PROxAb Shuttle in-vivo

2024-06-03 Created
2024-06-14 Add 2 Metabolites

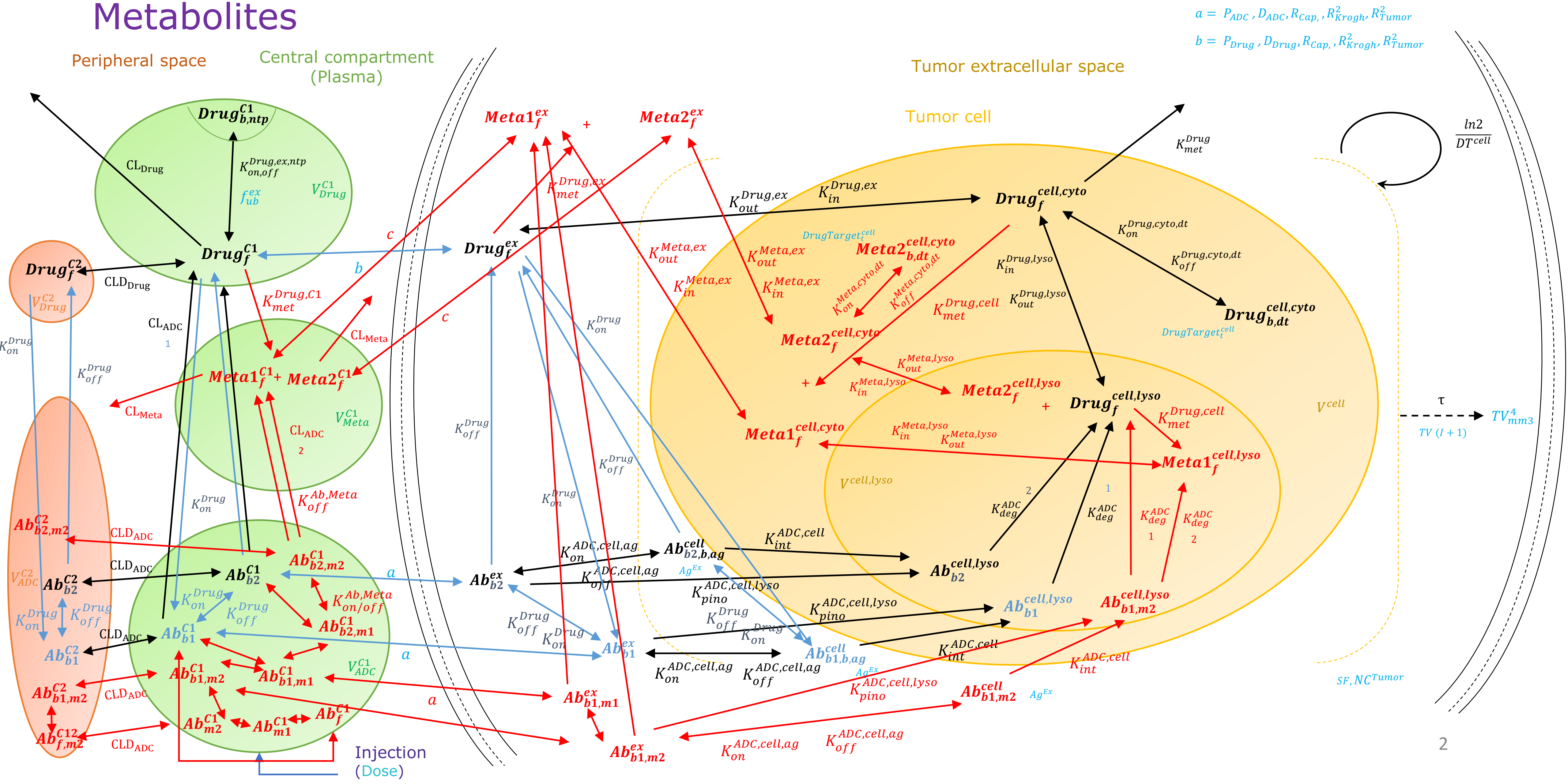
!! Be aware app parameters labeled with Ab correspond to those in this presentation labeled with ADC !!

E.g.

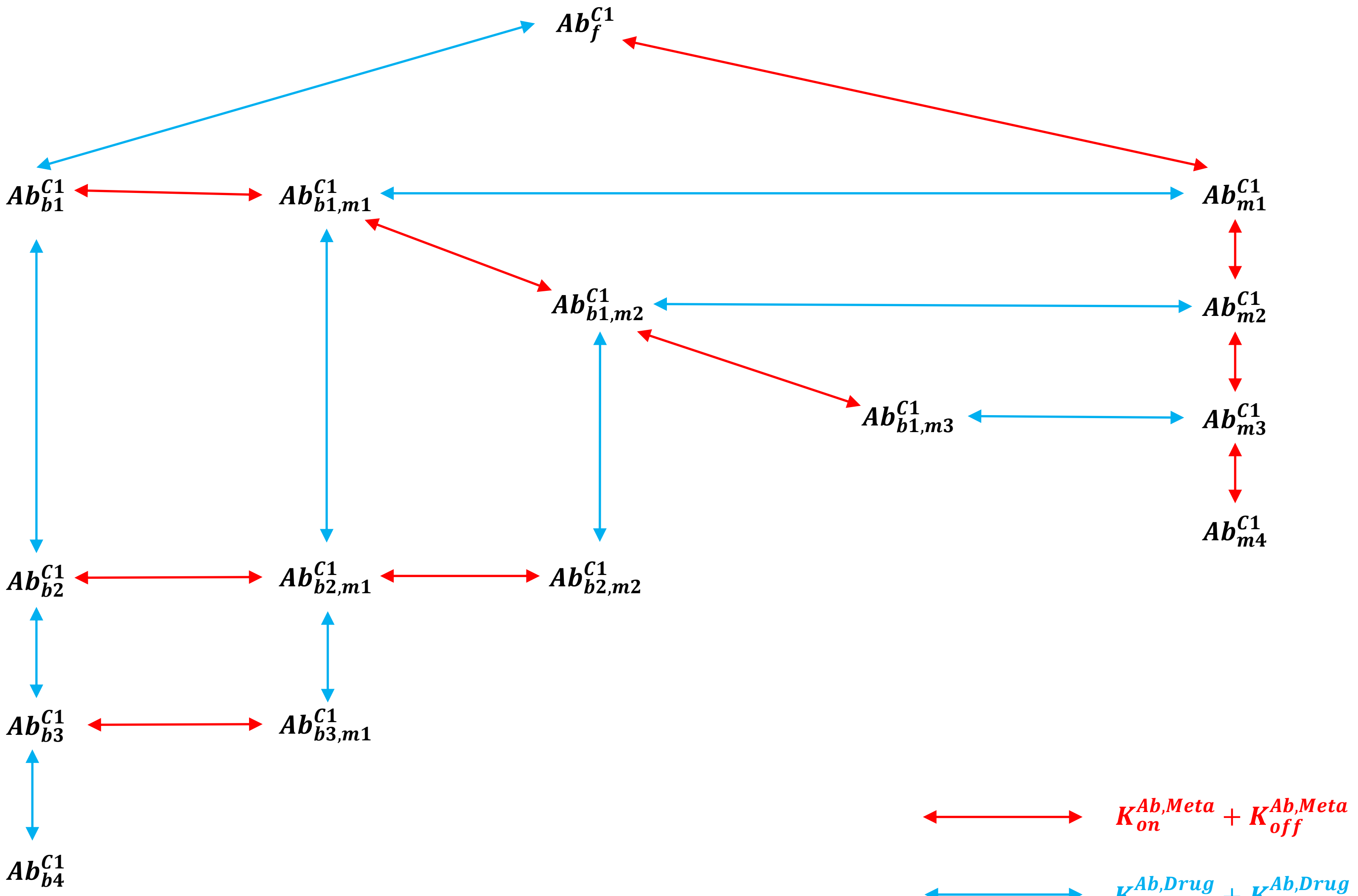
presentation CL_{ADC} = CL_{Ab} app

Mathematical description of mechanisms in-vivo

Metabolites

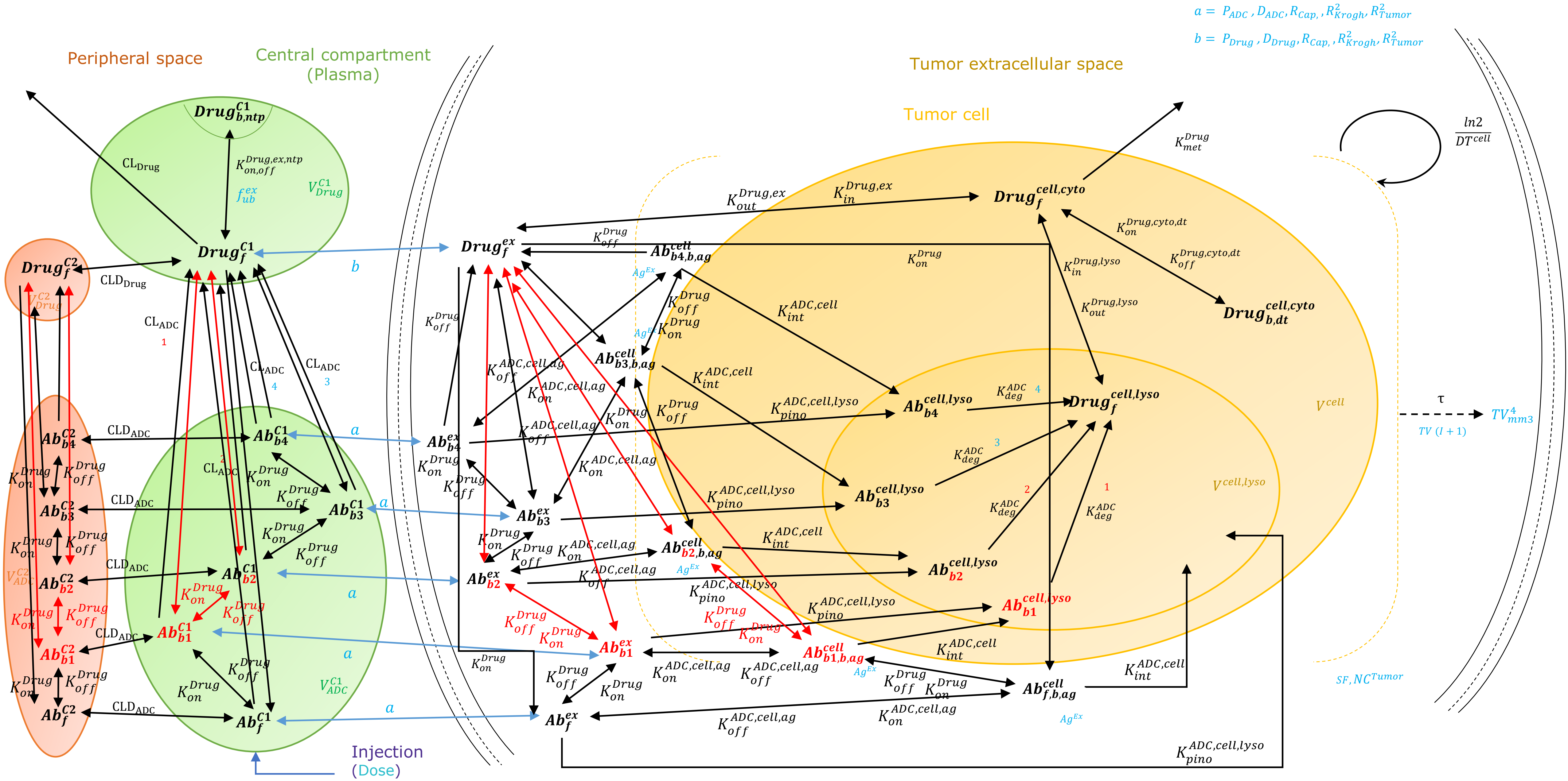


(Un-)Binding of Protacs and Metabolites in central compartment and tumor extracellular space



Same reactions apply
to tumor extracellular space *ex*.
But in peripheral space *C2*
we have only drug (un-)binding

