PROxAb Shuttle in-vivo

2024-06-03 Created
2024-06-14 Add metabolites
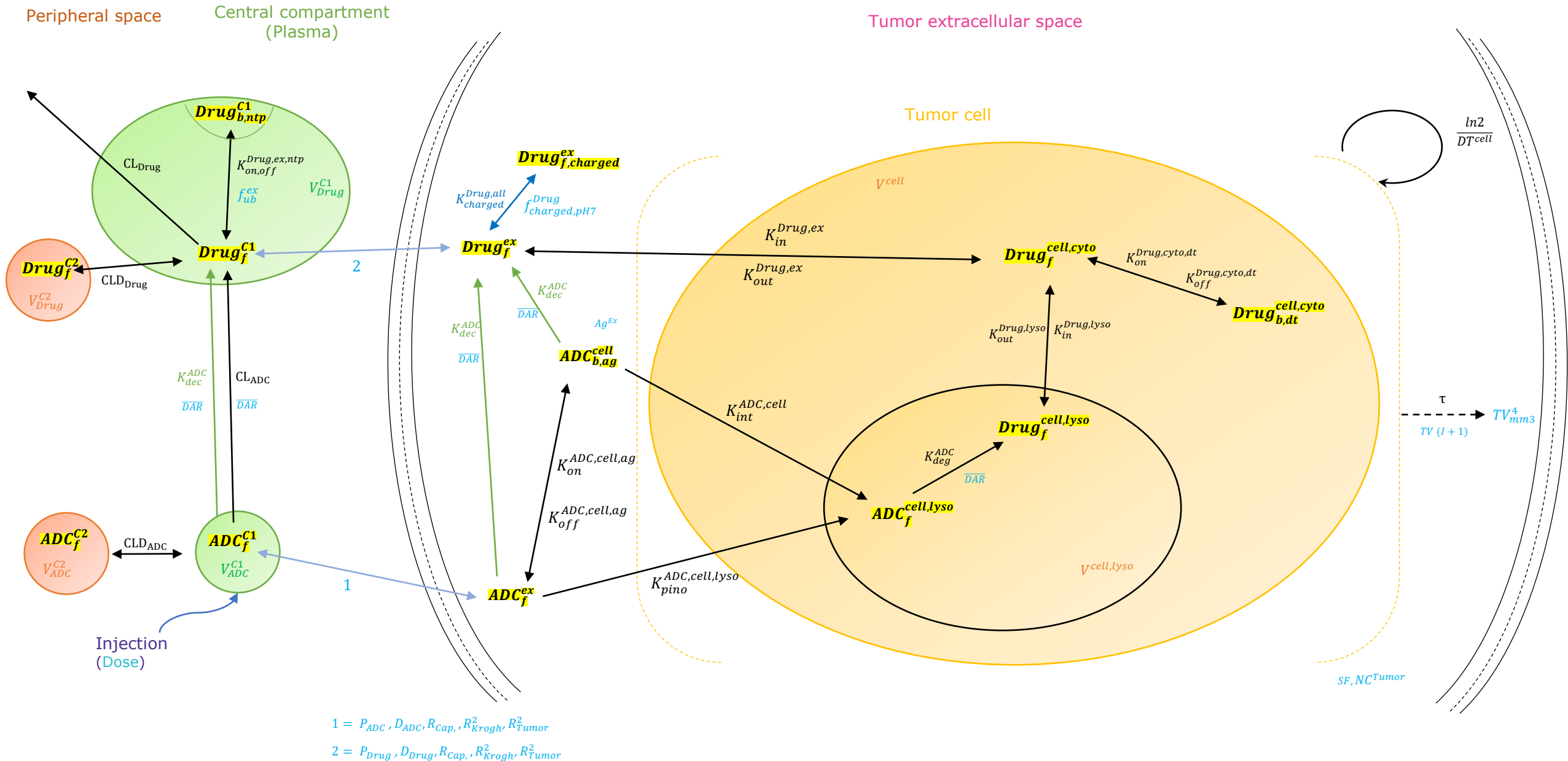2024-08-09 Add ADC with 2 free arms
2024-08-09 MoA Protacs (ubiquitination in 1 step)

