Influence de la masse antigétique sur la PK des anticorps thérapeutiques – modèles TMDD

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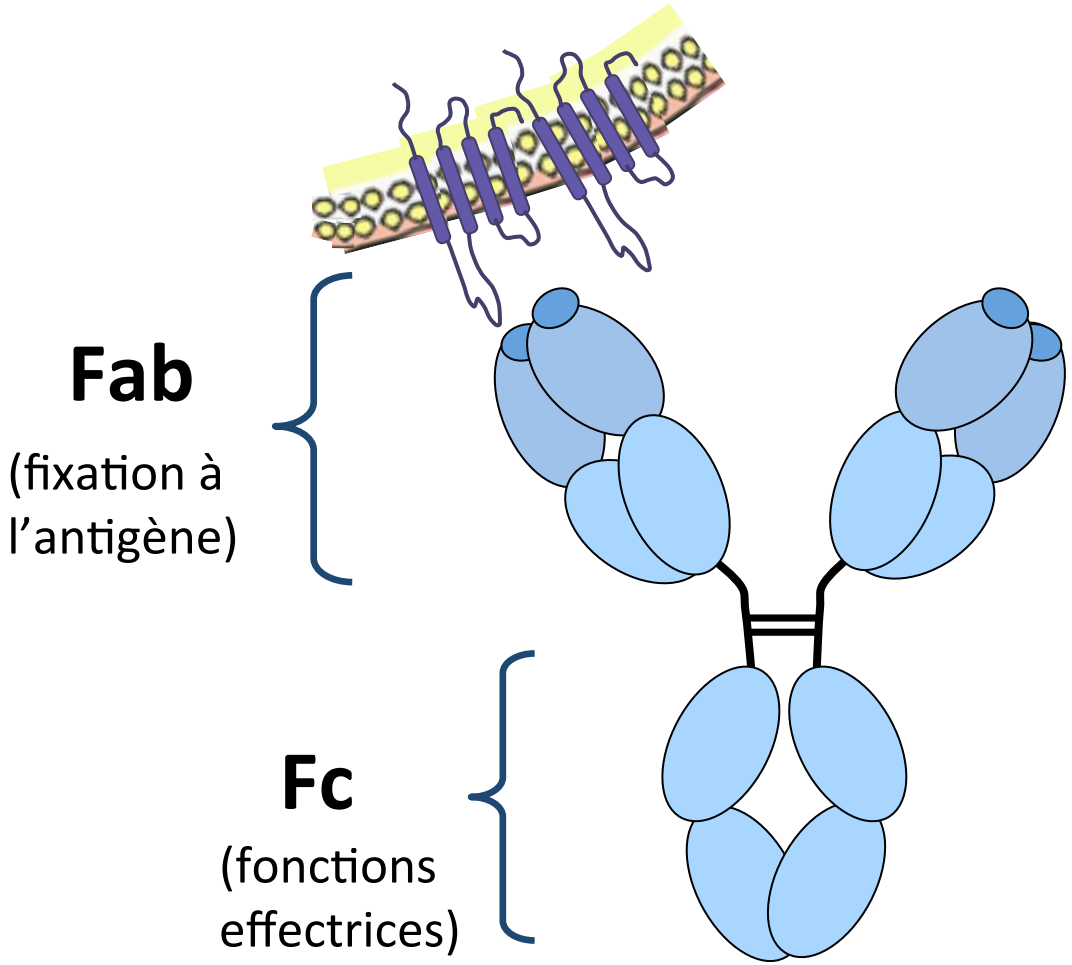
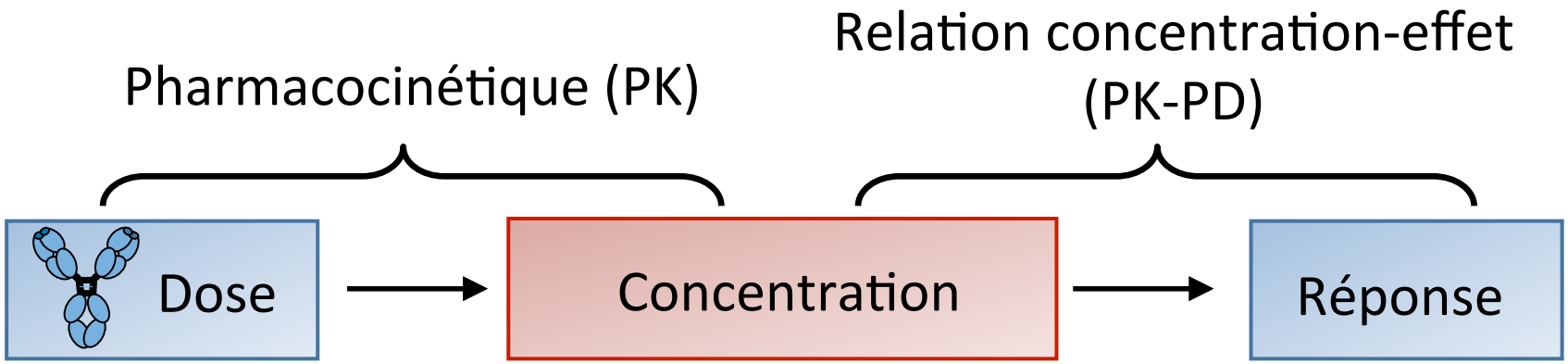
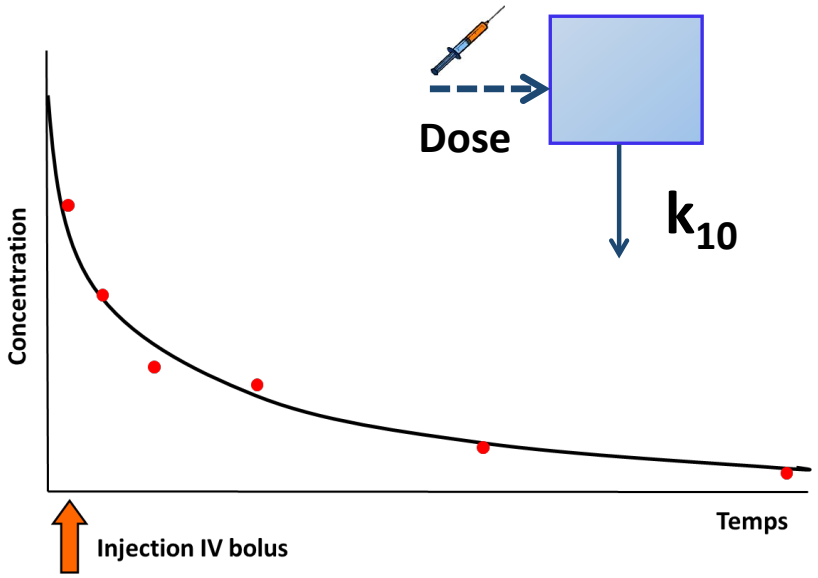
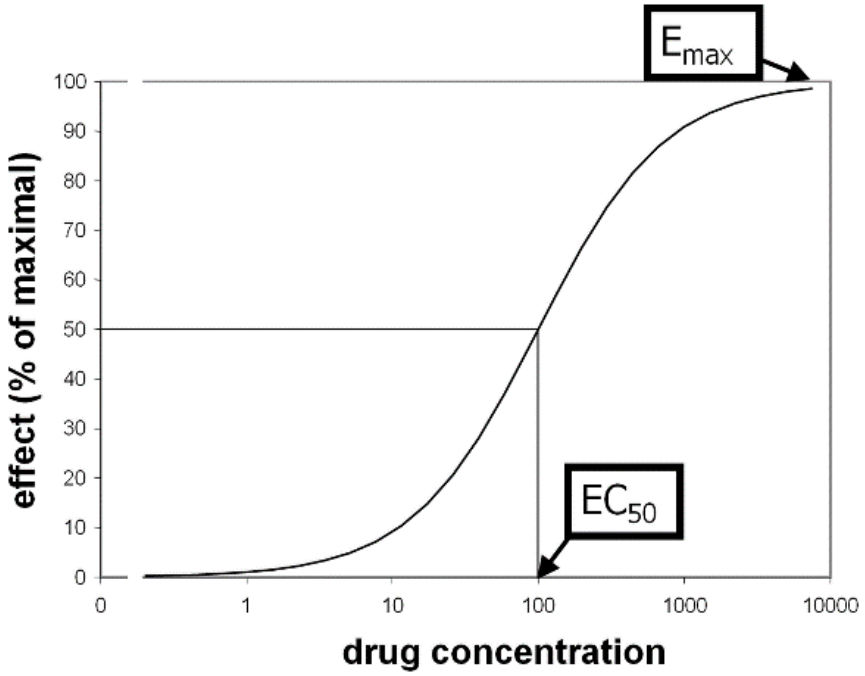
Les anticorps thérapeutiques (mAbs)