Mathematical description of mechanisms in-vivo



Amount (nmol/kg) of free Antibody (bound to 0 Protacs) in central compartment/plasma

$$\frac{d(Ab_f^{C1})}{dt} = \underbrace{-\frac{CL_{ADC}}{V_{ADC}^{C1}} \times Ab_f^{C1}}_{\text{To clearance of ADC}} \underbrace{- \frac{CLD_{ADC}}{V_{ADC}^{C1}} \times Ab_f^{C1}}_{\text{To peripheral space}} \underbrace{+ \frac{CLD_{ADC}}{V_{ADC}^{C2}} \times Ab_f^{C2}}_{\text{From peripheral space}}$$

$$\underbrace{-\left(\frac{Ab_f^{C1}}{V_{ADC}^{C1}} - \frac{Ab_f^{ex}}{\varepsilon^{ADC}}\right) \times \frac{V^{tumor}}{BW} \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{ADC}}{R_{Tumor}^2}\right)}_{\text{To tumor extracellular space}} \underbrace{-K_{on}^{Ab,Drug} \times max \times Ab_f^{C1} \times Drug_f^{C1}}_{\text{To binding to drug}} \underbrace{+ K_{off}^{Ab,Drug} \times Ab_{b1}^{C1}}_{\text{From unbinding of drug}}$$

$$\underbrace{-K_{on}^{Ab,Meta} \times max \times Ab_f^{C1} \times Meta1_f^{C1}}_{\text{To binding to metabolite}} \underbrace{+ K_{off}^{Ab,Meta} \times Ab_{m1}^{C1}}_{\text{From unbinding of metabolite}}$$

Units: $$\frac{nmol}{kg \times h} = \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{kg} - \frac{\frac{l}{h}/kg}{l/kg} \times nmol/kg + \frac{\frac{l}{h}/kg}{l/kg} \times nmol/kg - \left(\frac{nmol/kg}{l/kg} - \frac{nmol/l}{1}\right) \times \frac{l}{kg} \times \left(\frac{\frac{um}{h} \times um}{um^2} + \frac{cm^2/h}{cm^2}\right)$$
$$- \frac{l}{h} \times \left(\frac{1}{l/kg \times kg}\right) \times \frac{nmol}{kg} - \frac{1}{\frac{nmol}{l} \times h} \times \frac{nmol}{kg} \times (1 - 1 - 1) \times 1 \times \frac{nmol}{kg \times \frac{l}{kg}} + \frac{1}{h} \times 1 \times 1 \times \frac{nmol}{kg} - \frac{1}{\frac{nmol}{l} \times h} \times \frac{nmol}{kg} \times \frac{nmol}{kg \times \frac{l}{kg}} + \frac{1}{h} \times \frac{nmol}{kg}$$

Amount (nmol/kg) of Antibody bound to i Protacs in central compartment/plasma, i = 1,2,3

$$\frac{d(Ab_{bi}^{C1})}{dt} = \underbrace{-\frac{CL_{ADC}}{V_{ADC}^{C1}} \times Ab_{bi}^{C1}}_{\text{To clearance of ADC}} \underbrace{- \frac{CLD_{ADC}}{V_{ADC}^{C1}} \times Ab_{bi}^{C1}}_{\text{To peripheral space}} \underbrace{+ \frac{CLD_{ADC}}{V_{ADC}^{C2}} \times Ab_{bi}^{C2}}_{\text{From peripheral space}}$$

$$\underbrace{-\left(\frac{Ab_{bi}^{C1}}{V_{ADC}^{C1}} - \frac{Ab_{bi}^{ex}}{\varepsilon^{ADC}}\right) \times \frac{V^{tumor}}{BW} \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R_{Krogh}^{2}} + \frac{6 \times D_{ADC}}{R_{Tumor}^{2}}\right)}_{\text{To tumor extracellular space}} \underbrace{-K_{on}^{Ab,Drug} \times (max - i) \times Ab_{bi}^{C1} \times Drug_{f}^{C1}}_{\text{To binding to drug}} \underbrace{+ K_{off}^{Ab,Drug} \times Ab_{bi+1}^{C1}}_{\text{From unbinding of drug}}$$

$$\underbrace{+K_{on}^{Ab,Drug} \times (max - i + 1) \times Ab_{bi-1}^{C1} \times Drug_{f}^{C1}}_{\text{From binding to drug}} \underbrace{- K_{off}^{Ab,Drug} \times Ab_{bi}^{C1}}_{\text{To unbinding of drug}} \underbrace{- K_{on}^{Ab,Meta} \times (max - i) \times Ab_{bi}^{C1} \times Meta1_{f}^{C1}}_{\text{To binding to metabolite}} \underbrace{+ K_{off}^{Ab,M}}_{\text{From unbin}}$$

Units: $\frac{nmol}{kg \times h} = \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{kg} - \frac{\frac{l}{h}/kg}{l/kg} \times nmol/kg + \frac{\frac{l}{h}/kg}{l/kg} \times nmol/kg - \left(\frac{nmol/kg}{l/kg} - \frac{nmol/l}{1}\right) \times \frac{l}{kg} \times \left(\frac{\frac{um}{h} \times um}{um^2} + \frac{cm^2/h}{cm^2}\right)$

$- \frac{l}{h} \times \left(\frac{1}{l/kg \times kg}\right) \times \frac{nmol}{kg} - \frac{1}{\frac{nmol}{l} \times h} \times \frac{nmol}{kg} \times (1 - 1 - 1) \times 1 \times \frac{nmol}{kg \times \frac{l}{kg}} + \frac{1}{h} \times 1 \times 1 \times \frac{nmol}{kg} - \frac{1}{\frac{nmol}{l} \times h} \times \frac{nmol}{kg} \times \frac{nmol}{kg \times \frac{l}{kg}} + \frac{1}{h} \times \frac{nmol}{kg}$

Amount (nmol/kg) of Antibody bound to 4 Protacs in central compartment/plasma

$$\frac{d(Ab_{b4}^{C1})}{dt} = \underbrace{-\frac{CL_{ADC}}{V_{ADC}^{C1}} \times Ab_{b4}^{C1}}_{\text{To clearance of ADC}} \underbrace{- \frac{CLD_{ADC}}{V_{ADC}^{C1}} \times Ab_{b4}^{C1}}_{\text{To peripheral space}} \underbrace{+ \frac{CLD_{ADC}}{V_{ADC}^{C2}} \times Ab_{b4}^{C2}}_{\text{From peripheral space}}$$

$$\underbrace{-\left(\frac{Ab_{b4}^{C1}}{V_{ADC}^{C1}} - \frac{Ab_{b4}^{ex}}{\varepsilon^{ADC}}\right) \times \frac{V^{tumor}}{BW} \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{ADC}}{R_{Tumor}^2}\right)}_{\text{To tumor extracellular space}}$$

$$\underbrace{+K_{on}^{Ab,Drug} \times Ab_{b3}^{C1} \times Drug_f^{C1}}_{\text{From binding to drug}} \underbrace{- K_{off}^{Ab,Drug} \times Ab_{b4}^{C1}}_{\text{To unbinding of drug}}$$

Units: $\frac{nmol}{kg \times h} = \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{kg} - \frac{\frac{l}{h}/kg}{l/kg} \times nmol/kg + \frac{\frac{l}{h}/kg}{l/kg} \times nmol/kg - \left(\frac{nmol/kg}{l/kg} - \frac{nmol/l}{1}\right) \times \frac{l}{kg} \times \left(\frac{\frac{um}{h} \times um}{um^2} + \frac{cm^2/h}{cm^2}\right)$

$- \frac{l}{h} \times \left(\frac{1}{l/kg \times kg}\right) \times \frac{nmol}{kg} - \frac{1}{\frac{nmol}{l} \times h} \times \frac{nmol}{kg} \times (1 - 1 - 1) \times 1 \times \frac{nmol}{kg \times \frac{l}{kg}} + \frac{1}{h} \times 1 \times 1 \times \frac{nmol}{kg} - \frac{1}{\frac{nmol}{l} \times h} \times \frac{nmol}{kg} \times \frac{nmol}{kg \times \frac{l}{kg}} + \frac{1}{h} \times \frac{nmol}{kg}$

Amount (nmol/kg) of Antibody bound to j Metabolites1 in central compartment/plasma, j = 1,2,3

$$\frac{d(Ab_{mj}^{C1})}{dt} = \underbrace{-\frac{CL_{ADC}}{V_{ADC}^{C1}} \times Ab_{mj}^{C1}}_{\text{To clearance of ADC}} \underbrace{-\frac{CLD_{ADC}}{V_{ADC}^{C1}} \times Ab_{mj}^{C1}}_{\text{To peripheral space}} \underbrace{+\frac{CLD_{ADC}}{V_{ADC}^{C2}} \times Ab_{mj}^{C2}}_{\text{From peripheral space}}$$

$$\underbrace{-\left(\frac{Ab_{mj}^{C1}}{V_{ADC}^{C1}} - \frac{Ab_{mj}^{ex}}{\varepsilon^{ADC}}\right) \times \frac{V^{tumor}}{BW} \times \left(\frac{2\times P_{ADC}\times R_{Cap}}{R_{Krogh}^{2}} + \frac{6\times D_{ADC}}{R_{Tumor}^{2}}\right)}_{\text{To tumor extracellular space}} \underbrace{-K_{on}^{Ab,Drug} \times (max - j) \times Ab_{mj}^{C1}}_{\text{To binding to drug}} \times Drug_{f}^{C1} \underbrace{+ K_{off}^{Ab,Drug}}_{\text{From unbinding of drug}} \times Ab_{b1,mj}^{C1}$$

$$\underbrace{+K_{on}^{Ab,Meta} \times (max - j + 1) \times Ab_{mj-1}^{C1} \times Meta1_{f}^{C1}}_{\text{From binding to metabolite}} \underbrace{- K_{off}^{Ab,Meta} \times Ab_{mj}^{C1}}_{\text{To unbinding of metabolite}} \underbrace{- K_{on}^{Ab,Meta} \times (max - j) \times Ab_{mj}^{C1} \times Meta1_{f}^{C1}}_{\text{To binding to metabolite}} \underbrace{+ K_{o}}_{\text{From unbin}}$$

Units: $$\frac{nmol}{kg\times h} = \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{kg} - \frac{\frac{l}{h}/kg}{l/kg} \times nmol/kg + \frac{\frac{l}{h}/kg}{l/kg} \times nmol/kg - \left(\frac{nmol/kg}{l/kg} - \frac{nmol/l}{1}\right) \times \frac{l}{kg} \times \left(\frac{\frac{um}{h}\times um}{um^2} + \frac{cm^2/h}{cm^2}\right)$$
$$- \frac{l}{h} \times \left(\frac{1}{l/kg\times kg}\right) \times \frac{nmol}{kg} - \frac{1}{\frac{nmol}{l}\times h} \times \frac{nmol}{kg} \times (1-1-1) \times 1 \times \frac{nmol}{kg\times\frac{l}{kg}} + \frac{1}{h} \times 1 \times 1 \times \frac{nmol}{kg} - \frac{1}{\frac{nmol}{l}\times h} \times \frac{nmol}{kg} \times \frac{nmol}{kg\times\frac{l}{kg}} + \frac{1}{h} \times \frac{nmol}{kg}$$

Amount (nmol/kg) of Antibody bound to 4 Metabolites1 in central compartment/plasma

$$\frac{d(Ab_{m4}^{C1})}{dt} = \underbrace{-\frac{CL_{ADC}}{V_{ADC}^{C1}} \times Ab_{m4}^{C1}}_{\text{To clearance of ADC}} \underbrace{-\frac{CLD_{ADC}}{V_{ADC}^{C1}} \times Ab_{m4}^{C1}}_{\text{To peripheral space}} \underbrace{+\frac{CLD_{ADC}}{V_{ADC}^{C2}} \times Ab_{m4}^{C2}}_{\text{From peripheral space}}$$

$$\underbrace{-\left(\frac{Ab_{m4}^{C1}}{V_{ADC}^{C1}} - \frac{Ab_{m4}^{ex}}{\varepsilon^{ADC}}\right) \times \frac{V^{tumor}}{BW} \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{ADC}}{R_{Tumor}^2}\right)}_{\text{To tumor extracellular space}}$$

$$\underbrace{+K_{on}^{Ab,Meta} \times Ab_{m3}^{C1} \times Meta1_f^{C1}}_{\text{From binding to metabolite}} \underbrace{- K_{off}^{Ab,Meta} \times Ab_{m4}^{C1}}_{\text{To unbinding of metabolite}}$$