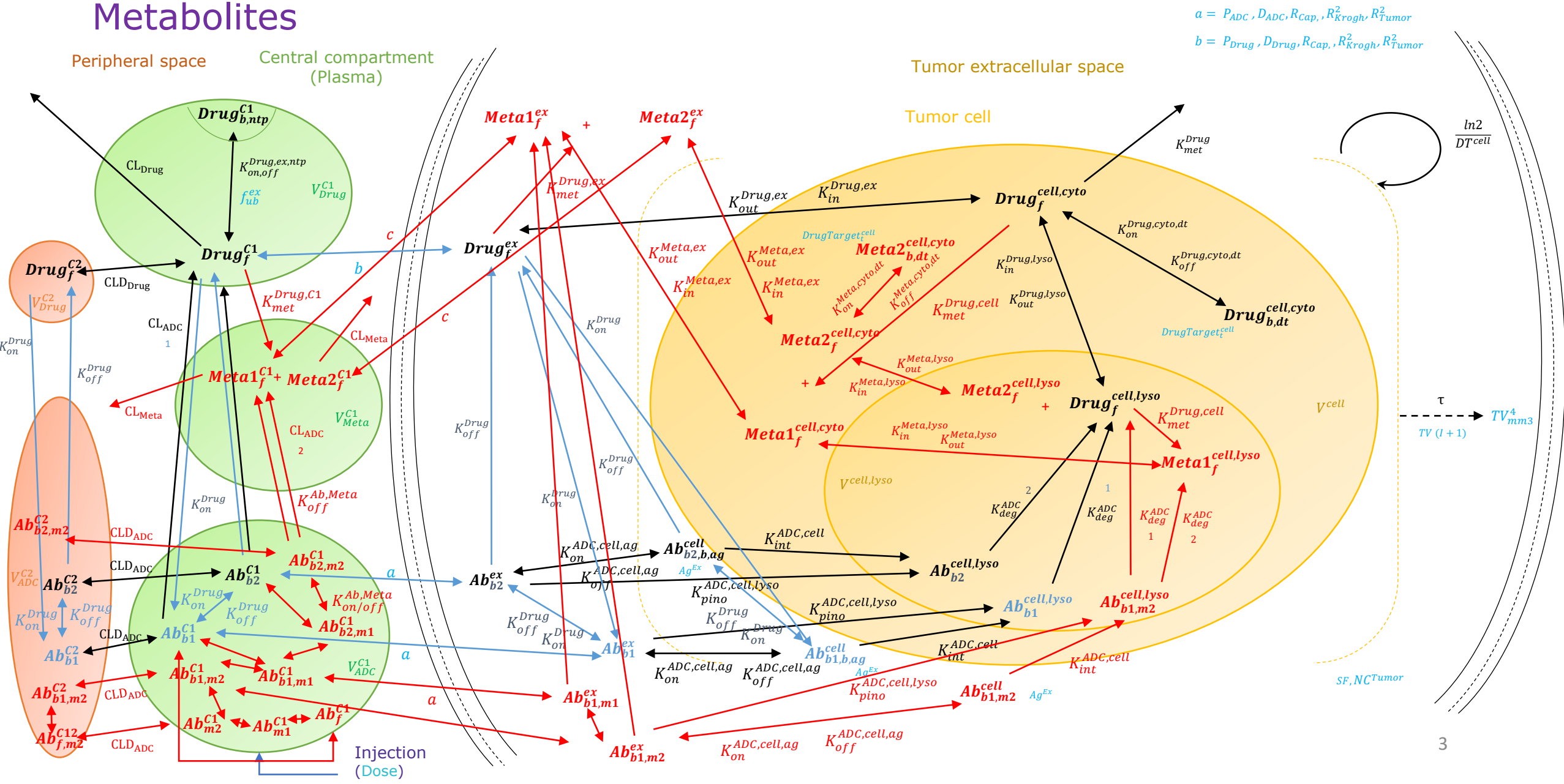!! Be aware app parameters labeled with Ab correspond to those in this presentation labeled with ADC !! E.g.