Relation dose-concentration-effet







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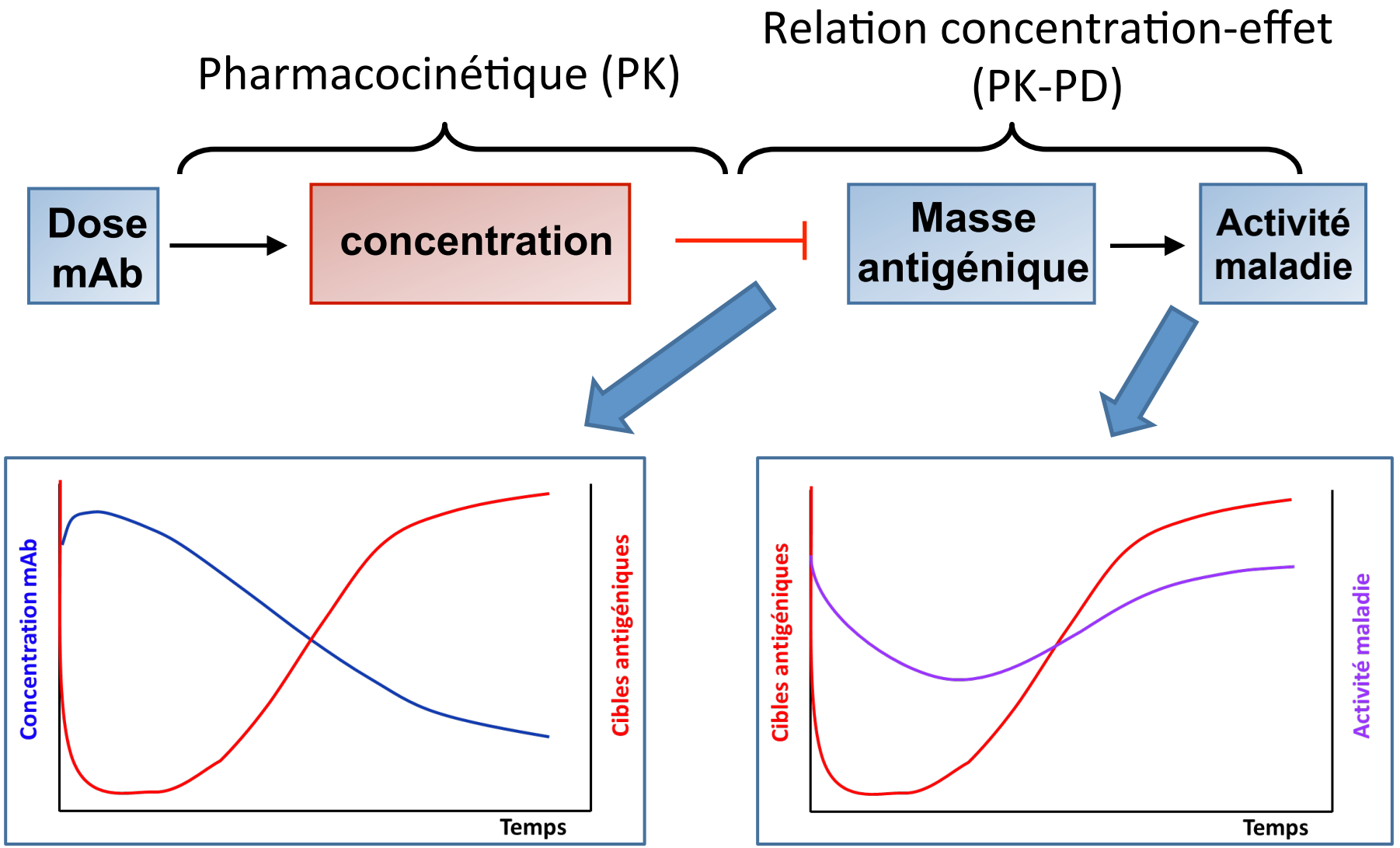
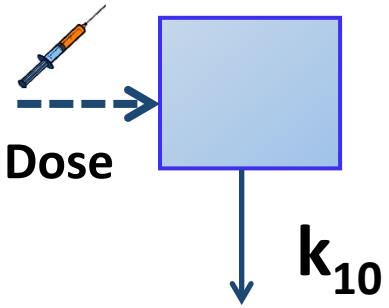
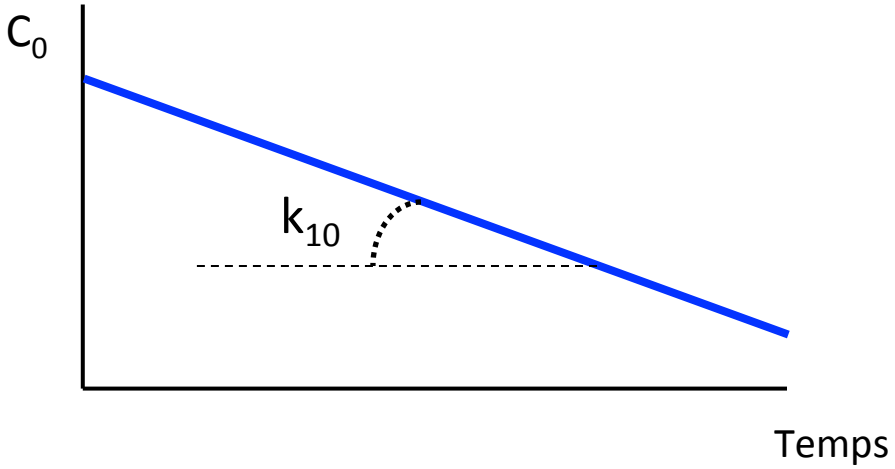