Units: $\frac{nmol}{kg \times h} = \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{kg} - \frac{\frac{l}{h}/kg}{l/kg} \times nmol/kg + \frac{\frac{l}{h}/kg}{l/kg} \times nmol/kg - \left(\frac{nmol/kg}{l/kg} - \frac{nmol/l}{1}\right) \times \frac{l}{kg} \times \left(\frac{\frac{um}{h} \times um}{um^2} + \frac{cm^2/h}{cm^2}\right)$
$- \frac{l}{h} \times \left(\frac{1}{l/kg \times kg}\right) \times \frac{nmol}{kg} - \frac{1}{\frac{nmol}{l} \times h} \times \frac{nmol}{kg} \times (1 - 1 - 1) \times 1 \times \frac{nmol}{kg \times \frac{l}{kg}} + \frac{1}{h} \times 1 \times 1 \times \frac{nmol}{kg} - \frac{1}{\frac{nmol}{l} \times h} \times \frac{nmol}{kg} \times \frac{nmol}{kg \times \frac{l}{kg}} + \frac{1}{h} \times \frac{nmol}{kg}$

Amount (nmol/kg) of Antibody bound to i Protac and j Metabolites1 in central compartment/plasma, i = 1,2 and j = 1,2

$$\frac{d(Ab^{C1}_{bi,mj})}{dt} = \underbrace{-\frac{CL_{ADC}}{V^{C1}_{ADC}} \times Ab^{C1}_{bi,mj}}_{\text{To clearance of ADC}} \underbrace{-\frac{CLD_{ADC}}{V^{C1}_{ADC}} \times Ab^{C1}_{bi,mj}}_{\text{To peripheral space}} \underbrace{+\frac{CLD_{ADC}}{V^{C2}_{ADC}} \times Ab^{C2}_{bi,mj}}_{\text{From peripheral space}}$$

$$\underbrace{-\left(\frac{Ab^{C1}_{bi,mj}}{V^{C1}_{ADC}} - \frac{Ab^{ex}_{bi,mj}}{\varepsilon^{ADC}}\right) \times \frac{V^{tumor}}{BW} \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R^2_{Krogh}} + \frac{6 \times D_{ADC}}{R^2_{Tumor}}\right)}_{\text{To tumor extracellular space}} \underbrace{-K^{Ab,Drug}_{on} \times (max - i - j) \times Ab^{C1}_{bi,mj} \times Drug^{C1}_{f}}_{\text{To binding to drug}} \underbrace{+K^{Ab,Drug}_{off} \times A}_{\text{From unbinding of}}$$

$$\underbrace{+K^{Ab,Drug}_{on} \times (max - i + 1 - j) \times Ab^{C1}_{bi-1,mj} \times Drug^{C1}_{f}}_{\text{From binding to drug}} \underbrace{- K^{Ab,Drug}_{off} \times Ab^{C1}_{bi,mj}}_{\text{To unbinding of drug}} \underbrace{- K^{Ab,Meta}_{on} \times (max - i - j) \times Ab^{C1}_{bi,mj} \times M}_{\text{To binding to metabolite}}$$

$$\underbrace{+K^{Ab,Meta}_{off} \times Ab^{C1}_{bi,mj+1}}_{\text{From unbinding of metabolite}} \underbrace{+ K^{Ab,Meta}_{on} \times (max - i - j + 1) \times Ab^{C1}_{bi,mj-1} \times Meta1^{C1}_{f}}_{\text{From binding to metabolite}} \underbrace{- K^{Ab,Meta}_{off} \times Ab^{C1}_{bi,mj}}_{\text{To unbinding of metabolite}}$$

Amount (nmol/kg) of Antibody bound to i Protac and j Metabolites1 in central compartment/plasma, i = 1,2,3 and j = 1,2,3 with i + j = max

$$\frac{d(Ab_{bi,mj}^{C1})}{dt} = \underbrace{-\frac{CL_{ADC}}{V_{ADC}^{C1}} \times Ab_{bi,mj}^{C1}}_{\text{To clearance of ADC}} \underbrace{- \frac{CLD_{ADC}}{V_{ADC}^{C1}} \times Ab_{bi,mj}^{C1}}_{\text{To peripheral space}} \underbrace{+ \frac{CLD_{ADC}}{V_{ADC}^{C2}} \times Ab_{bi,mj}^{C2}}_{\text{From peripheral space}}$$

$$\underbrace{-\left(\frac{Ab_{bi,mj}^{C1}}{V_{ADC}^{C1}} - \frac{Ab_{bi,mj}^{ex}}{\varepsilon^{ADC}}\right) \times \frac{V^{tumor}}{BW} \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R_{Krogh}^{2}} + \frac{6 \times D_{ADC}}{R_{Tumor}^{2}}\right)}_{\text{To tumor extracellular space}}$$

$$\underbrace{+K_{on}^{Ab,Drug} \times (max - i + 1 - j) \times Ab_{bi-1,mj}^{C1} \times Drug_{f}^{C1}}_{\text{From binding to drug}} \underbrace{- K_{off}^{Ab,Drug} \times Ab_{bi,mj}^{C1}}_{\text{To unbinding of drug}}$$

$$+\underbrace{K_{on}^{Ab,Meta} \times (max - i - j + 1) \times Ab_{bi,mj-1}^{C1} \times Meta1_{f}^{C1}}_{\text{From binding to metabolite}} \underbrace{- K_{off}^{Ab,Meta} \times Ab_{bi,mj}^{C1}}_{\text{To unbinding of metabolite}}$$

Concentration (nM) of free (unbound) Drug in central compartment/plasma

$$\frac{d(Drug_f^{C1})}{dt} = \underbrace{-\frac{CL_{Drug}}{V_{Drug}^{C1}} \times Drug_f^{C1}}_{\text{To clearance of drug}} \underbrace{-\frac{CLD_{Drug}}{V_{Drug}^{C1}} \times Drug_f^{C1}}_{\text{To peripheral space}} \underbrace{+\frac{CLD_{Drug}}{V_{Drug}^{C1}} \times Drug_f^{C2}}_{\text{From peripheral space}} \underbrace{+\frac{\sum_{i=1,j=0}^{max} CL_{ADC} \times i \times \frac{Ab_{bi,mj}^{C1}}{V_{ADC}^{C1}}}{V_{Drug}^{C1}}}_{\text{From clearance of Ab bound to i Protacs}}$$

$$\underbrace{-\left(Drug_f^{C1} - \frac{Drug_f^{ex}}{V^{tumor} \times \varepsilon^{Drug}}\right) \times \frac{V^{tumor}}{V_{Drug}^{C1} \times BW} \times \left(\frac{2 \times P_{Drug} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{Drug}}{R_{Tumor}^2}\right)}_{\text{To tumor extracellular space}}$$

$$\underbrace{-K_{on,off}^{Drug,ex,ntp} \times (1 - f_{ub}^{ex}) \times Drug_f^{C1} + K_{on,off}^{Drug,ex,ntp} \times f_{ub}^{ex} \times Drug_{b,ntp}^{C1}}_{\text{To and from protein binding}} \underbrace{- K_{met}^{Drug,C1} \times Drug_f^{C1}}_{\text{To metabolism}}$$

Units: $$\frac{nmol}{l \times h} = -\frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{l} - \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{l} + \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{l} + \frac{\frac{1}{h} \times \frac{nmol}{kg} \times 1}{l/kg} + \frac{\frac{l}{h}/kg \times 1 \times \frac{nmol/kg}{l/kg}}{l/kg}$$

$$-\left(\frac{nmol}{l} - \frac{nmol}{l \times 1}\right) \times \frac{l}{l/kg \times kg} \times \left(\frac{\frac{um}{h} \times um}{um^2} + \frac{cm^2/h}{cm^2}\right) \frac{1}{h} \times \frac{nmol}{l} + \frac{1}{h} \times 1 \times \frac{nmol}{l} + \frac{1}{h} \times 1 \times \frac{1 \times nmol}{kg \times \frac{l}{kg}} - \frac{1}{h} \times \frac{l \times 1}{kg \times \frac{l}{kg}} \times \frac{nmol}{l}$$

Concentration (nM) of drug bound to unspecific protein in central compartment/plasma

$$\frac{d(Drug_{b,ntp}^{C1})}{dt} = \underbrace{K_{on,off}^{Drug,ex,ntp} \times (1 - f_{ub}^{ex}) \times Drug_{f}^{C1}}_{\text{To unspecific protein binding}} - \underbrace{K_{on,off}^{Drug,ex,ntp} \times f_{ub}^{ex} \times Drug_{b,ntp}^{C1}}_{\text{To unspecific protein unbinding}}$$

Units: $\frac{nmol}{l \times h} = \frac{1}{h} \times 1 \times \frac{nmol}{l} - \frac{1}{h} \times 1 \times \frac{nmol}{l}$

Concentration (nM) of free (unbound) Metabolite1 in central compartment/plasma

$$\frac{d(Meta1_f^{C1})}{dt} = \underbrace{-\frac{CL_{Meta}}{V_{Meta}^{C1}} \times Meta1_f^{C1}}_{\text{To clearance}} + \underbrace{\frac{\sum_{i=0,j=1}^{max} CL_{ADC} \times j \times \frac{Ab_{bi,mj}^{C1}}{V_{ADC}^{C1}}}{V_{Meta}^{C1}}}_{\text{From clearance of Ab bound to j Metabolites1}} + \underbrace{K_{met}^{Drug,C1} \times Drug_f^{C1}}_{\text{From metabolism}}$$

$$\underbrace{-\left(Meta1_f^{C1} - \frac{Meta1_f^{ex}}{V^{tumor} \times \varepsilon^{Meta}}\right) \times \frac{V^{tumor}}{V_{Meta}^{C1} \times BW} \times \left(\frac{2 \times P_{Meta} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{Meta}}{R_{Tumor}^2}\right)}_{\text{To tumor extracellular space}}$$

Units: $$\frac{nmol}{l \times h} = -\frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{l} - \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{l} + \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{l} + \frac{\frac{1}{h} \times \frac{nmol}{kg} \times 1}{l/kg} + \frac{\frac{l}{h}/kg \times 1 \times \frac{nmol/kg}{l/kg}}{l/kg}$$

$$-\left(\frac{nmol}{l} - \frac{nmol}{l \times 1}\right) \times \frac{l}{l/kg \times kg} \times \left(\frac{\frac{um}{h} \times um}{um^2} + \frac{cm^2/h}{cm^2}\right) \frac{1}{h} \times \frac{nmol}{l} + \frac{1}{h} \times 1 \times \frac{nmol}{l} + \frac{1}{h} \times 1 \times \frac{1 \times nmol}{kg \times \frac{l}{kg}} - \frac{1}{h} \times \frac{l \times 1}{kg \times \frac{l}{kg}} \times \frac{nmol}{l}$$

Concentration (nM) of free Metabolite2 in central compartment/plasma

$$\frac{d(Meta2_f^{C1})}{dt} = \underbrace{-\frac{CL_{Meta}}{V_{Meta}^{C1}} \times Meta2_f^{C1}}_{\text{To clearance}} + \underbrace{K_{met}^{Drug,C1} \times Drug_f^{C1}}_{\text{From metabolism}}$$

$$\underbrace{-\left(Meta2_f^{C1} - \frac{Meta2_f^{ex}}{V^{tumor} \times \varepsilon^{Meta}}\right) \times \frac{V^{tumor}}{V_{Meta}^{C1} \times BW} \times \left(\frac{2 \times P_{Meta} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{Meta}}{R_{Tumor}^2}\right)}_{\text{To tumor extracellular space}}$$

Units:

$$\frac{nmol}{l \times h} = -\frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{l} - \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{l} + \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{l} + \frac{\frac{1}{h} \times \frac{nmol}{kg} \times 1}{l/kg} + \frac{\frac{l}{h}/kg \times 1 \times \frac{nmol/kg}{l/kg}}{l/kg}$$

$$-\left(\frac{nmol}{l} - \frac{nmol}{l \times 1}\right) \times \frac{l}{l/kg \times kg} \times \left(\frac{\frac{um}{h} \times um}{um^2} + \frac{cm^2/h}{cm^2}\right) \frac{1}{h} \times \frac{nmol}{l} + \frac{1}{h} \times 1 \times \frac{nmol}{l} + \frac{1}{h} \times 1 \times \frac{1 \times nmol}{kg \times \frac{l}{kg}} - \frac{1}{h} \times \frac{l \times 1}{kg \times \frac{l}{kg}} \times \frac{nmol}{l}$$

Amount (nmol/kg) of free Antibody (bound to 0 Protacs) in peripheral compartment

$$\frac{d\,(Ab_f^{C2})}{dt} = \underbrace{\frac{CLD_{ADC}}{V_{ADC}^{C1}} \times Ab_f^{C1}}_{\text{From central space}} - \underbrace{\frac{CLD_{ADC}}{V_{ADC}^{C2}} \times Ab_f^{C2}}_{\text{To central space}}$$

$$\underbrace{-K_{on}^{Ab,Drug} \times max \times Ab_f^{C2} \times Drug_f^{C2}}_{\text{To binding to drug}} + \underbrace{K_{off}^{Ab,Drug} \times Ab_{b1}^{C2}}_{\text{From unbinding of drug}}$$