presentation CL_{ADC} = CL_{Ab} app
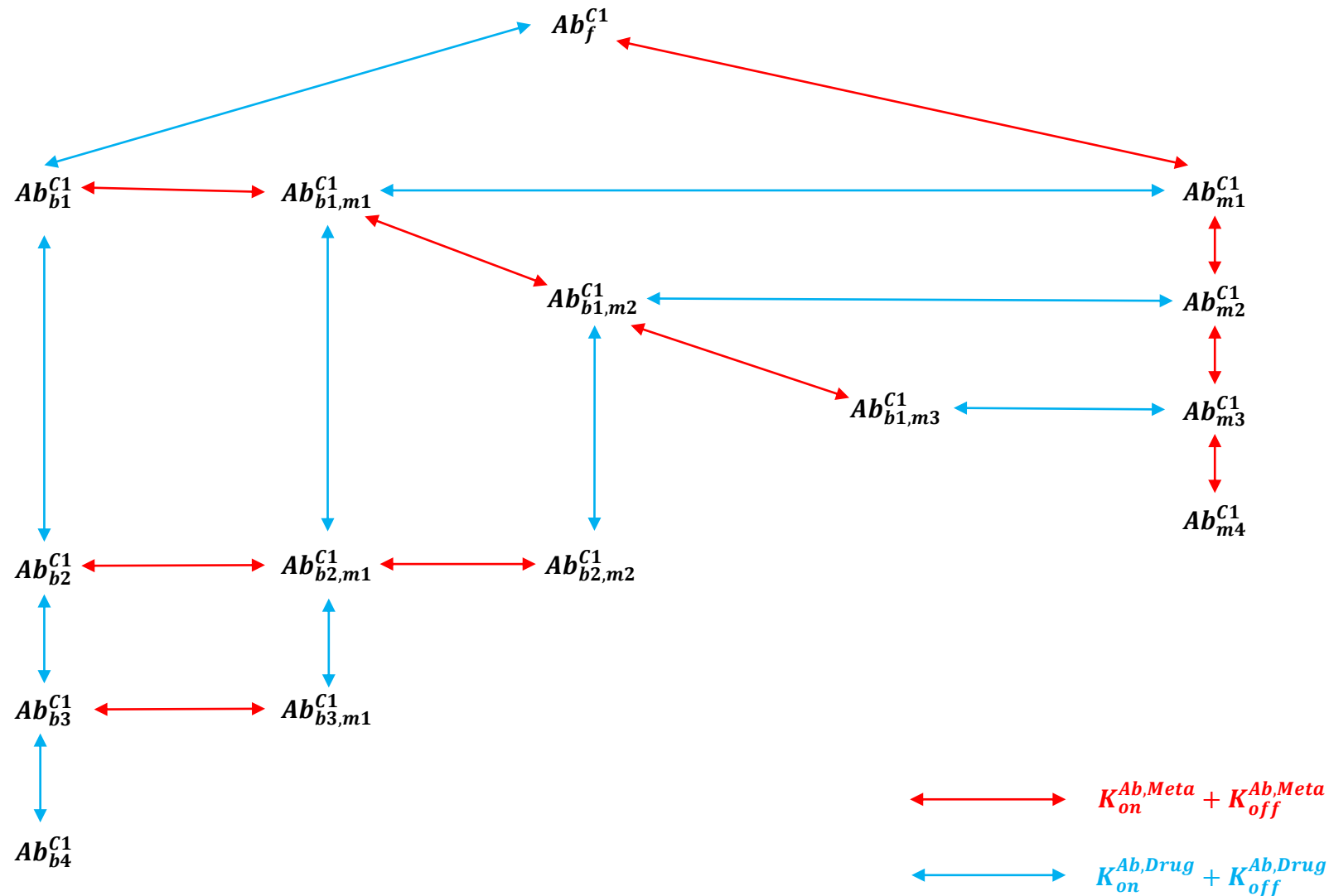
Mathematical description of mechanisms in-vivo