Modèle pharmacocinétique 1 compartiment



$$dC/dt = - k_{10} . C$$

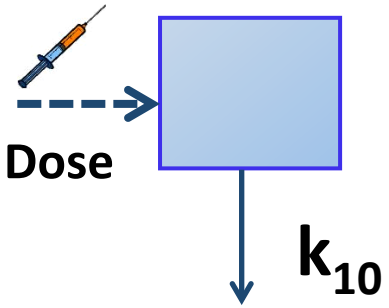
$$C(t) = C_0 \exp (-k_{10} . t)$$



Dose (IV bolus)
k_e : constante d'élimination

Pharmacocinétique des mAbs

PK infliximab (anti-TNF), maladie de Crohn (n=111)



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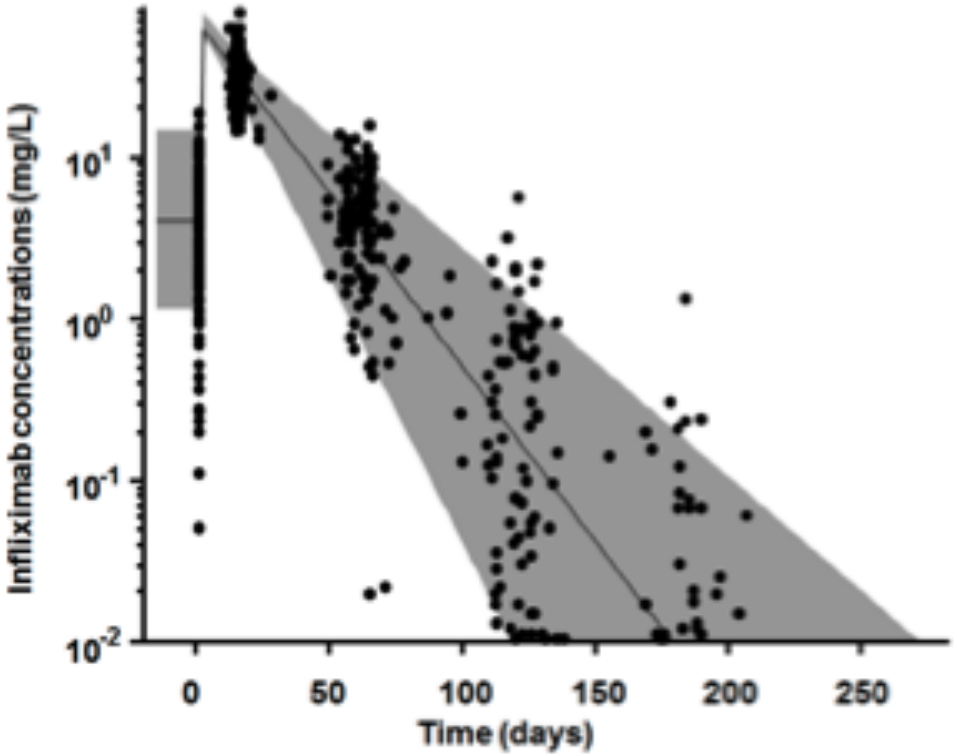
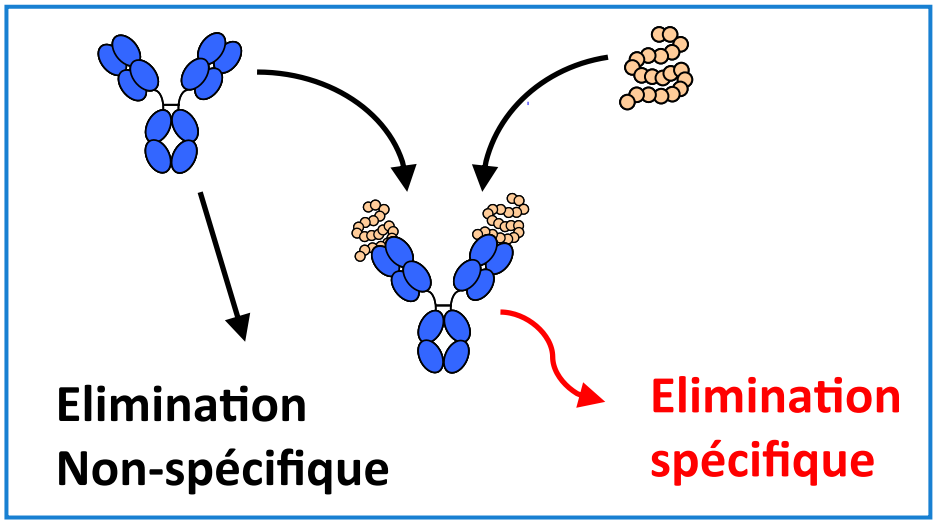


Ternant, CPK, 2016

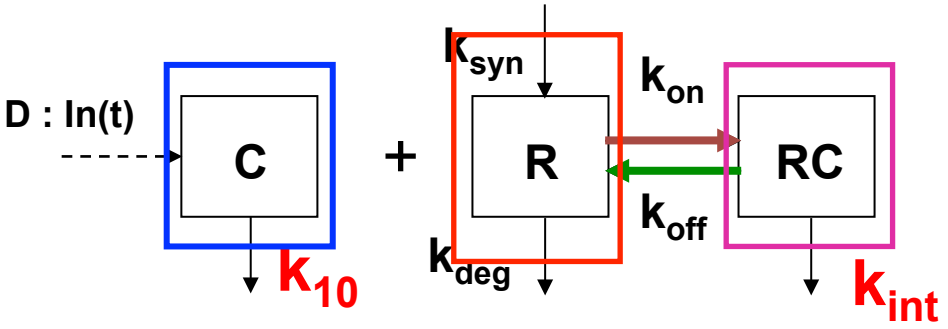
Variabilité PK – masse antigénique



Elimination non-linéaire et masse antigénique

Modèle TMDD

Mager & Jusko, J Pharmacokinet Pharmacodyn, 2001



(1) $dC/dt = In(t) - k_{10}.C - k_{on}.R.C + k_{off}.RC$ — $C(0) = 0, D/V$

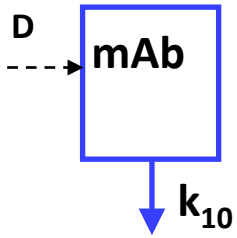
(2) $dR/dt = k_{syn} - k_{deg}.R - k_{on}.R.C + k_{off}.RC$ — $R(0) = R_{SS}$