Units:

$$\frac{nmol}{kg \times h} = \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{kg} \quad - \frac{\frac{l}{h}/kg}{l/kg} \times nmol/kg$$

Amount (nmol/kg) of Antibody bound to i Protacs in peripheral compartment , i = 1,2,3

$$\frac{d\,(Ab_{bi}^{C2})}{dt} = \underbrace{\frac{CLD_{ADC}}{V_{ADC}^{C1}} \times Ab_{bi}^{C1}}_{\text{From central space}} - \underbrace{\frac{CLD_{ADC}}{V_{ADC}^{C2}} \times Ab_{bi}^{C2}}_{\text{To central space}}$$

$$\underbrace{-K_{on}^{Ab,Drug} \times (max - i) \times Ab_{bi}^{C2} \times Drug_{f}^{C2}}_{\text{To binding to drug}} + \underbrace{K_{off}^{Ab,Drug} \times Ab_{bi+1}^{C2}}_{\text{From unbinding of drug}}$$

$$\underbrace{+K_{on}^{Ab,Drug} \times (max - i + 1) \times Ab_{i-1}^{C2} \times Drug_{f}^{C2}}_{\text{From binding to drug}} - \underbrace{K_{off}^{Ab,Drug} \times Ab_{bi}^{C2}}_{\text{To unbinding of drug}}$$

Units:

$$\frac{nmol}{kg \times h} = \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{kg} \quad - \frac{\frac{l}{h}/kg}{l/kg} \times nmol/kg$$

Amount (nmol/kg) of Antibody bound to 4 Protacs in peripheral compartment

$$\frac{d\,(Ab_{b4}^{C2})}{dt} = \underbrace{\frac{CLD_{ADC}}{V_{ADC}^{C1}} \times Ab_{b4}^{C1}}_{\text{From central space}} - \underbrace{\frac{CLD_{ADC}}{V_{ADC}^{C2}} \times Ab_{b4}^{C2}}_{\text{To central space}}$$

$$\underbrace{+K_{on}^{Ab,Drug} \times Ab_{b3}^{C2} \times Drug_{f}^{C2}}_{\text{From binding to drug}} - \underbrace{K_{off}^{Ab,Drug} \times Ab_{b4}^{C2}}_{\text{To unbinding of drug}}$$

Units:

$$\frac{nmol}{kg \times h} = \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{kg} - \frac{\frac{l}{h}/kg}{l/kg} \times nmol/kg$$

Amount (nmol/kg) of Antibody bound to j Metabolites1 in peripheral compartment, j = 1,2,3

$$\frac{d\ (Ab_{mj}^{C2})}{dt} = \underbrace{\frac{CLD_{ADC}}{V_{ADC}^{C1}} \times Ab_{mj}^{C1}}_{\text{From central space}} - \underbrace{\frac{CLD_{ADC}}{V_{ADC}^{C2}} \times Ab_{mj}^{C2}}_{\text{To central space}}$$

$$\underbrace{-K_{on}^{Ab,Drug} \times (max - j) \times Ab_{mj}^{C2} \times Drug_{f}^{C2}}_{\text{To binding to drug}} + \underbrace{K_{off}^{Ab,Drug} \times Ab_{b1,mj}^{C2}}_{\text{From unbinding of drug}}$$

Units:

$$\frac{nmol}{kg \times h} = \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{kg} \qquad - \frac{\frac{l}{h}/kg}{l/kg} \times nmol/kg$$

Amount (nmol/kg) of Antibody bound to 4 Metabolites1 in peripheral compartment

$$\frac{d\ (Ab_{m4}^{C2})}{dt} = \underbrace{\frac{CLD_{ADC}}{V_{ADC}^{C1}} \times Ab_{m4}^{C1}}_{\text{From central space}} - \underbrace{\frac{CLD_{ADC}}{V_{ADC}^{C2}} \times Ab_{m4}^{C2}}_{\text{To central space}}$$

Units:

$$\frac{nmol}{kg \times h} = \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{kg} - \frac{\frac{l}{h}/kg}{l/kg} \times nmol/kg$$

Amount (nmol/kg) of Antibody bound to i Protac and j Metabolites1 in peripheral compartment, i = 1,2 and j = 1,2

$$\frac{d(Ab_{bi,mj}^{C2})}{dt} = \underbrace{\frac{CLD_{ADC}}{V_{ADC}^{C1}} \times Ab_{bi,mj}^{C1}}_{\text{From central space}} - \underbrace{\frac{CLD_{ADC}}{V_{ADC}^{C2}} \times Ab_{bi,mj}^{C2}}_{\text{To central space}}$$

$$\underbrace{-K_{on}^{Ab,Drug} \times (max - i - j) \times Ab_{bi,mj}^{C2} \times Drug_f^{C2}}_{\text{To binding to drug}} + \underbrace{K_{off}^{Ab,Drug} \times Ab_{bi+1,mj}^{C2}}_{\text{From unbinding of drug}}$$

$$\underbrace{+K_{on}^{Ab,Drug} \times (max - i + 1 - j) \times Ab_{bi-1,mj}^{C2} \times Drug_f^{C2}}_{\text{From binding to drug}} - \underbrace{K_{off}^{Ab,Drug} \times Ab_{bi,mj}^{C2}}_{\text{To unbinding of drug}}$$

Amount (nmol/kg) of Antibody bound to i Protac and j Metabolites1 in peripheral compartment, i = 1,2,3 and j = 1,2,3 with i + j = max

$$\frac{d(Ab_{bi,mj}^{C2})}{dt} = \underbrace{\frac{CLD_{ADC}}{V_{ADC}^{C1}} \times Ab_{bi,mj}^{C1}}_{\text{From central space}} - \underbrace{\frac{CLD_{ADC}}{V_{ADC}^{C2}} \times Ab_{bi,mj}^{C2}}_{\text{To central space}}$$

$$\underbrace{+K_{on}^{Ab,Drug} \times (max - i + 1 - j) \times Ab_{bi-1,mj}^{C2} \times Drug_{f}^{C2}}_{\text{From binding to drug}} - \underbrace{K_{off}^{Ab,Drug} \times Ab_{bi,mj}^{C2}}_{\text{To unbinding of drug}}$$

Concentration (nM) of free drug in peripheral compartment

$$\frac{d(Drug_f^{C2})}{dt} = \underbrace{\frac{CLD_{Drug}}{V_{Drug}^{C2}} \times Drug_f^{C1}}_{\text{From central space}} - \underbrace{\frac{CLD_{Drug}}{V_{Drug}^{C2}} \times Drug_f^{C2}}_{\text{To central space}}$$

Units:

$$\frac{nmol}{l \times h} = \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{l} \qquad - \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{l}$$

Concentration (nM) of free Antibody (bound to 0 Protacs) in tumor extracellular space

$$\frac{d(Ab_f^{ex})}{dt} = \underbrace{\left(\frac{\mathrm{Ab}_f^{C1}}{V_{ADC}^{C1}} - \frac{Ab_f^{ex}}{\varepsilon^{ADC}}\right) \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{ADC}}{R_{Tumor}^2}\right)}_{\text{From central space}}$$

$$+ \underbrace{\left(-K_{on}^{ADC,cell,ag} \times \frac{Ab_f^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - Ab_{f,b,ag}^{cell} - \sum_{i=1}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j\le max} Ab_{bi,mj,b,ag}^{cell}\right) + K_{off}^{ADC,cell,ag} \times Ab_{f,b,ag}^{cell}\right)}_{\text{Binding and unbinding of ADC to receptors on tumor cell}}$$

$$\times \frac{NC^{tumor} \times SF}{V^{tumor}} + \underbrace{\frac{1}{\tau} \times V_{dyi,3,mm3}^{tumor} \times 10^5 \times \left(Ab_{f,b,ag}^{cell}\right) \times \frac{SF}{V^{tumor}}}_{\text{From intracellular content of dying cells}} \underbrace{- K_{pino}^{ADC,cell,lyso} \times \left(\frac{NCL^{tumor}}{\varepsilon^{ADC}}\right) \times Ab_f^{ex}}_{\text{To pinocytosis}}$$

$$\underbrace{-K_{on}^{Ab,Drug} \times max \times \frac{Ab_f^{ex}}{\varepsilon^{ADC}} \times \frac{Drug_f^{ex}}{V^{tumor}}}_{\text{To binding to drug}} \underbrace{+ K_{off}^{Ab,Drug} \times \frac{Ab_{b1}^{ex}}{\varepsilon^{ADC}}}_{\text{From unbinding of drug}} \underbrace{- K_{on}^{Ab,Meta} \times max \times \frac{Ab_f^{ex}}{\varepsilon^{ADC}} \times \frac{Meta1_f^{ex}}{V^{tumor}}}_{\text{To binding to metabolite}} \underbrace{+ K_{off}^{Ab,Meta} \times \frac{Ab_{m1}^{ex}}{\varepsilon^{ADC}}}_{\text{From unbinding of metabolite}}$$

Concentration (nM) of Antibody bound to i Protacs in tumor extracellular space, i = 1,2,3

$$\frac{d(Ab_{bi}^{ex})}{dt} = \underbrace{\left(\frac{\mathrm{Ab}_{bi}^{C1}}{V_{ADC}^{C1}} - \frac{Ab_{bi}^{ex}}{\varepsilon^{ADC}}\right) \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R_{Krogh}^{2}} + \frac{6 \times D_{ADC}}{R_{Tumor}^{2}}\right)}_{\text{From central space}}$$

$$+ \underbrace{\left(-K_{on}^{ADC,cell,ag} \times \frac{Ab_{bi}^{ex}}{\varepsilon^{ADC}} \times \left(Ag_{t}^{cell} - Ab_{f,b,ag}^{cell} - \sum_{i=1}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j \le max} Ab_{bi,mj,b,ag}^{cell}\right) + K_{off}^{ADC,cell,ag} \times Ab_{bi,b,ag}^{cell}\right)}_{\text{Binding and unbinding of ADC to receptors on tumor cell}}$$

$$\times \frac{NC^{tumor} \times SF}{V^{tumor}} + \underbrace{\frac{1}{\tau} \times V_{dyi,3,mm3}^{tumor} \times 10^{5} \times \left(Ab_{bi,b,ag}^{cell} + Ab_{bi}^{cell,lyso}\right) \times \frac{SF}{V^{tumor}}}_{\text{From intracellular content of dying cells}} - \underbrace{K_{pino}^{ADC,cell,lyso} \times \left(\frac{NCL^{tumor}}{\varepsilon^{ADC}}\right) \times Ab_{bi}^{ex}}_{\text{To pinocytosis}}$$

$$\underbrace{-K_{on}^{Ab,Drug} \times (max - i) \times \frac{Ab_{bi}^{ex}}{\varepsilon^{ADC}} \times \frac{Drug_{f}^{ex}}{V^{tumor}}}_{\text{To binding to drug}} + \underbrace{K_{off}^{Ab,Drug} \times \frac{Ab_{bi+1}^{ex}}{\varepsilon^{ADC}}}_{\text{From unbinding of drug}} + \underbrace{K_{on}^{Ab,Drug} \times (max - i + 1) \times \frac{Ab_{bi-1}^{ex}}{\varepsilon^{ADC}} \times \frac{Drug_{f}^{ex}}{V^{tumor}}}_{\text{From binding to drug}} - \underbrace{K_{off}^{Ab,Drug} \times \frac{Ab_{bi}^{ex}}{\varepsilon^{ADC}}}_{\text{To unbinding of drug}}$$

$$\underbrace{-K_{on}^{Ab,Meta} \times (max - i) \times \frac{Ab_{bi}^{ex}}{\varepsilon^{ADC}} \times \frac{Meta1_{f}^{ex}}{V^{tumor}}}_{\text{To binding to metabolite}} + \underbrace{K_{off}^{Ab,Meta} \times \frac{Ab_{bi,m1}^{ex}}{\varepsilon^{ADC}}}_{\text{From unbinding of metabolite}}$$