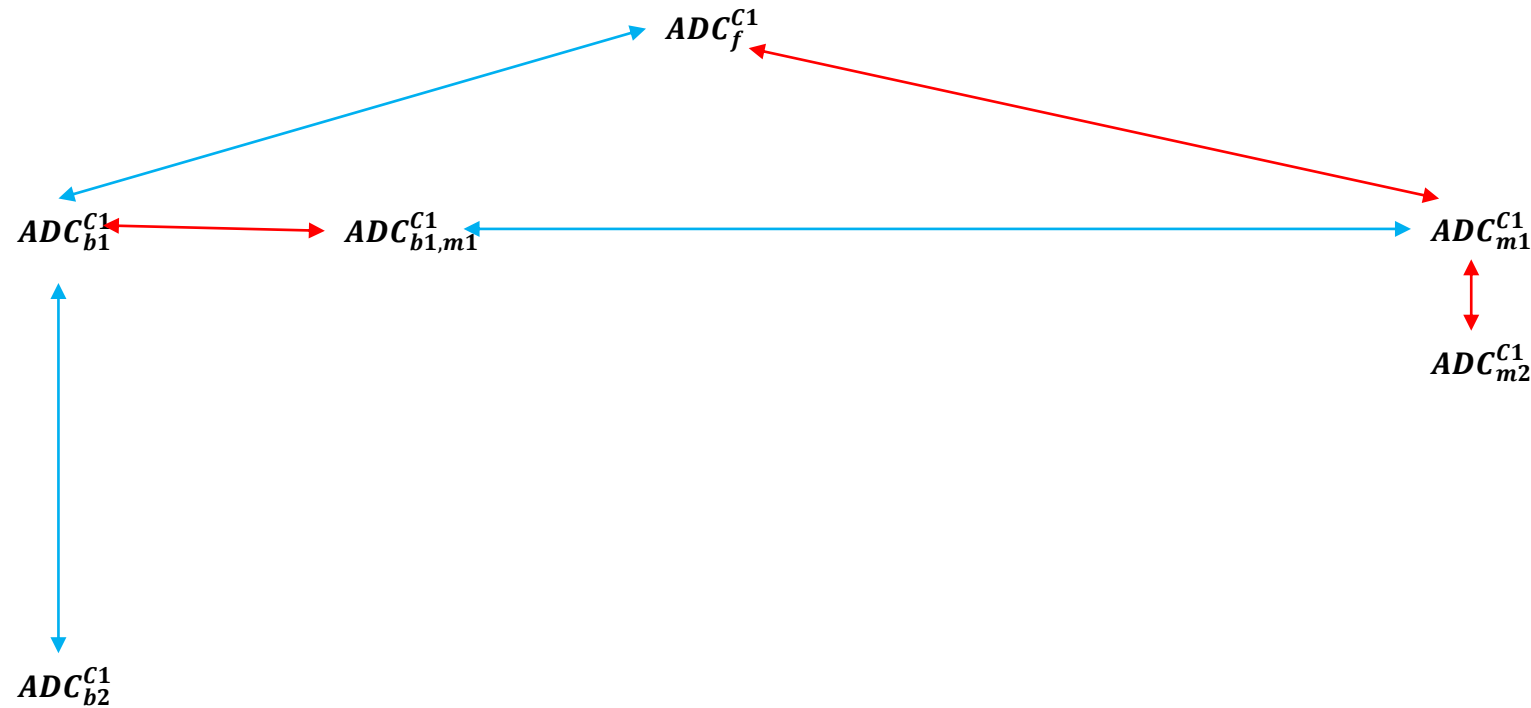
Mathematical description of mechanisms in-vivo
Metabolites