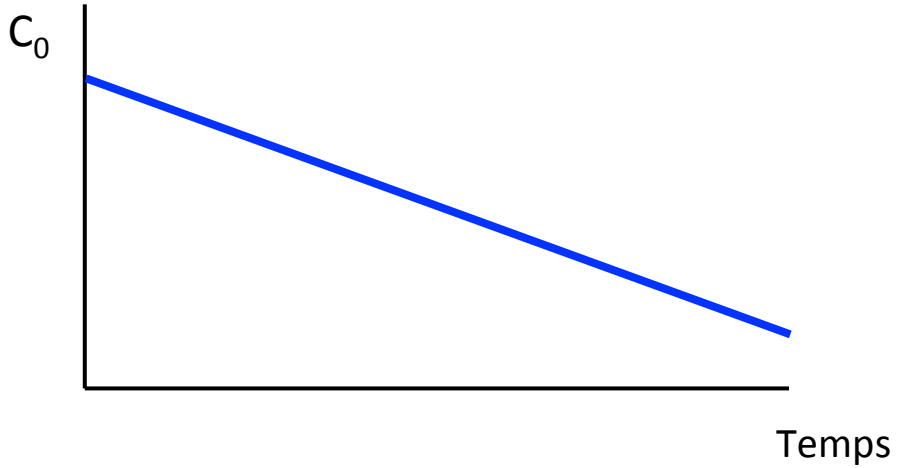
(3) $dRC/dt = k_{on}.R.C - k_{off}.RC + k_{int}.RC$ — $RC(0) = 0$

- C : concentration (molaire) cpt central
- A_P : quantité (molaire) cpt périphérique
- R : quantité cible, dont récepteur (molaire)
- RC : concentration complexe (molaire)

Elimination non-linéaire et masse antigénique

- Elimination médiée par la cible
  - Pas de cible antigénique ⇨ $CL_{cible} = 0$
  - ⇨ $Elim_{totale}$ = Elim endogène

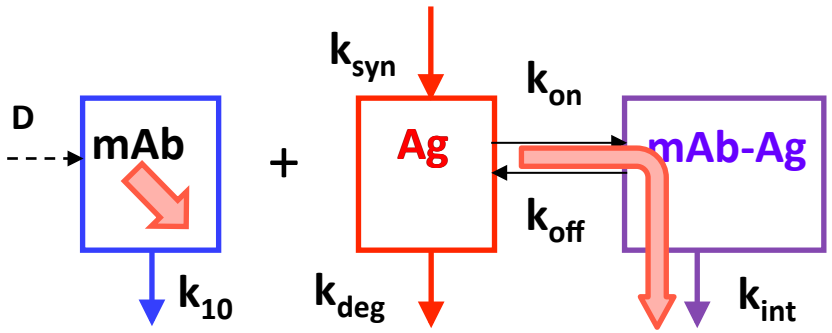


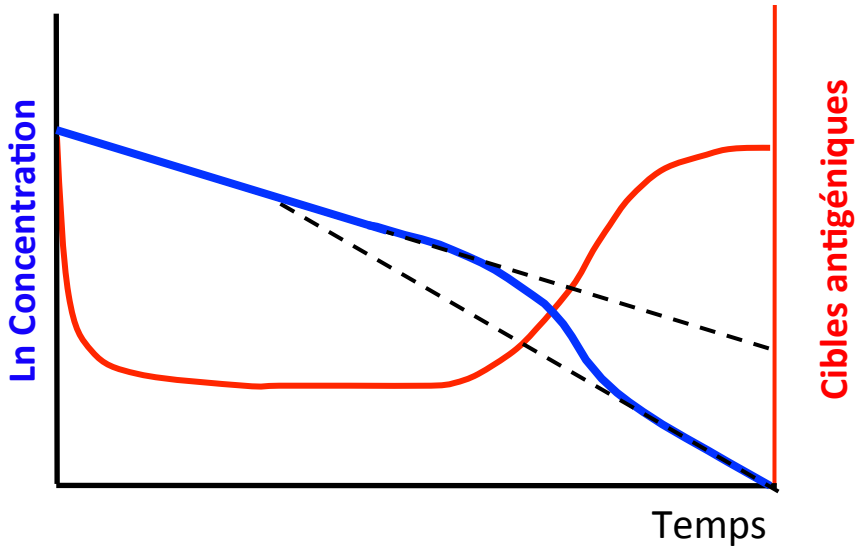


mAb libre
Cible libre
Complexe mAb-cible

Elimination non-linéaire et masse antigénique

- Elimination médiée par la cible
  - Quantité cibles ↗ ⇨ ↗ $ELim_{cible}$ ↗
  - ⇨ $Elim_{totale}$ ↗

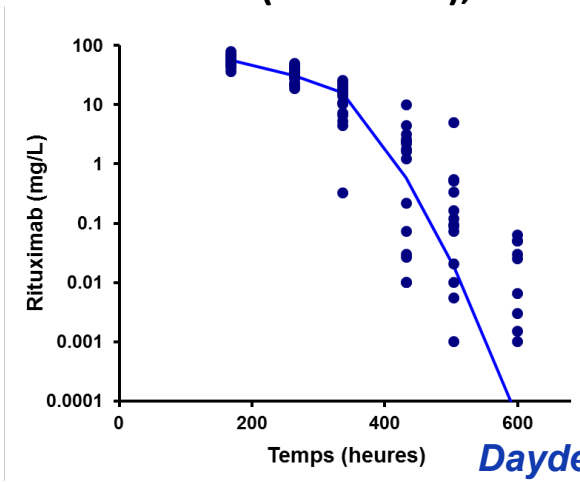




mAb libre
Cible libre
Complexe mAb-cible

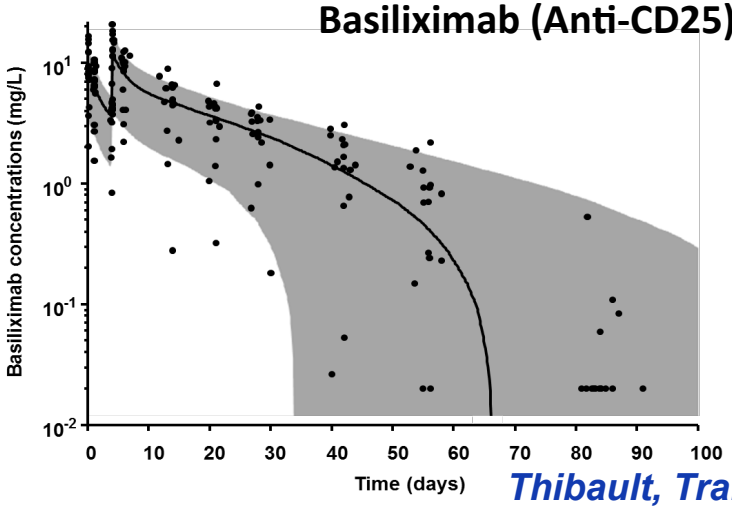
Elimination non-linéaire et masse antigénique

