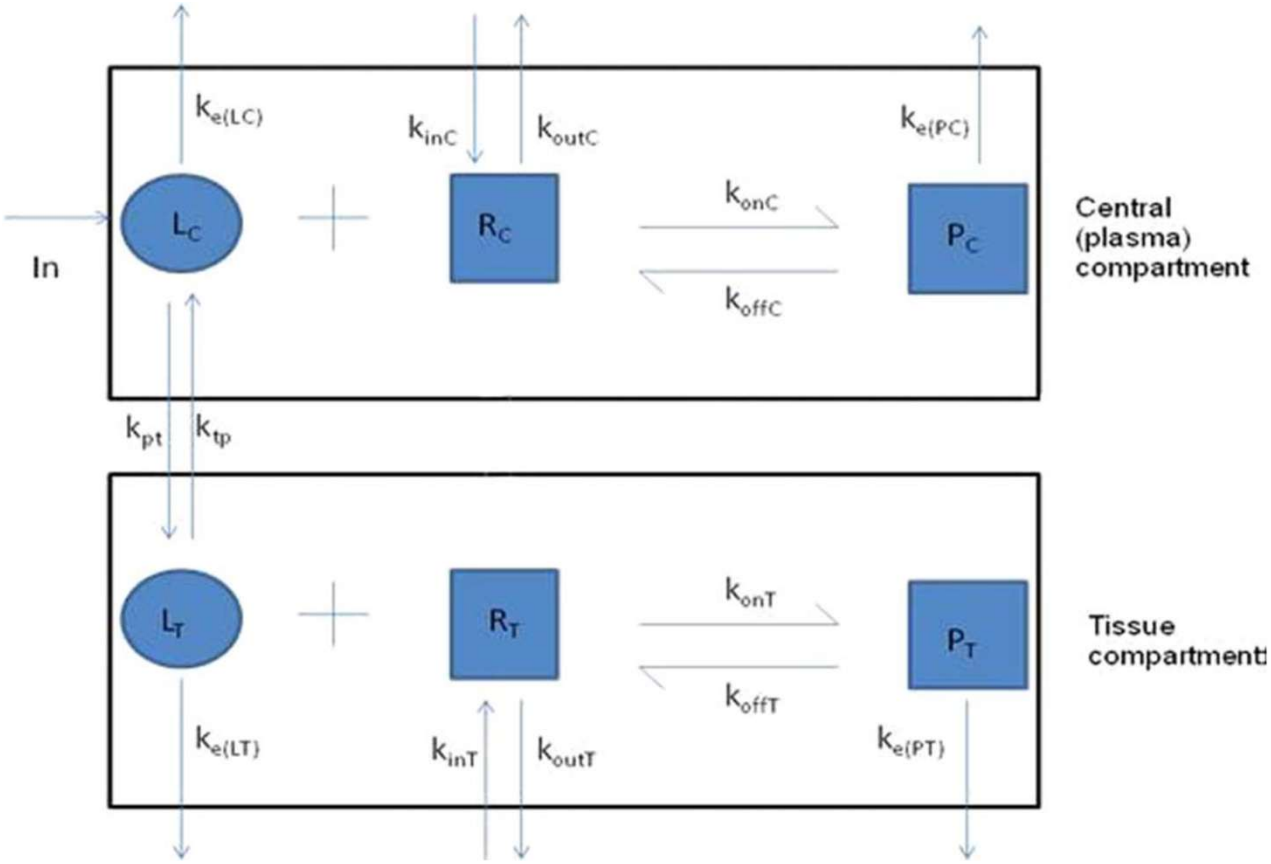


Extensions to two-compartment models



Two drugs competing for the same receptor site.

Extensions to two-compartment models



Drug-receptor binding occurs in both compartments.