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

$$Ab_f^{C1}$$

$$Ab_{b1}^{C1} \longleftrightarrow Ab_{b1,m1}^{C1} \longleftrightarrow Ab_{m1}^{C1}$$

$$Ab_{b1,m2}^{C1} \longleftrightarrow Ab_{m2}^{C1}$$

$$Ab_{b1,m3}^{C1} \longleftrightarrow Ab_{m3}^{C1}$$

$$Ab_{m4}^{C1}$$

$$Ab_{b2}^{C1} \longleftrightarrow Ab_{b2,m1}^{C1} \longleftrightarrow Ab_{b2,m2}^{C1}$$

$$Ab_{b3}^{C1} \longleftrightarrow Ab_{b3,m1}^{C1}$$

$$Ab_{b4}^{C1}$$

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

$$\longleftrightarrow \quad K_{on}^{Ab,Meta} + K_{off}^{Ab,Meta}$$

$$\longleftrightarrow \quad K_{on}^{Ab,Drug} + K_{off}^{Ab,Drug}$$

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

ADC_f^{C1}

ADC_{b1}^{C1} $ADC_{b1,m1}^{C1}$ ADC_{m1}^{C1}

ADC_{m2}^{C1}

ADC_{b2}^{C1}

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

$K_{on}^{Ab,Meta} + K_{off}^{Ab,Meta}$

$K_{on}^{Ab,Drug} + K_{off}^{Ab,Drug}$
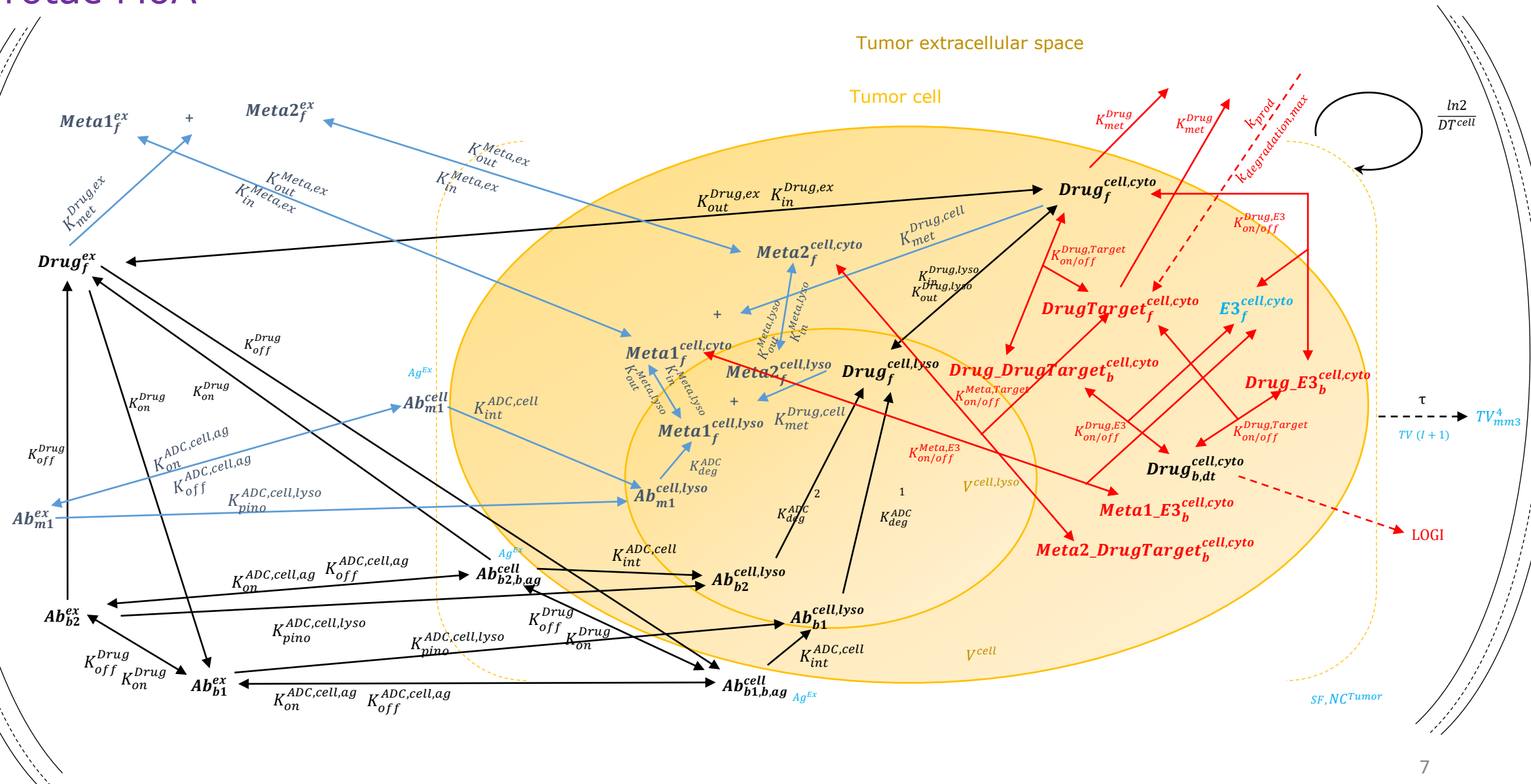
Mathematical description of mechanisms in-vivo
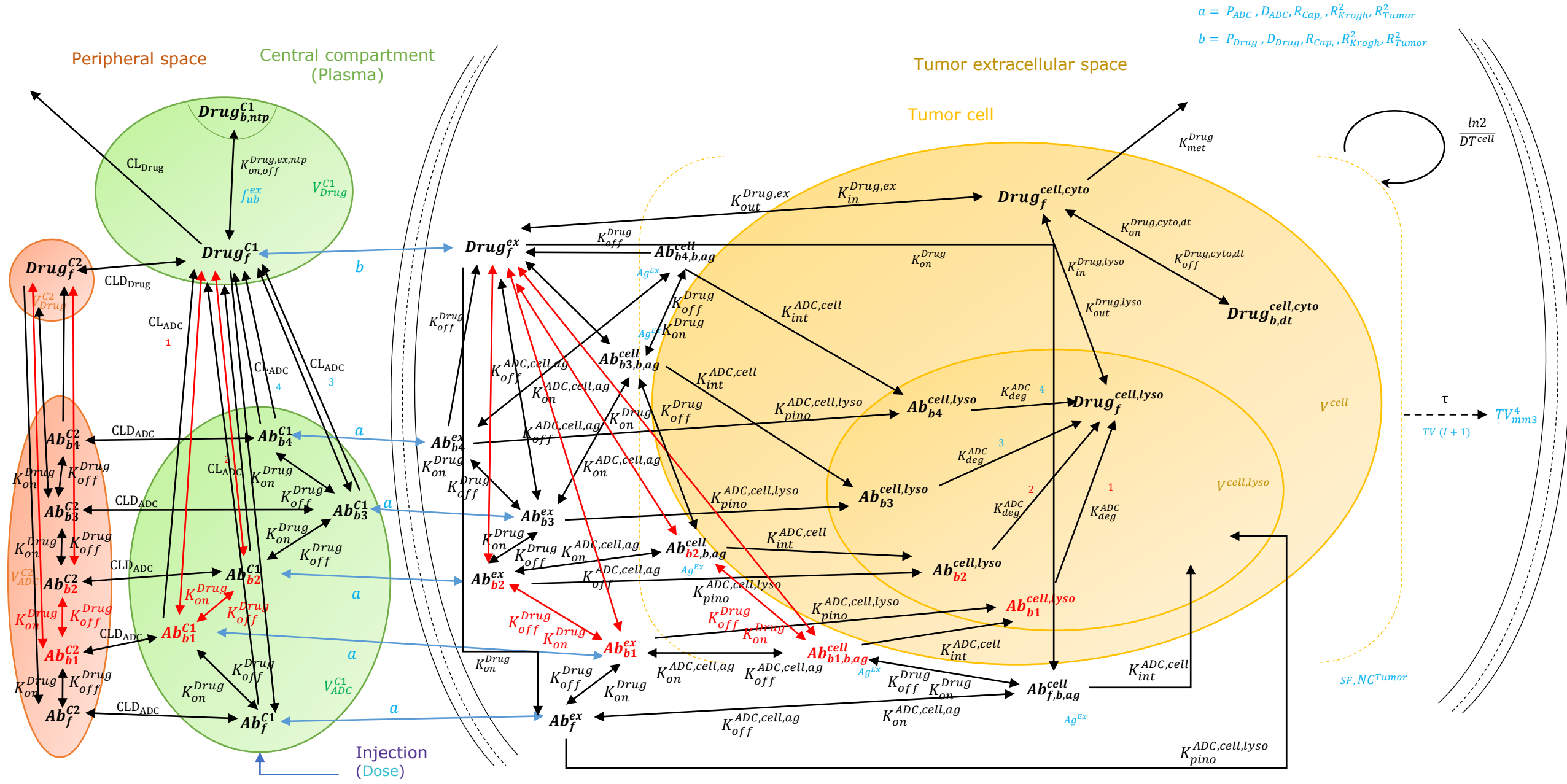
$$\frac{d(\overline{DAR})}{dt} = -K_{dec}^{ADC} \times \overline{DAR}$$