Rituximab (anti-CD20), souris CD20+



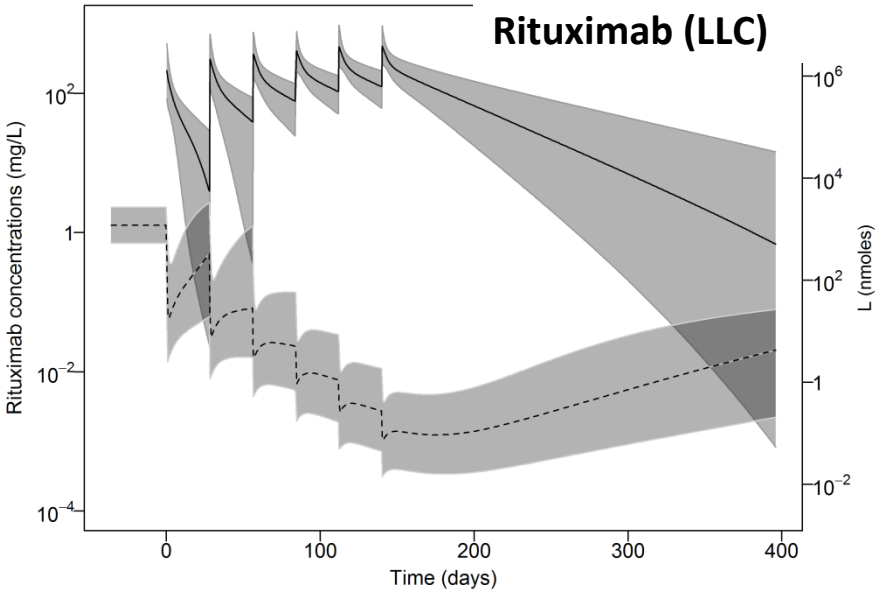
Daydé, Blood, 2016

Basiliximab (Anti-CD25)



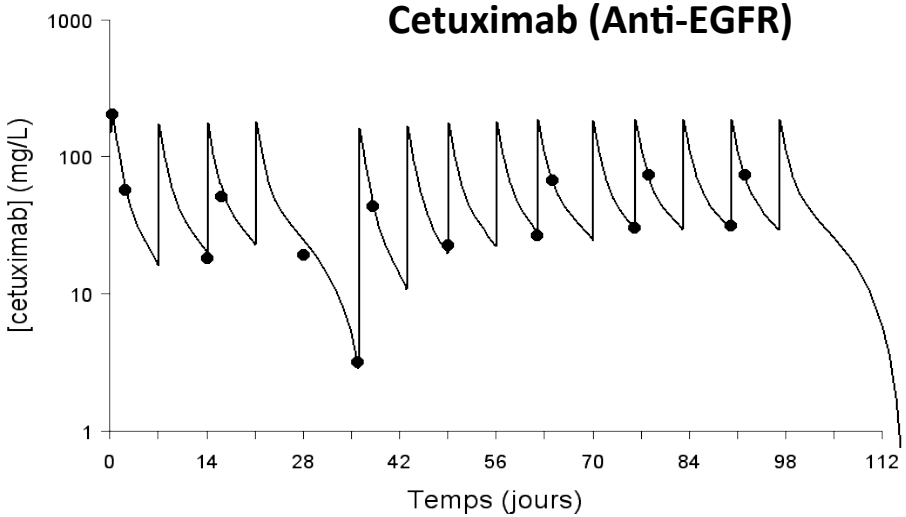
Thibault, Transpl Int, 2016

Rituximab (LLC)



Tout, CPK, 2016

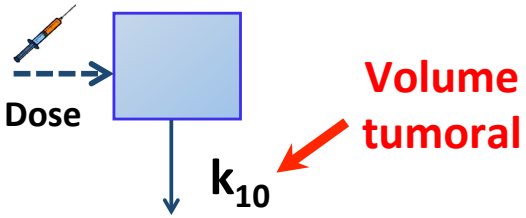
Cetuximab (Anti-EGFR)