Concentration (nM) of Antibody bound to 4 Protacs in tumor extracellular space

$$\frac{d(Ab_{b4}^{ex})}{dt} = \underbrace{\left(\frac{\mathrm{Ab}_{b4}^{C1}}{V_{ADC}^{C1}} - \frac{Ab_{b4}^{ex}}{\varepsilon^{ADC}}\right) \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R_{Krogh}^{2}} + \frac{6 \times D_{ADC}}{R_{Tumor}^{2}}\right)}_{\text{From central space}}$$

$$+ \underbrace{\left(-K_{on}^{ADC,cell,ag} \times \frac{Ab_{b4}^{ex}}{\varepsilon^{ADC}} \times \left(Ag_{t}^{cell} - Ab_{f,b,ag}^{cell} - \sum_{i=1}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j\leq max} Ab_{bi,mj,b,ag}^{cell}\right) + K_{off}^{ADC,cell,ag} \times Ab_{b4,b,ag}^{cell}\right)}_{\text{Binding and unbinding of ADC to receptors on tumor cell}}$$

$$\times \frac{NC^{tumor} \times SF}{V^{tumor}} \underbrace{+ \frac{1}{\tau} \times V_{dyi,3,mm3}^{tumor} \times 10^{5} \times \left(Ab_{b4,b,ag}^{cell} + Ab_{b4}^{cell,lyso}\right) \times \frac{SF}{V^{tumor}}}_{\text{From intracellular content of dying cells}} \underbrace{- K_{pino}^{ADC,cell,lyso} \times \left(\frac{NCL^{tumor}}{\varepsilon^{ADC}}\right) \times Ab_{b4}^{ex}}_{\text{To pinocytosis}}$$

$$\underbrace{+K_{on}^{Ab,Drug} \times \frac{Ab_{b3}^{ex}}{\varepsilon^{ADC}} \times \frac{Drug_{f}^{ex}}{V^{tumor}}}_{\text{To binding to drug}} \underbrace{- K_{off}^{Ab,Drug} \times \frac{Ab_{b4}^{ex}}{\varepsilon^{ADC}}}_{\text{From unbinding of drug}}$$

Concentration (nM) of Antibody bound to j Metabolites1 in tumor extracellular space, j = 1,2,3

$$\frac{d(Ab_{mj}^{ex})}{dt} = \underbrace{\left(\frac{Ab_{mj}^{C1}}{V_{ADC}^{C1}} - \frac{Ab_{mj}^{ex}}{\varepsilon^{ADC}}\right) \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{ADC}}{R_{Tumor}^2}\right)}_{\text{From central space}}$$

$$+ \underbrace{\left(-K_{on}^{ADC,cell,ag} \times \frac{Ab_{mj}^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - Ab_{f,b,ag}^{cell} - \sum_{i=1}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j \le max} Ab_{bi,mj,b,ag}^{cell}\right) + K_{off}^{ADC,cell,ag} \times\right.}_{\text{Binding and unbinding of ADC to receptors on tumor cell}}$$

$$\times \frac{NC^{tumor} \times SF}{V^{tumor}} + \underbrace{\frac{1}{\tau} \times V_{dyi,3,mm3}^{tumor} \times 10^5 \times \left(Ab_{mj,b,ag}^{cell} + Ab_{mj}^{cell,lyso}\right) \times \frac{SF}{V^{tumor}}}_{\text{From intracellular content of dying cells}} \underbrace{- K_{pino}^{ADC,cell,lyso} \times \left(\frac{NCL^{tumor}}{\varepsilon^{ADC}}\right) \times Ab_{mj}^{ex}}_{\text{To pinocytosis}}$$

$$\underbrace{-K_{on}^{Ab,Drug} \times (max - j) \times \frac{Ab_{mj}^{ex}}{\varepsilon^{ADC}} \times \frac{Drug_f^{ex}}{V^{tumor}}}_{\text{To binding to drug}} \underbrace{+ K_{off}^{Ab,Drug} \times \frac{Ab_{b1,mj}^{ex}}{\varepsilon^{ADC}}}_{\text{From unbinding of drug}} \underbrace{+ K_{on}^{Ab,Meta} \times (max - j + 1) \times \frac{Ab_{mj-1}^{ex}}{\varepsilon^{ADC}} \times \frac{Meta1_f^{ex}}{V^{tumor}}}_{\text{From binding to metabolite}}$$

$$\underbrace{-K_{off}^{Ab,Meta} \times \frac{Ab_{mj}^{ex}}{\varepsilon^{ADC}}}_{\text{To unbinding of metabolite}} \underbrace{- K_{on}^{Ab,Meta} \times (max - j) \times \frac{Ab_{mj}^{ex}}{\varepsilon^{ADC}} \times \frac{Meta1_f^{ex}}{V^{tumor}}}_{\text{To binding to metabolite}} \underbrace{+ K_{off}^{Ab,Meta} \times \frac{Ab_{mj+1}^{ex}}{\varepsilon^{ADC}}}_{\text{From unbinding of metabolite}}$$

Concentration (nM) of Antibody bound to 4 Metabolites1 in tumor extracellular space

$$\frac{d(Ab_{m4}^{ex})}{dt} = \underbrace{\left(\frac{Ab_{m4}^{C1}}{V_{ADC}^{C1}} - \frac{Ab_{m4}^{ex}}{\varepsilon^{ADC}}\right) \times \left(\frac{2\times P_{ADC}\times R_{Cap}}{R_{Krogh}^2} + \frac{6\times D_{ADC}}{R_{Tumor}^2}\right)}_{\text{From central space}}$$

$$+\underbrace{\left(-K_{on}^{ADC,cell,ag} \times \frac{Ab_{m4}^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - Ab_{f,b,ag}^{cell} - \sum_{i=1}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j\le max} Ab_{bi,mj,b,ag}^{cell}\right) + K_{off}^{ADC,cell,ag} \times \right.}_{\text{Binding and unbinding of ADC to receptors on tumor cell}}$$

$$\times \frac{NC^{tumor}\times SF}{V^{tumor}} + \underbrace{\frac{1}{\tau}\times V_{dyi,3,mm3}^{tumor}\times 10^5 \times \left(Ab_{m4,b,ag}^{cell} + Ab_{m4}^{cell,lyso}\right) \times \frac{SF}{V^{tumor}}}_{\text{From intracellular content of dying cells}} \underbrace{- K_{pino}^{ADC,cell,lyso}\times\left(\frac{NCL^{tumor}}{\varepsilon^{ADC}}\right)\times Ab_{m4}^{ex}}_{\text{To pinocytosis}}$$

$$\underbrace{+K_{on}^{Ab,Meta}\times\frac{Ab_{m3}^{ex}}{\varepsilon^{ADC}}\times\frac{Meta1_f^{ex}}{V^{tumor}}}_{\text{From binding to metabolite}} \underbrace{- K_{off}^{Ab,Meta}\times\frac{Ab_{m4}^{ex}}{\varepsilon^{ADC}}}_{\text{To unbinding of metabolite}}$$

Concentration (nM) of Antibody bound to i Protac and j Metabolites1 in tumor extracellular space, i = 1,2 and j = 1,2

$$\frac{d(Ab^{ex}_{bi,mj})}{dt} = \underbrace{\left(\frac{Ab^{C1}_{bi,mj}}{V^{C1}_{ADC}} - \frac{Ab^{ex}_{bi,mj}}{\varepsilon^{ADC}}\right) \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R^{2}_{Krogh}} + \frac{6 \times D_{ADC}}{R^{2}_{Tumor}}\right)}_{\text{From central space}}$$

$$+\Bigg(\underbrace{-K^{ADC,cell,ag}_{on} \times \frac{Ab^{ex}_{bi,mj}}{\varepsilon^{ADC}} \times \left(Ag^{cell}_{t} - Ab^{cell}_{f,b,ag} - \sum_{i=1}^{max} Ab^{cell}_{bi,b,ag} - \sum_{j=1}^{max} Ab^{cell}_{mj,b,ag} - \sum_{i,j=1}^{i+j\leq max} Ab^{cell}_{bi,mj,b,ag}\right) + K^{ADC,cell,ag}_{off} \times}_{\text{Binding and unbinding of ADC to receptors on tumor cell}}$$

$$\times \frac{NC^{tumor} \times SF}{V^{tumor}} + \underbrace{\frac{1}{\tau} \times V^{tumor}_{dyi,3,mm3} \times 10^{5} \times \left(Ab^{cell}_{bi,mj,b,ag} + Ab^{cell,lyso}_{bi,mj}\right) \times \frac{SF}{V^{tumor}}}_{\text{From intracellular content of dying cells}} \underbrace{- K^{ADC,cell,lyso}_{pino} \times \left(\frac{NCL^{tumor}}{\varepsilon^{ADC}}\right) \times Ab^{ex}_{bi,m}}_{\text{To pinocytosis}}$$

$$\underbrace{-K^{Ab,Drug}_{on} \times (max - i - j) \times \frac{Ab^{ex}_{bi,mj}}{\varepsilon^{ADC}} \times \frac{Drug^{ex}_{f}}{V^{tumor}}}_{\text{To binding to drug}} + \underbrace{K^{Ab,Drug}_{off} \times \frac{Ab^{ex}_{bi+1,mj}}{\varepsilon^{ADC}}}_{\text{From unbinding of drug}}$$

$$\underbrace{+K^{Ab,Drug}_{on} \times (max - i + 1 - j) \times \frac{Ab^{ex}_{bi-1,mj}}{\varepsilon^{ADC}} \times \frac{Drug^{ex}_{f}}{V^{tumor}}}_{\text{From binding to drug}} \underbrace{- K^{Ab,Drug}_{off} \times \frac{Ab^{ex}_{bi,mj}}{\varepsilon^{ADC}}}_{\text{To unbinding of drug}} \underbrace{- K^{Ab,Meta}_{on} \times (max - i - j) \times \frac{Ab^{ex}_{bi,mj}}{\varepsilon^{ADC}} \times \frac{M}{V}}_{\text{To binding to metabolite}}$$

$$+K^{Ab,Meta}_{off} \times \frac{Ab^{ex}_{bi,mj+1}}{\varepsilon^{ADC}} + K^{Ab,Meta}_{on} \times (max - i - j + 1) \times \frac{Ab^{ex}_{bi,mj-1}}{\varepsilon^{ADC}} \times \frac{Meta1^{ex}_{f}}{V^{tumor}} - K^{Ab,Meta}_{off} \times \frac{Ab^{ex}_{bi,mj}}{\varepsilon^{ADC}}$$

Concentration (nM) of Antibody bound to i Protac and j Metabolites1 in tumor extracellular space, i = 1,2,3 and j = 1,2,3 with i + j = max

$$\frac{d(Ab_{bi,mj}^{ex})}{dt} = \underbrace{\left(\frac{Ab_{bi,mj}^{C1}}{V_{ADC}^{C1}} - \frac{Ab_{bi,mj}^{ex}}{\varepsilon^{ADC}}\right) \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R_{Krogh}^{2}} + \frac{6 \times D_{ADC}}{R_{Tumor}^{2}}\right)}_{\text{From central space}}$$

$$+\left(\underbrace{-K_{on}^{ADC,cell,ag} \times \frac{Ab_{bi,mj}^{ex}}{\varepsilon^{ADC}} \times \left(Ag_{t}^{cell} - Ab_{f,b,ag}^{cell} - \sum_{i=1}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j\leq max} Ab_{bi,mj,b,ag}^{cell}\right) + K_{off}^{ADC,cell,ag}}_{\text{Binding and unbinding of ADC to receptors on tumor cell}} \times\right.$$

$$\times \frac{NC^{tumor} \times SF}{V^{tumor}} + \underbrace{\frac{1}{\tau} \times V_{dyi,3,mm3}^{tumor} \times 10^{5} \times \left(Ab_{bi,mj,b,ag}^{cell} + Ab_{bi,mj}^{cell,lyso}\right) \times \frac{SF}{V^{tumor}}}_{\text{From intracellular content of dying cells}} \underbrace{- K_{pino}^{ADC,cell,lyso} \times \left(\frac{NCL^{tumor}}{\varepsilon^{ADC}}\right) \times Ab_{bi,mj}^{ex}}_{\text{To pinocytosis}}$$

$$\underbrace{+K_{on}^{Ab,Drug} \times (max - i + 1 - j) \times \frac{Ab_{bi-1,mj}^{ex}}{\varepsilon^{ADC}} \times \frac{Drug_{f}^{ex}}{V^{tumor}}}_{\text{From binding to drug}} \underbrace{- K_{off}^{Ab,Drug} \times \frac{Ab_{bi,mj}^{ex}}{\varepsilon^{ADC}}}_{\text{To unbinding of drug}}$$

$$\underbrace{+K_{on}^{Ab,Meta} \times (max - i - j + 1) \times \frac{Ab_{bi,mj-1}^{ex}}{\varepsilon^{ADC}} \times \frac{Meta1_{f}^{ex}}{V^{tumor}}}_{\text{From binding to metabolite}} \underbrace{- K_{off}^{Ab,Meta} \times \frac{Ab_{bi,mj}^{ex}}{\varepsilon^{ADC}}}_{\text{To unbinding of metabolite}}$$