Due to non-specific deconjugation of ADC

Mean DAR in plasma (only Protacs)

$$meanDAR = \frac{\left(Ab_f^{C1} \times 0 + \sum_{i=1}^{max} Ab_{bi}^{C1} \times i + \sum_{j=1}^{max-1} Ab_{b1,mj}^{C1} \times 1 + \sum_{j=1}^{max-2} Ab_{b2,mj}^{C1} \times 2 + Ab_{b3,m1}^{C1} \times 3\right) \times \frac{BW}{SF}}{\left(\sum_{i=0}^{max} Ab_{bi}^{C1} + \sum_{j=1}^{max} Ab_{mj}^{C1} + \sum_{i,j=1}^{i+j \leq max} Ab_{bi,mj}^{C1}\right) \times \frac{BW}{SF}}$$

$$+ \left(\frac{\sum_{i=1}^{2} ADC_{bi}^{C1} \times i + ADC_{b1,m1}^{C1}}{\sum_{i=0}^{2} ADC_{bi}^{C1} + \sum_{j=1}^{2} ADC_{mj}^{C1} + ADC_{b1,m1}^{C1}} + DAR\right) \times \frac{\sum_{i=0}^{2} ADC_{bi}^{C1} + \sum_{j=1}^{2} ADC_{mj}^{C1} + ADC_{b1,m1}^{C1}}{\sum_{i=0}^{2} ADC_{bi}^{C1} + \sum_{j=1}^{2} ADC_{mj}^{C1} + ADC_{b1,m1}^{C1} + \left(\sum_{i=0}^{max} Ab_{bi}^{C1} + \sum_{j=1}^{max} Ab_{mj}^{C1} + \sum_{i,j=1}^{i+j \leq}\right.}$$

$$\boxed{\text{Amount of free ADC (nmol/kg) (bound to 0 Protacs) in central compartment}}$$

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

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

$$-\underbrace{K_{on}^{Ab,Drug} \times 2 \times ADC_f^{C1} \times Drug_f^{C1}}_{\text{To binding to drug}} + \underbrace{K_{off}^{Ab,Drug} \times ADC_{b1}^{C1}}_{\text{From unbinding of drug}} - \underbrace{K_{on}^{Ab,Meta} \times 2 \times ADC_f^{C1} \times Meta1_f^{C1}}_{\text{To binding to metabolite}} + \underbrace{K_{off}^{Ab,Meta} \times ADC_{m1}^{C1}}_{\text{From unbinding of metabolite}}$$

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 ADC bound to 1 Protac in central compartment/plasma

$$\frac{d(ADC_{b1}^{C1})}{dt} = -\frac{CL_{ADC}}{V_{ADC}^{C1}} \times ADC_{b1}^{C1} - \frac{CLD_{ADC}}{V_{ADC}^{C1}} \times ADC_{b1}^{C1} + \frac{CLD_{ADC}}{V_{ADC}^{C2}} \times ADC_{b1}^{C2}$$

To clearance of ADC   To peripheral space   From peripheral space

$$-\left(\frac{ADC_{b1}^{C1}}{V_{ADC}^{C1}} - \frac{ADC_{b1}^{ex}}{\varepsilon^{ADC}}\right) \times \frac{V^{tumor}}{BW} \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{ADC}}{R_{Tumor}^2}\right) - K_{on}^{Ab,Drug} \times ADC_{b1}^{C1} \times Drug_f^{C1} + K_{off}^{Ab,Drug} \times ADC_{b2}^{C1}$$

To tumor extracellular space   To binding to drug   From unbinding of drug

$$+K_{on}^{Ab,Drug} \times 2 \times ADC_f^{C1} \times Drug_f^{C1} - K_{off}^{Ab,Drug} \times ADC_{b1}^{C1} - K_{on}^{Ab,Meta} \times ADC_{b1}^{C1} \times Meta1_f^{C1} + K_{off}^{Ab,Meta} \times ADC_{b1,m1}^{C1}$$

From binding to drug   To unbinding of drug   To binding to metabolite   From unbinding of metabolite

Amount (nmol/kg) of ADC bound to 2 Protacs in central compartment/plasma

$$\frac{d(ADC_{b2}^{C1})}{dt} = -\underbrace{\frac{CL_{ADC}}{V_{ADC}^{C1}} \times ADC_{b2}^{C1}}_{\text{To clearance of ADC}} - \underbrace{\frac{CLD_{ADC}}{V_{ADC}^{C1}} \times ADC_{b2}^{C1}}_{\text{To peripheral space}} + \underbrace{\frac{CLD_{ADC}}{V_{ADC}^{C2}} \times ADC_{b2}^{C2}}_{\text{From peripheral space}}$$

$$-\underbrace{\left(\frac{ADC_{b2}^{C1}}{V_{ADC}^{C1}} - \frac{ADC_{b2}^{ex}}{\varepsilon^{ADC}} \right) \times \frac{V^{tumor}}{BW} \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{ADC}}{R_{Tumor}^2} \right)}_{\text{To tumor extracellular space}}$$

$$+\underbrace{K_{on}^{Ab,Drug} \times ADC_{b1}^{C1} \times Drug_f^{C1}}_{\text{From binding to drug}} - \underbrace{K_{off}^{Ab,Drug} \times ADC_{b2}^{C1}}_{\text{To unbinding of drug}}$$