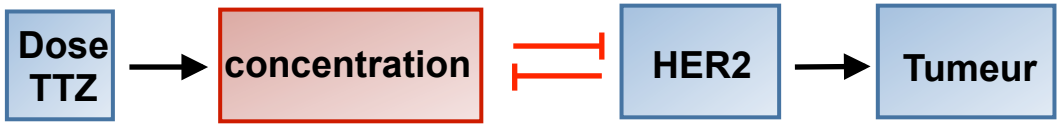


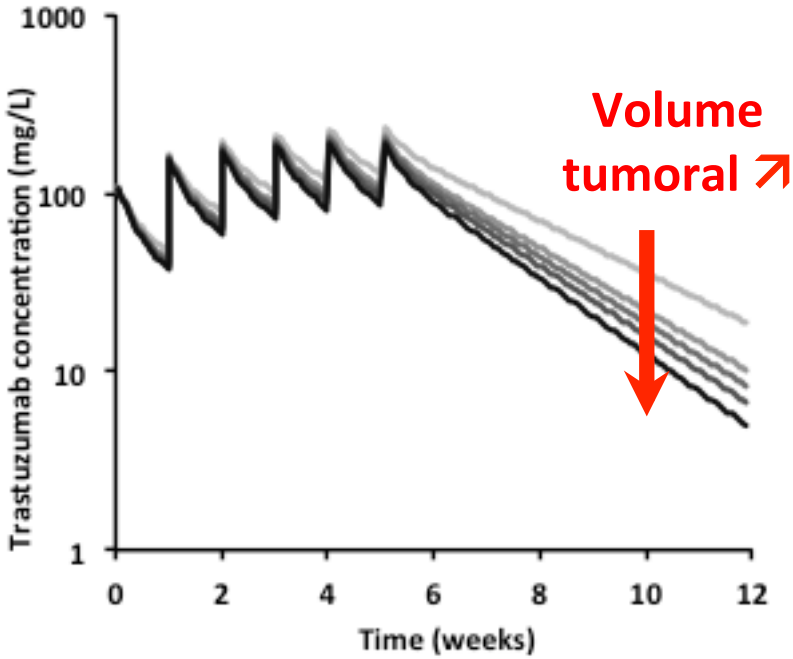
Azzopardi, CCR, 2012

Variabilité PK – masse antigénique

Trastuzumab (Anti-HER2), cancer du sein





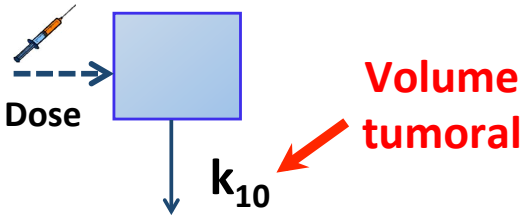


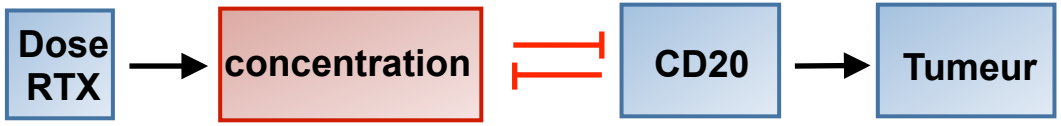
Taille tumeur ↗
⇨ **↗ Cible**
⇨ **↗ Elim médiée par la cible**
⇨ **↗ Elim totale**

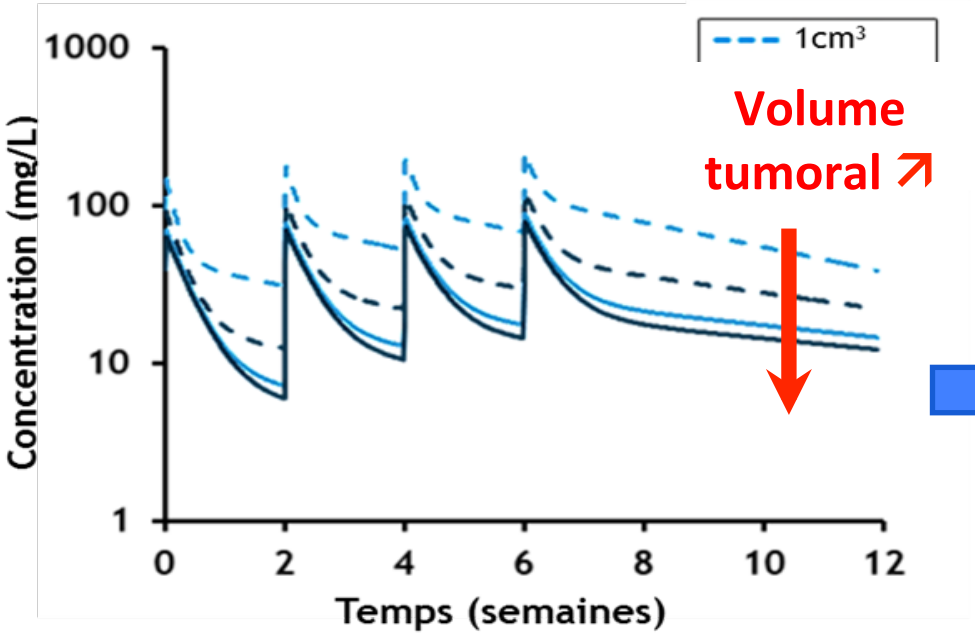
Bernadou, BJCP, 2016

Variabilité PK – masse antigénique

Rituximab (Anti-CD20), lymphomes



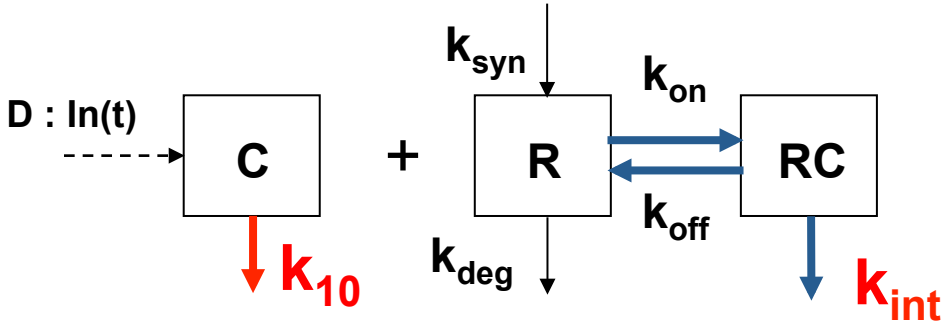


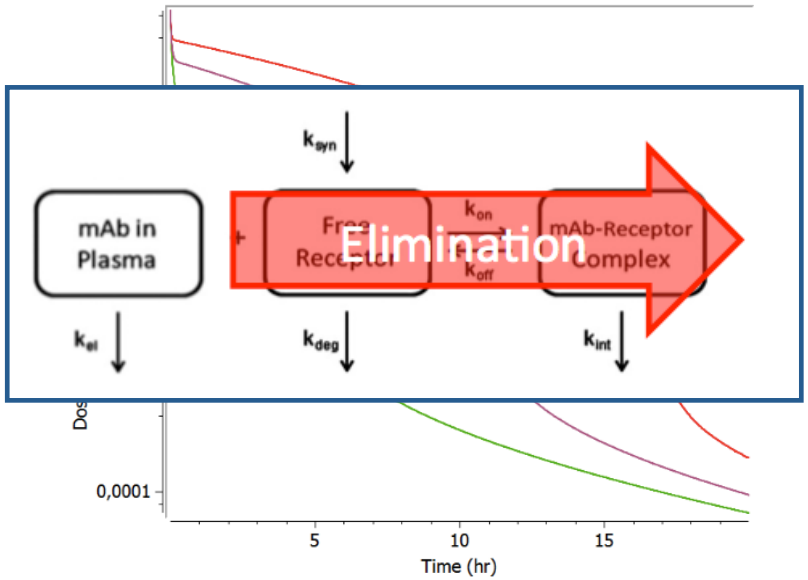


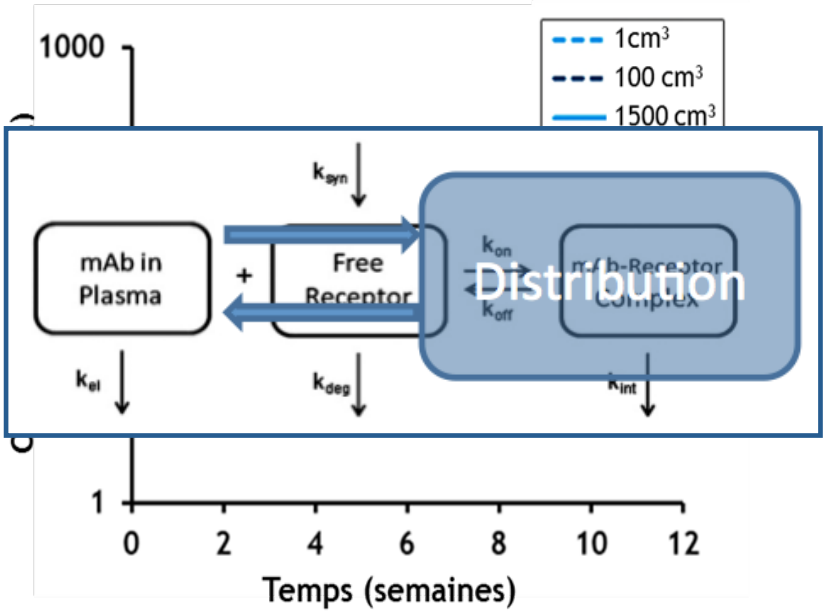
Taille tumeur ↗
⇨ **↗ Cible**
⇨ **↗ Rétention par cible**
⇨ **↗ effet « éponge »**