Amount (nmol) of drug in tumor extracellular space

$$\frac{d(Drug_f^{ex})}{dt} = \underbrace{\left(Drug_f^{C1} - \frac{Drug_f^{ex}}{V^{tumor} \times \varepsilon^{Drug}}\right) \times V^{tumor} \times \left(\frac{2 \times P_{Drug} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{Drug}}{R_{Tumor}^2}\right)}_{\text{From central space}} \underbrace{\cancel{+ K_{dec}^{ADC} \times \frac{ADC_f^{ex}}{\varepsilon^{ADC}} \times \overline{DAR} \times V^{tumor}}}_{\text{From non-specific deconjugation of ADC}}$$

$$\underbrace{\underbrace{+\left(\cancel{K_{dec}^{ADC} \times ADC_{b,ag}^{cell} \times \overline{DAR} +}\right.}_{\text{Non-specific deconj. of ADC}} \underbrace{\left. K_{out}^{Drug,ex} \times Drug_f^{cell,cyto}\right) \times NC^{tumor} \times SF}_{\text{Efflux of drug from the cell}}}_{\text{From cells}} \underbrace{- K_{met}^{Drug,ex} \times Drug_f^{ex}}_{\text{To metabolism}}$$

$$\underbrace{-K_{in}^{Drug,ex} \times NC^{tumor} \times \left(\frac{V^{cell}}{V^{tumor} \times \varepsilon^{Drug}}\right) \times Drug_f^{ex}}_{\text{To influx into cells}} \underbrace{+ \frac{1}{\tau} \times V_{dyi,3,mm3}^{tumor} \times 10^5 \times \left(\mathrm{Drug}_f^{cell,cyto} + Drug_{b,dt}^{cell,cyto} + \mathrm{Drug}_f^{cell,lyso}\right) \times SF}_{\text{From intracellular content of dying cells}}$$

Units:

$$\frac{nmol}{h} = \left(\frac{nmol}{l} - \frac{nmol}{l \times 1}\right) \times l \times \left(\frac{\frac{um}{h} \times um}{um^2} + \frac{cm^2/h}{cm^2}\right) + \frac{1}{h} \times \frac{nmol}{l} \times 1 \times l \quad + \left(\frac{1}{h} \times 1 \times 1 + \frac{1}{h} \times 1\right) \times 1 \times nmol$$

$$-\frac{1}{h} \times 1 \times \left(\frac{l}{l \times 1}\right) \times nmol + \frac{1}{h} \times mm^3 \times \frac{1}{mm^3} \times (1+1) \times nmol$$

Amount (nmol) of free (unbound) Metabolite1 in tumor extracellular space

$$\frac{d(Meta1_f^{ex})}{dt} = \underbrace{K_{met}^{Drug,ex} \times Drug_f^{ex}}_{\text{From metabolism}} + \underbrace{\left(Meta1_f^{C1} - \frac{Meta1_f^{ex}}{V^{tumor} \times \varepsilon^{Meta}}\right) \times V^{tumor} \times \left(\frac{2 \times P_{Meta} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{Meta}}{R_{Tumor}^2}\right)}_{\text{From central space}}$$

$$\underbrace{+K_{out}^{Meta,ex} \times Meta1_f^{cell,cyto} \times NC^{tumor} \times SF}_{\text{Fromm efflux of drug from the cell}} \underbrace{- K_{in}^{Meta,ex} \times NC^{tumor} \times \left(\frac{V^{cell}}{V^{tumor} \times \varepsilon^{Meta}}\right) \times Meta1_f^{ex}}_{\text{To influx into cells}}$$

$$\underbrace{+\frac{1}{\tau} \times V_{dyi,3,mm3}^{tumor} \times 10^5 \times \left(Meta1_f^{cell,cyto} + Meta1_f^{cell,lyso}\right) \times SF}_{\text{From intracellular content of dying cells}}$$

Units: $$\frac{nmol}{l \times h} = -\frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{l} - \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{l} + \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{l} + \frac{\frac{1}{h} \times \frac{nmol}{kg} \times 1}{l/kg} + \frac{\frac{l}{h}/kg \times 1 \times \frac{nmol/kg}{l/kg}}{l/kg}$$

$$-\left(\frac{nmol}{l} - \frac{nmol}{l \times 1}\right) \times \frac{l}{l/kg \times kg} \times \left(\frac{\frac{um}{h} \times um}{um^2} + \frac{cm^2/h}{cm^2}\right) \frac{1}{h} \times \frac{nmol}{l} + \frac{1}{h} \times 1 \times \frac{nmol}{l} + \frac{1}{h} \times 1 \times \frac{1 \times nmol}{kg \times \frac{l}{kg}} - \frac{1}{h} \times \frac{l \times 1}{kg \times \frac{l}{kg}} \times \frac{nmol}{l}$$

Amount (nmol) of free (unbound) Metabolite2 in tumor extracellular space

$$\frac{d(Meta2_f^{ex})}{dt} = \underbrace{K_{met}^{Drug,ex} \times Drug_f^{ex}}_{\text{From metabolism}} + \underbrace{\left(Meta2_f^{C1} - \frac{Meta2_f^{ex}}{V^{tumor} \times \varepsilon^{Meta}}\right) \times V^{tumor} \times \left(\frac{2 \times P_{Meta} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{Meta}}{R_{Tumor}^2}\right)}_{\text{From central space}}$$

$$\underbrace{+K_{out}^{Meta,ex} \times Meta2_f^{cell,cyto} \times NC^{tumor} \times SF}_{\text{Fromm efflux of drug from the cell}} \underbrace{- K_{in}^{Meta,ex} \times NC^{tumor} \times \left(\frac{V^{cell}}{V^{tumor} \times \varepsilon^{Meta}}\right) \times Meta2_f^{ex}}_{\text{To influx into cells}}$$

$$+\frac{1}{\tau} \underbrace{\times V_{dyi,3,mm3}^{tumor} \times 10^5 \times \left(Meta2_f^{cell,cyto} + Meta2_{b,dt}^{cell,cyto} + Meta2_f^{cell,lyso}\right) \times SF}_{\text{From intracellular content of dying cells}}$$

Units: $$\frac{nmol}{l \times h} = -\frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{l} - \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{l} + \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{l} + \frac{\frac{1}{h} \times \frac{nmol}{kg} \times 1}{l/kg} + \frac{\frac{l}{h}/kg \times 1 \times \frac{nmol/kg}{l/kg}}{l/kg}$$

$$- \left(\frac{nmol}{l} - \frac{nmol}{l \times 1}\right) \times \frac{l}{l/kg \times kg} \times \left(\frac{\frac{um}{h} \times um}{um^2} + \frac{cm^2/h}{cm^2}\right) \frac{1}{h} \times \frac{nmol}{l} + \frac{1}{h} \times 1 \times \frac{nmol}{l} + \frac{1}{h} \times 1 \times \frac{1 \times nmol}{kg \times \frac{l}{kg}} - \frac{1}{h} \times \frac{l \times 1}{kg \times \frac{l}{kg}} \times \frac{nmol}{l}$$

Number of free Antibody (bound to 0 Protacs) molecules bound to binding target on a single cell

$$\frac{d(Ab_{f,b,ag}^{cell})}{dt} = \underbrace{K_{on}^{ADC,cell,ag} \times \frac{Ab_f^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - Ab_{f,b,ag}^{cell} - \sum_{i=1}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j\le max} Ab_{bi,mj,b,ag}^{cell} \right)}_{\text{From binding to receptor}}$$

$$\underbrace{-K_{off}^{ADC,cell,ag} \times Ab_{f,b,ag}^{cell}}_{\text{To unbinding from receptor}} \underbrace{- K_{int}^{ADC,cell} \times Ab_{f,b,ag}^{cell}}_{\text{To internalization into cell}} \underbrace{- \frac{\ln(2)}{DT^{tumor}} \times Ab_{f,b,ag}^{cell}}_{\text{To dilution as cells grow and divide}} \underbrace{- K_{on}^{Ab,Drug} \times max \times Ab_{f,b,ag}^{cell} \times \frac{Drug_f^{ex}}{V^{tumor}}}_{\text{To binding to drug}}$$

$$\underbrace{+ K_{off}^{Ab,Drug} \times Ab_{b1,b,ag}^{cell}}_{\text{From unbinding of drug}} \underbrace{- K_{on}^{Ab,Meta} \times max \times Ab_{f,b,ag}^{cell} \times \frac{Meta1_f^{ex}}{V^{tumor}}}_{\text{To binding to metabolite}} \underbrace{+ K_{off}^{Ab,Meta} \times Ab_{m1,b,ag}^{cell}}_{\text{From unbinding of metabolite}}$$

Units: $\frac{1}{h} = \frac{1}{\frac{nmol}{l} \times h} \times \frac{nmol/l}{1} \times (1 - 1 - 1) - \frac{1}{h} \times 1 - \frac{1}{h} \times 1 - \frac{1}{h} \times 1 - \frac{1}{h} \times 1$

Number of Antibody molecules bound to i Protacs bound to binding target on a single cell, i = 1,2,3

$$\frac{d(Ab^{cell}_{bi,b,ag})}{dt} = \underbrace{K_{on}^{ADC,cell,ag} \times \frac{Ab^{ex}_{bi}}{\varepsilon^{ADC}} \times \left(Ag^{cell}_{t} - Ab^{cell}_{f,b,ag} - \sum_{i=1}^{max} Ab^{cell}_{bi,b,ag} - \sum_{j=1}^{max} Ab^{cell}_{mj,b,ag} - \sum_{i,j=1}^{i+j\le max} Ab^{cell}_{bi,mj,b,ag} \right)}_{\text{From binding to receptor}}$$

$$\underbrace{-K_{off}^{ADC,cell,ag} \times Ab^{cell}_{bi,b,ag}}_{\text{To unbinding from receptor}} \underbrace{- K_{int}^{ADC,cell} \times Ab^{cell}_{bi,b,ag}}_{\text{To internalization into cell}} \underbrace{- \frac{\ln(2)}{DT^{tumor}} \times Ab^{cell}_{bi,b,ag}}_{\text{To dilution as cells grow and divide}} \underbrace{- K_{on}^{Ab,Drug} \times (max - i) \times Ab^{cell}_{bi,b,ag} \times \frac{Drug^{ex}_{f}}{V^{tumor}}}_{\text{To binding to drug}}$$

$$\underbrace{+K_{off}^{Ab,Drug} \times Ab^{cell}_{bi+1,b,ag}}_{\text{From unbinding of drug}} \underbrace{+ K_{on}^{Ab,Drug} \times (max - i + 1) \times Ab^{cell}_{bi-1,b,ag} \times \frac{Drug^{ex}_{f}}{V^{tumor}}}_{\text{From binding to drug}} \underbrace{- K_{off}^{Ab,Drug} \times Ab^{cell}_{bi,b,ag}}_{\text{To unbinding of drug}}$$

$$\underbrace{-K_{on}^{Ab,Meta} \times (max - i) \times Ab^{cell}_{bi,b,ag} \times \frac{Meta1^{ex}_{f}}{V^{tumor}}}_{\text{To binding to metabolite}} \underbrace{+ K_{off}^{Ab,Meta} \times Ab^{cell}_{bi,m1,b,ag}}_{\text{From unbinding of metabolite}}$$

Units: $\frac{1}{h} = \frac{1}{\frac{nmol}{l} \times h} \times \frac{nmol/l}{1} \times (1 - 1 - 1) - \frac{1}{h} \times 1 - \frac{1}{h} \times 1 - \frac{1}{h} \times 1 - \frac{1}{h} \times 1$

Number of Antibody molecules bound to 4 Protacs bound to binding target on a single cell

$$\frac{d(Ab_{b4,b,ag}^{cell})}{dt} = \underbrace{K_{on}^{ADC,cell,ag} \times \frac{Ab_{b4}^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - Ab_{f,b,ag}^{cell} - \sum_{i=1}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j\leq max} Ab_{bi,mj,b,ag}^{cell} \right)}_{\text{From binding to receptor}}$$

$$\underbrace{-K_{off}^{ADC,cell,ag} \times Ab_{b4,b,ag}^{cell}}_{\text{To unbinding from receptor}} \underbrace{- K_{int}^{ADC,cell} \times Ab_{b4,b,ag}^{cell}}_{\text{To internalization into cell}} \underbrace{- \frac{\ln(2)}{DT^{tumor}} \times Ab_{b4,b,ag}^{cell}}_{\text{To dilution as cells grow and divide}}$$

$$\underbrace{+K_{on}^{Ab,Drug} \times Ab_{b3,b,ag}^{cell} \times \frac{Drug_f^{ex}}{V^{tumor}}}_{\text{From binding to drug}} \underbrace{- K_{off}^{Ab,Drug} \times Ab_{b4,b,ag}^{cell}}_{\text{To unbinding of drug}}$$