Tout, Blood, 2017

Elimination non-linéaire et masse antigénique



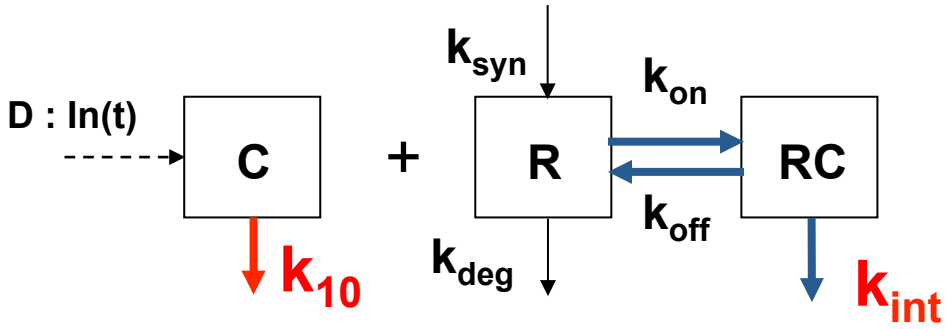




Daydé, Blood, 2016

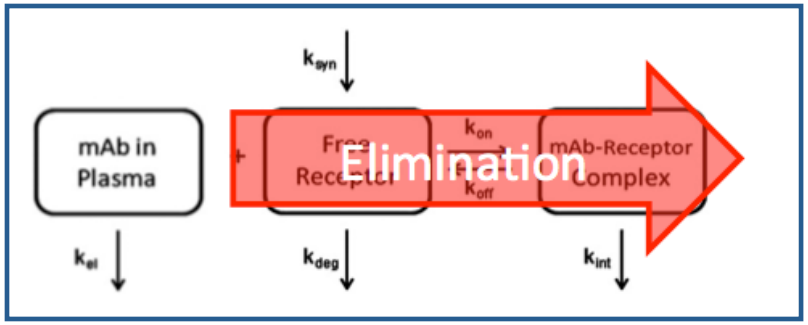
Objectifs

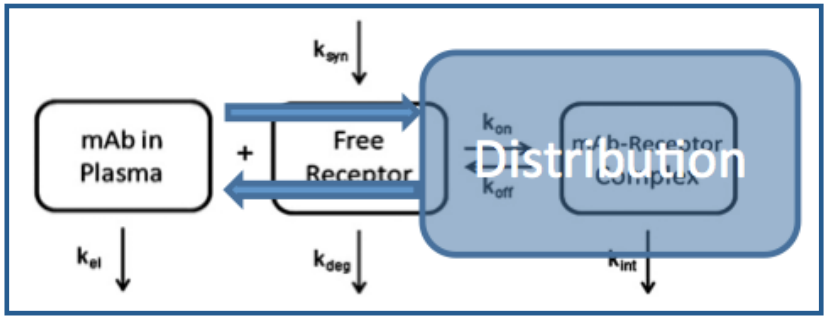
- Questions
  - L'effet « éponge » peut-il être décrit à l'aide de TMDD ?
  - Quelles sont les conditions permettant l'émergence de «sink» ou «sponge» ?
- Collaboration avec UMR CNRS 7350 «LMPT», Tours (V. Perrolaz, S. Madec)
  - Analyse de stabilité : étudier l'association entre masse antigénique (R) et élimination (k_{10}) du système TMDD 3x3

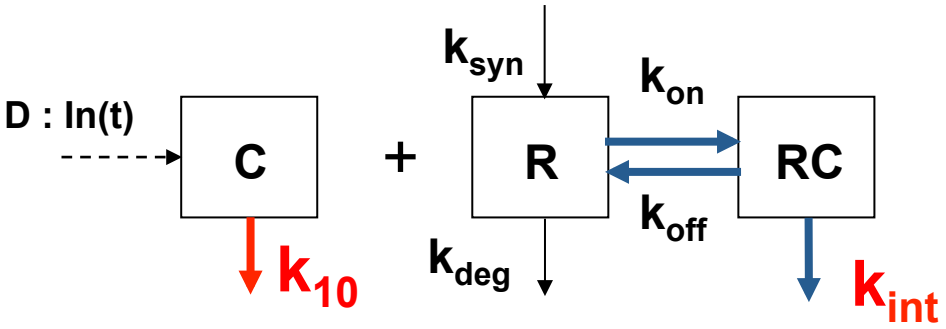


Théorème

- Rapport k_{10}/k_{int} est à l'origine de l'effet «sink» ou «sponge»
  - $k_{10}/k_{int} < 1 \Rightarrow k_{10} < k_{int} \Rightarrow$ «sink»
  - $k_{10}/k_{int} > 1 \Rightarrow k_{10} > k_{int} \Rightarrow$ «sponge»