Units: $$\frac{1}{h} = \frac{1}{\frac{nmol}{l} \times h} \times \frac{nmol/l}{1} \times (1 - 1 - 1) - \frac{1}{h} \times 1 - \frac{1}{h} \times 1 - \frac{1}{h} \times 1 - \frac{1}{h} \times 1$$

Number of Antibody molecules bound to j Metabolites1 bound to binding target on a single cell, j = 1,2,3

$$\frac{d(Ab_{mj,b,ag}^{cell})}{dt} = \underbrace{K_{on}^{ADC,cell,ag} \times \frac{Ab_{mj}^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - Ab_{f,b,ag}^{cell} - \sum_{i=1}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j\leq max} Ab_{bi,mj,b,ag}^{cell} \right)}_{\text{From binding to receptor}}$$

$$\underbrace{-K_{off}^{ADC,cell,ag} \times Ab_{mj,b,ag}^{cell}}_{\text{To unbinding from receptor}} \underbrace{- K_{int}^{ADC,cell} \times Ab_{mj,b,ag}^{cell}}_{\text{To internalization into cell}} \underbrace{- \frac{\ln(2)}{DT^{tumor}} \times Ab_{mj,b,ag}^{cell}}_{\text{To dilution as cells grow and divide}} \underbrace{- K_{on}^{Ab,Drug} \times (max - j) \times Ab_{mj,b,ag}^{cell} \times \frac{Drug_f^{ex}}{V^{tumor}}}_{\text{From binding to drug}}$$

$$\underbrace{+K_{off}^{Ab,Drug} \times Ab_{b1,mj,b,ag}^{cell}}_{\text{To unbinding of drug}} \underbrace{+ K_{on}^{Ab,Meta} \times (max - j + 1) \times Ab_{mj-1,b,ag}^{cell} \times \frac{Meta1_f^{ex}}{V^{tumor}}}_{\text{From binding to metabolite}}$$

$$\underbrace{-K_{off}^{Ab,Meta} \times Ab_{mj,b,ag}^{cell}}_{\text{To unbinding of metabolite}} \underbrace{- K_{on}^{Ab,Meta} \times (max - j) \times Ab_{mj,b,ag}^{cell} \times \frac{Meta1_f^{ex}}{V^{tumor}}}_{\text{To binding to metabolite}} \underbrace{+ K_{off}^{Ab,Meta} \times Ab_{mj+1,b,ag}^{cell}}_{\text{From unbinding of metabolite}}$$

Number of Antibody molecules bound to 4 Metabolites1 bound to binding target on a single cell

$$\frac{d(Ab^{cell}_{m4,b,ag})}{dt} = \underbrace{K^{ADC,cell,ag}_{on} \times \frac{Ab^{ex}_{m4}}{\varepsilon^{ADC}} \times \left(Ag^{cell}_{t} - Ab^{cell}_{f,b,ag} - \sum_{i=1}^{max} Ab^{cell}_{bi,b,ag} - \sum_{j=1}^{max} Ab^{cell}_{mj,b,ag} - \sum_{i,j=1}^{i+j\leq max} Ab^{cell}_{bi,mj,b,ag} \right)}_{\text{From binding to receptor}}$$

$$\underbrace{-K^{ADC,cell,ag}_{off} \times Ab^{cell}_{m4,b,ag}}_{\text{To unbinding from receptor}} \underbrace{- K^{ADC,cell}_{int} \times Ab^{cell}_{m4,b,ag}}_{\text{To internalization into cell}} \underbrace{- \frac{\ln(2)}{DT^{tumor}} \times Ab^{cell}_{m4,b,ag}}_{\text{To dilution as cells grow and divide}}$$

$$\underbrace{+K^{Ab,Meta}_{on} \times Ab^{cell}_{m3,b,ag} \times \frac{Meta1^{ex}_{f}}{V^{tumor}}}_{\text{From binding to metabolite}} \underbrace{- K^{Ab,Meta}_{off} \times Ab^{cell}_{m4,b,ag}}_{\text{To unbinding of metabolite}}$$

Number of Antibody molecules bound i Protacs and j Metabolites1 bound to binding target on a single cell, i = 1,2 and j = 1,2

$$\frac{d(Ab^{cell}_{bi,mj,b,ag})}{dt} = \underbrace{K_{on}^{ADC,cell,ag} \times \frac{Ab^{ex}_{bi,mj}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - Ab^{cell}_{f,b,ag} - \sum_{i=1}^{max} Ab^{cell}_{bi,b,ag} - \sum_{j=1}^{max} Ab^{cell}_{mj,b,ag} - \sum_{i,j=1}^{i+j\leq max} Ab^{cell}_{bi,mj,b,ag} \right)}_{\text{From binding to receptor}}$$

$$\underbrace{-K_{off}^{ADC,cell,ag} \times Ab^{cell}_{bi,mj,b,ag}}_{\text{To unbinding from receptor}} \underbrace{- K_{int}^{ADC,cell} \times Ab^{cell}_{bi,mj,b,ag}}_{\text{To internalization into cell}} \underbrace{- \frac{\ln(2)}{DT^{tumor}} \times Ab^{cell}_{bi,mj,b,ag}}_{\text{To dilution as cells grow and divide}}$$

$$\underbrace{-K_{on}^{Ab,Drug} \times (max - i - j) \times Ab^{cell}_{bi,mj,b,ag} \times \frac{Drug_f^{ex}}{V^{tumor}}}_{\text{To binding to drug}} \underbrace{+ K_{off}^{Ab,Drug} \times Ab^{cell}_{bi+1,mj,b,ag}}_{\text{From unbinding of drug}} \underbrace{- K_{off}^{Ab,Drug} \times Ab^{cell}_{bi,mj,b,ag}}_{\text{To unbinding of drug}}$$

$$\underbrace{+K_{on}^{Ab,Drug} \times (max - i + 1 - j) \times Ab^{cell}_{bi-1,mj,b,ag} \times \frac{Drug_f^{ex}}{V^{tumor}}}_{\text{From binding to drug}} \underbrace{- K_{on}^{Ab,Meta} \times (max - i - j) \times Ab^{cell}_{bi,mj,b,ag} \times \frac{Meta1_f^{ex}}{V^{tumor}}}_{\text{To binding to metabolite}}$$

$$\underbrace{+K_{off}^{Ab,Meta} \times Ab^{cell}_{bi,mj+1,b,ag}}_{\text{From unbinding of metabolite}} \underbrace{+ K_{on}^{Ab,Meta} \times (max - i - j + 1) \times Ab^{cell}_{bi,mj-1,b,ag} \times \frac{Meta1_f^{ex}}{V^{tumor}}}_{\text{From binding to metabolite}} \underbrace{- K_{off}^{Ab,Meta} \times Ab^{cell}_{bi,mj,b,ag}}_{\text{To unbinding of metabolite}}$$

Number of Antibody molecules bound i Protacs and j Metabolites1 bound to binding target on a single cell, i = 1,2,3 and j = 1,2,3 with i + j = max

$$\frac{d(Ab_{bi,mj,b,ag}^{cell})}{dt} = \underbrace{K_{on}^{ADC,cell,ag} \times \frac{Ab_{bi,mj}^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - Ab_{f,b,ag}^{cell} - \sum_{i=1}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j\leq max} Ab_{bi,mj,b,ag}^{cell} \right)}_{\text{From binding to receptor}}$$

$$\underbrace{-K_{off}^{ADC,cell,ag} \times Ab_{bi,mj,b,ag}^{cell}}_{\text{To unbinding from receptor}} \underbrace{- K_{int}^{ADC,cell} \times Ab_{bi,mj,b,ag}^{cell}}_{\text{To internalization into cell}} \underbrace{- \frac{\ln(2)}{DT^{tumor}} \times Ab_{bi,mj,b,ag}^{cell}}_{\text{To dilution as cells grow and divide}}$$

$$\underbrace{+K_{on}^{Ab,Drug} \times (max - i + 1 - j) \times Ab_{bi-1,mj,b,ag}^{cell} \times \frac{Drug_f^{ex}}{V^{tumor}}}_{\text{From binding to drug}} \underbrace{- K_{off}^{Ab,Drug} \times Ab_{bi,mj,b,ag}^{cell}}_{\text{To unbinding of drug}}$$

$$\underbrace{+K_{on}^{Ab,Meta} \times (max - i - j + 1) \times Ab_{bi,mj-1,b,ag}^{cell} \times \frac{Meta1_f^{ex}}{V^{tumor}}}_{\text{From binding to metabolite}} \underbrace{- K_{off}^{Ab,Meta} \times Ab_{bi,mj,b,ag}^{cell}}_{\text{To unbinding of metabolite}}$$

Number of Antibody molecules bound to i Protacs internalized in endosomal/lysosomal space on a single cell, i = 1,2,3,4

$$\frac{d(Ab_{bi}^{cell,lyso})}{dt} = \underbrace{K_{int}^{ADC,cell} \times Ab_{bi,b,ag}^{cell}}_{\text{From internalization into cell}}$$

$$\underbrace{-K_{deg}^{ADC} \times Ab_{bi}^{cell,lyso}}_{\text{To degradation}} \underbrace{+ K_{pino}^{ADC,cell,lyso} \times \frac{Ab_{bi}^{ex}}{\varepsilon^{ADC} \times SF}}_{\text{From pinocytosis}} \underbrace{- \frac{\ln(2)}{DT^{tumor}} \times Ab_{bi}^{cell,lyso}}_{\text{To dilution as cells grow and divide}}$$

Units: $\frac{1}{h} = \quad \frac{1}{h} \times 1 \quad -\frac{1}{h} \times 1 \quad +\frac{l}{h} \times \frac{nmol/l}{1 \times nmol} \quad -\frac{1}{h} \times 1$

Number of Antibody molecules bound to j Metabolites1 internalized in endosomal/lysosomal space on a single cell, j = 1,2,3,4

$$\frac{d(Ab_{mj}^{cell,lyso})}{dt} = \underbrace{K_{int}^{ADC,cell} \times Ab_{mj,b,ag}^{cell}}_{\text{From internalization into cell}}$$

$$\underbrace{-K_{deg}^{ADC} \times Ab_{mj}^{cell,lyso}}_{\text{To degradation}} \underbrace{+ K_{pino}^{ADC,cell,lyso} \times \frac{Ab_{mj}^{ex}}{\varepsilon^{ADC} \times SF}}_{\text{From pinocytosis}} \underbrace{- \frac{\ln(2)}{DT^{tumor}} \times Ab_{mj}^{cell,lyso}}_{\text{To dilution as cells grow and divide}}$$

Units: $\frac{1}{h} = \quad \frac{1}{h} \times 1 \quad - \frac{1}{h} \times 1 \quad + \frac{l}{h} \times \frac{nmol/l}{1 \times nmol} \quad - \frac{1}{h} \times 1$

Number of Antibody molecules bound to i Protacs and j Metabolites1 internalized in endosomal/lysosomal space on a single cell, i = 1,2,3,4 and j = 1,2,3,4 with i + j <= max

$$\frac{d(Ab_{bi,mj}^{cell,lyso})}{dt} = \underbrace{K_{int}^{ADC,cell} \times Ab_{bi,mj,b,ag}^{cell}}_{\text{From internalization into cell}}$$

$$\underbrace{-K_{deg}^{ADC} \times Ab_{bi,mj}^{cell,lyso}}_{\text{To degradation}} \underbrace{+ K_{pino}^{ADC,cell,lyso} \times \frac{Ab_{bi,mj}^{ex}}{\varepsilon^{ADC} \times SF}}_{\text{From pinocytosis}} \underbrace{- \frac{\ln(2)}{DT^{tumor}} \times Ab_{bi,mj}^{cell,lyso}}_{\text{To dilution as cells grow and divide}}$$

Units: $\frac{1}{h} = \quad \frac{1}{h} \times 1 \quad - \frac{1}{h} \times 1 \quad + \frac{l}{h} \times \frac{nmol/l}{1 \times nmol} \quad - \frac{1}{h} \times 1$

Number of free (unbound) drug molecules in endosomal/lysosomal space on a single cell

$$\frac{d(Drug_f^{cell,lyso})}{dt} = \underbrace{\sum_{i,j=1}^{max} K_{deg}^{ADC} \times \left(Ab_{bi}^{cell,lyso} + Ab_{bi,mj}^{cell,lyso}\right) \times i}_{\text{From degradation of ADC}} - \underbrace{K_{out}^{Drug,lyso} \times \left(\frac{V^{cell}}{V^{cell,lyso}}\right) \times Drug_f^{cell,lyso}}_{\text{To cytosol}}$$

$$+\underbrace{K_{in}^{Drug,lyso} \times Drug_f^{cell,cyto}}_{\text{From cytosol}} - \underbrace{\frac{\ln(2)}{DT^{tumor}} \times Drug_f^{cell,lyso}}_{\text{To dilution as cells grow and divide}} - \underbrace{K_{met}^{Drug,cell} \times Drug_f^{cell,lyso}}_{\text{To metabolism}}$$

Units:

$$\frac{1}{h} = \frac{1}{h} \times (1+1) \quad -\frac{1}{h} \times \left(\frac{l}{l}\right) \times 1 \quad +\frac{1}{h} \times 1 \quad -\frac{1}{h} \times 1$$

Number of free (unbound) Metabolite1 molecules in endosomal/lysosomal space on a single cell

$$\frac{d(Meta1_f^{cell,lyso})}{dt} = \underbrace{\sum_{i,j=1}^{max} K_{deg}^{ADC} \times \left(Ab_{mj}^{cell,lyso} + Ab_{bi,mj}^{cell,lyso}\right) \times j}_{\text{From degradation of ADC}} - \underbrace{K_{out}^{Meta,lyso} \times \left(\frac{V^{cell}}{V^{cell,lyso}}\right) \times Meta1_f^{cell,lyso}}_{\text{To cytosol}}$$

$$+\underbrace{K_{in}^{Meta,lyso} \times Meta1_f^{cell,cyto}}_{\text{From cytosol}} - \underbrace{\frac{\ln(2)}{DT^{tumor}} \times Meta1_f^{cell,lyso}}_{\text{To dilution as cells grow and divide}} + \underbrace{K_{met}^{Drug,cell} \times Drug_f^{cell,lyso}}_{\text{From metabolism}}$$

Units:

$$\frac{1}{h} = \frac{1}{h} \times (1+1) \quad -\frac{1}{h} \times \left(\frac{l}{l}\right) \times 1 \quad +\frac{1}{h} \times 1 \quad -\frac{1}{h} \times 1$$

Number of free (unbound) Metabolite2 molecules in endosomal/lysosomal space on a single cell

$$\frac{d(Meta2_f^{cell,lyso})}{dt} = \underbrace{-K_{out}^{Meta,lyso} \times \left(\frac{V^{cell}}{V^{cell,lyso}}\right) \times Meta2_f^{cell,lyso}}_{\text{To cytosol}}$$

$$\underbrace{+K_{in}^{Meta,lyso} \times Meta2_f^{cell,cyto}}_{\text{From cytosol}} \underbrace{- \frac{\ln(2)}{DT^{tumor}} \times Meta2_f^{cell,lyso}}_{\text{To dilution as cells grow and divide}} \underbrace{+ K_{met}^{Drug,cell} \times Drug_f^{cell,lyso}}_{\text{From metabolism}}$$

Units:

$$\frac{1}{h} = \frac{1}{h} \times (1 + 1) \quad - \frac{1}{h} \times \left(\frac{l}{l}\right) \times 1 \quad + \frac{1}{h} \times 1 \quad - \frac{1}{h} \times 1$$

Number of free (unbound) drug molecules in cytosol on a single cell

$$\frac{d(Drug_f^{cell,cyto})}{dt} = \underbrace{+K_{out}^{Drug,lyso} \times \left(\frac{V^{cell}}{V^{cell,lyso}}\right) \times Drug_f^{cell,lyso} - K_{in}^{Drug,lyso} \times Drug_f^{cell,cyto}}_{\text{From and to lysosome}} \underbrace{- K_{out}^{Drug,ex} \times Drug_f^{cell,cyto}}_{\text{To efflux}}$$

$$\underbrace{- \frac{K_{on}^{Drug,cyto,dt} \times SF}{V^{cell}} \times Drug_f^{cell,cyto} \times \left(\frac{DrugTarget_t^{cell,cyto} \times V^{cell}}{SF} - Drug_{b,dt}^{cell,cyto} - Meta2_{b,dt}^{cell,cyto}\right)}_{\text{To binding to drug target}} \underbrace{- K_{met}^{Drug} \times Drug_f^{cell,cyto}}_{\text{To metabolism}}$$

$$\underbrace{+K_{off}^{Drug,cyto,dt} \times Drug_{b,dt}^{cell,cyto}}_{\text{From unbinding from drug target}} \underbrace{+ K_{in}^{Drug,ex} \times \left(\frac{V^{cell}}{V^{tumor} \times \varepsilon^{Drug}}\right) \times \frac{Drug_f^{ex}}{SF}}_{\text{From influx}} \underbrace{- \frac{\ln(2)}{DT^{tumor}} \times Drug_f^{cell,cyto}}_{\text{To dilution as cells grow and divide}}$$

$$\underbrace{-K_{met}^{Drug,cell} \times Drug_f^{cell,cyto}}_{\text{To metabolism}}$$

Number of free (unbound) Metabolite1 molecules in cytosol on a single cell

$$\frac{d(Meta1_f^{cell,cyto})}{dt} = \underbrace{+K_{out}^{Meta,lyso} \times \left(\frac{V^{cell}}{V^{cell,lyso}}\right) \times Meta1_f^{cell,lyso} - K_{in}^{Meta,lyso} \times Meta1_f^{cell,cyto}}_{\text{From and to lysosome}}$$

$$\underbrace{-K_{out}^{Meta,ex} \times Meta1_f^{cell,cyto}}_{\text{To efflux}} + \underbrace{K_{in}^{Meta,ex} \times \left(\frac{V^{cell}}{V^{tumor} \times \varepsilon^{Meta}}\right) \times \frac{Meta1_f^{ex}}{SF}}_{\text{From influx}} \underbrace{- \frac{\ln(2)}{DT^{tumor}} \times Meta1_f^{cell,cyto}}_{\text{To dilution as cells grow and divide}}$$

$$\underbrace{+K_{met}^{Drug,cell} \times Drug_f^{cell,cyto}}_{\text{From metabolism}}$$

Number of free (unbound) Metabolite2 molecules in cytosol on a single cell

$$\frac{d(Meta2_f^{cell,cyto})}{dt} = \underbrace{+K_{out}^{Meta,lyso} \times \left(\frac{V^{cell}}{V^{cell,lyso}}\right) \times Meta2_f^{cell,lyso} - K_{in}^{Meta,lyso} \times Meta2_f^{cell,cyto}}_{\text{From and to lysosome}}$$

$$\underbrace{-\frac{K_{on}^{Meta,cyto,dt} \times SF}{V^{cell}} \times Meta2_f^{cell,cyto} \times \left(\frac{DrugTarget_t^{cell,cyto} \times V^{cell}}{SF} - Drug_{b,dt}^{cell,cyto} - Meta2_{b,dt}^{cell,cyto}\right)}_{\text{To binding to drug target}}$$

$$\underbrace{+K_{off}^{Meta,cyto,dt} \times Meta2_{b,dt}^{cell,cyto}}_{\text{From unbinding from drug target}} \underbrace{- K_{out}^{Meta,ex} \times Meta2_f^{cell,cyto}}_{\text{To efflux}} \underbrace{+ K_{in}^{Meta,ex} \times \left(\frac{V^{cell}}{V^{tumor} \times \varepsilon^{Meta}}\right) \times \frac{Meta2_f^{ex}}{SF}}_{\text{From influx}}$$

$$\underbrace{-\frac{\ln(2)}{DT^{tumor}} \times Meta2_f^{cell,cyto}}_{\text{To dilution as cells grow and divide}} \underbrace{+ K_{met}^{Drug,cell} \times Drug_f^{cell,cyto}}_{\text{From metabolism}}$$

Number of target-bound drug molecules in cytosol on a single cell

$$\frac{d(Drug_{b,dt}^{cell,cyto})}{dt} = \underbrace{\frac{K_{on}^{Drug,cyto,dt} \times SF}{V^{cell}} \times Drug_f^{cell,cyto} \times \left(\frac{DrugTarget_t^{cell,cyto} \times V^{cell}}{SF} - Drug_{b,dt}^{cell,cyto} - Meta2_{b,dt}^{cell,cyto}\right)}_{\text{From binding to drug target}}$$

$$\underbrace{-K_{off}^{Drug,cyto,dt} \times Drug_{b,dt}^{cell,cyto}}_{\text{To unbinding from drug target}} \underbrace{- \frac{\ln(2)}{DT^{tumor}} \times Drug_{b,dt}^{cell,cyto}}_{\text{To dilution as cells grow and divide}}$$

Units: $\frac{1}{h} = \frac{1}{h} \times 1 \times (1 - 1) \quad - \frac{1}{h} \times 1 \quad - \frac{1}{h} \times 1$

Number of target-bound Metabolite2 molecules in cytosol on a single cell

$$\frac{d(Meta2_{b,dt}^{cell,cyto})}{dt} = \underbrace{\frac{K_{on}^{Meta,cyto,dt} \times SF}{V^{cell}} \times Meta2_{f}^{cell,cyto} \times \left(\frac{DrugTarget_{t}^{cell,cyto} \times V^{cell}}{SF} - Drug_{b,dt}^{cell,cyto} - Meta2_{b,dt}^{cell,cyto}\right)}_{\text{From binding to drug target}}$$

$$\underbrace{-K_{off}^{Meta,cyto,dt} \times Meta2_{b,dt}^{cell,cyto}}_{\text{To unbinding from drug target}} \underbrace{- \frac{\ln(2)}{DT^{tumor}} \times Meta2_{b,dt}^{cell,cyto}}_{\text{To dilution as cells grow and divide}}$$

Units: $\frac{1}{h} = \frac{1}{h} \times 1 \times (1 - 1) \quad - \frac{1}{h} \times 1 \quad - \frac{1}{h} \times 1$

Tumor volume

$$V_{mm3}^{tumor} = V_{pro,mm3}^{tumor} + V_{dyi,1,mm3}^{tumor} + V_{dyi,2,mm3}^{tumor} + V_{dyi,3,mm3}^{tumor}$$

$$\frac{\mathrm{d}(V_{pro,mm3}^{tumor})}{\mathrm{dt}} = \left(\frac{\frac{\ln(2)}{\mathrm{DT}^{tumor}} \times \left(1 - \frac{V_{pro,mm3}^{tumor}}{V_{max}^{tumor}}\right)}{\left(1 + \left(\frac{\ln(2)}{\mathrm{DT}^{tumor}} \times \frac{V_{pro,mm3}^{tumor}}{k_{lin}}\right)^{\psi}\right)^{\frac{1}{\psi}}} - \mathrm{R_{Kill}} \right) \cdot V_{pro,mm3}^{tumor}$$

$$\frac{\mathrm{d}(V_{dyi,1,mm3}^{tumor})}{\mathrm{dt}} = \mathrm{R_{Kill}} \cdot V_{pro,mm3}^{tumor} - \frac{1}{\tau} \cdot V_{dyi,1,mm3}^{tumor}$$

$$\frac{\mathrm{d}(V_{dyi,2,mm3}^{tumor})}{\mathrm{dt}} = \frac{1}{\tau} \cdot (V_{dyi,1,mm3}^{tumor} - V_{dyi,2,mm3}^{tumor})$$

$$\frac{\mathrm{d}(V_{dyi,3,mm3}^{tumor})}{\mathrm{dt}} = \frac{1}{\tau} \cdot (V_{dyi,2,mm3}^{tumor} - V_{dyi,3,mm3}^{tumor})$$

Logistic (Thomas Rysiok)

$$t_l = \ln\left(\frac{Drug_f^{cell,cyto} \times SF}{V^{cell}}\right) - \ln(EC_{50})$$

$$LOGI = \frac{k_g}{1 + (\frac{k_g}{k_z} - 1) \times e^{-k_r \times k_g \times t_l}}$$

$$R_{kill} = k_{kill,\,max} \times \left(\frac{\ln(2)}{\mathrm{DT}^{tumor}}\right)^{f\_DT\_kill} \times LOGI$$