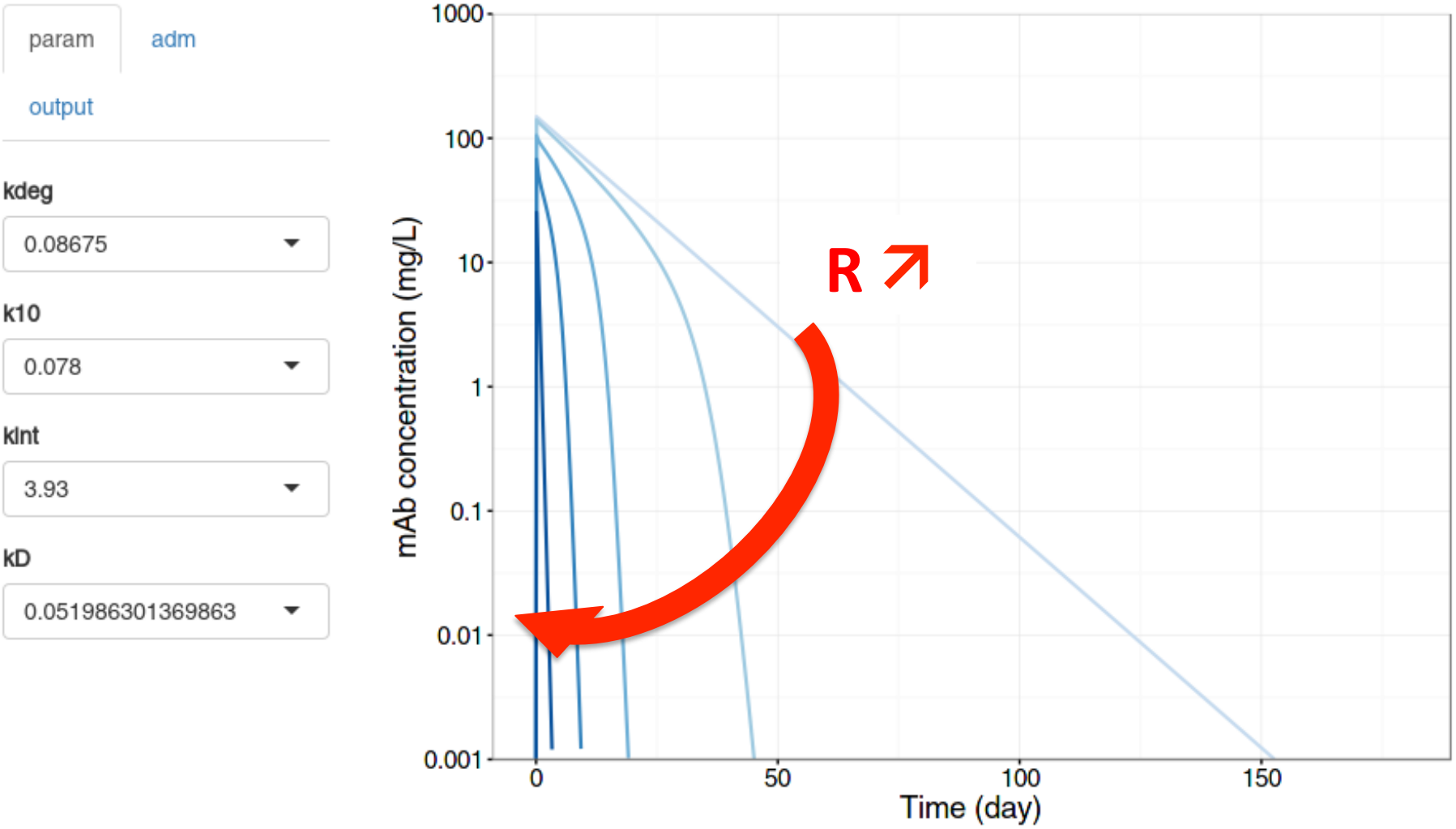






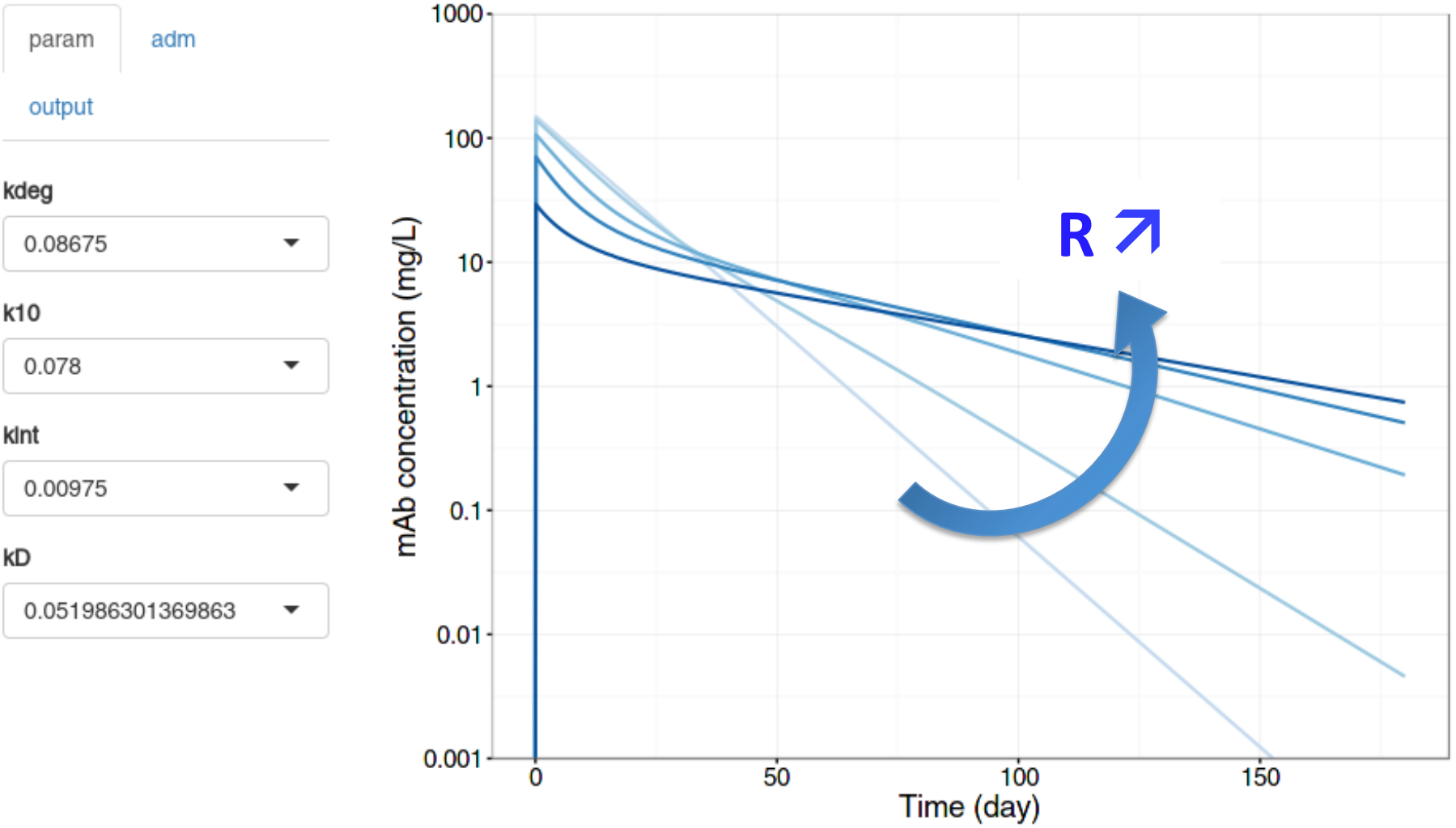
Simulations

- $k_{10}/k_{int} < 1 \Rightarrow k_{10} < k_{int} \Rightarrow$ «sink» : R ↗ ⇨ vitesse elim ↗



Simulations

- $k_{10}/k_{int} > 1 \Rightarrow k_{10} > k_{int} \Rightarrow$ «sponge» : R ↗ ⇨ vitesse elim ↘



Simulations

- $k_{10}/k_{int} = 1 \Rightarrow k_{10} = k_{int} \Rightarrow$ pas d'effet R sur vitesse elim