Amount (nmol/kg) of ADC bound to 1 Metabolite1 in central compartment/plasma

$$\frac{d(ADC_{m1}^{C1})}{dt} = -\frac{CL_{ADC}}{V_{ADC}^{C1}} \times ADC_{m1}^{C1} - \frac{CLD_{ADC}}{V_{ADC}^{C1}} \times ADC_{m1}^{C1} + \frac{CLD_{ADC}}{V_{ADC}^{C2}} \times ADC_{m1}^{C2}$$

To clearance of ADC ⎴ To peripheral space ⎴ From peripheral space

$$-\left(\frac{ADC_{m1}^{C1}}{V_{ADC}^{C1}} - \frac{ADC_{m1}^{ex}}{\varepsilon^{ADC}}\right) \times \frac{V^{tumor}}{BW} \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{ADC}}{R_{Tumor}^2}\right) - K_{on}^{Ab,Drug} \times ADC_{m1}^{C1} \times Drug_f^{C1} + K_{off}^{Ab,Drug} \times ADC_{b1,m1}^{C1}$$

To tumor extracellular space ⎴ To binding to drug ⎴ From unbinding of drug

$$+K_{on}^{Ab,Meta} \times 2 \times ADC_f^{C1} \times Meta1_f^{C1} - K_{off}^{Ab,Meta} \times ADC_{m1}^{C1} - K_{on}^{Ab,Meta} \times ADC_{m1}^{C1} \times Meta1_f^{C1} + K_{off}^{Ab,Meta} \times ADC_{m2}^{C1}$$

From binding to metabolite ⎴ To unbinding of metabolite ⎴ To binding to metabolite ⎴ From unbinding of metabolite

Amount (nmol/kg) of ADC bound to 2 Metabolites1 in central compartment/plasma

$$\frac{d(ADC_{m2}^{C1})}{dt} = -\underbrace{\frac{CL_{ADC}}{V_{ADC}^{C1}} \times ADC_{m2}^{C1}}_{\text{To clearance of ADC}} - \underbrace{\frac{CLD_{ADC}}{V_{ADC}^{C1}} \times ADC_{m2}^{C1}}_{\text{To peripheral space}} + \underbrace{\frac{CLD_{ADC}}{V_{ADC}^{C2}} \times ADC_{m2}^{C2}}_{\text{From peripheral space}}$$

$$-\underbrace{\left(\frac{ADC_{m2}^{C1}}{V_{ADC}^{C1}} - \frac{ADC_{m2}^{ex}}{\varepsilon^{ADC}}\right) \times \frac{V^{tumor}}{BW} \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{ADC}}{R_{Tumor}^2}\right)}_{\text{To tumor extracellular space}}$$

$$+\underbrace{K_{on}^{Ab,Meta} \times ADC_{m1}^{C1} \times Meta1_f^{C1}}_{\text{From binding to metabolite}} - \underbrace{K_{off}^{Ab,Meta} \times ADC_{m2}^{C1}}_{\text{To unbinding of metabolite}}$$

Amount (nmol/kg) of ADC bound to 1 Protac and 1 Metabolite1 in central compartment/plasma

$$\frac{d(ADC_{b1,m1}^{C1})}{dt} = -\frac{CL_{ADC}}{V_{ADC}^{C1}} \times ADC_{b1,m1}^{C1} - \frac{CLD_{ADC}}{V_{ADC}^{C1}} \times ADC_{b1,m1}^{C1} + \frac{CLD_{ADC}}{V_{ADC}^{C2}} \times ADC_{b1,m1}^{C2}$$

To clearance of ADC   To peripheral space   From peripheral space

$$-\left(\frac{ADC_{b1,m1}^{C1}}{V_{ADC}^{C1}} - \frac{ADC_{b1,m1}^{ex}}{\varepsilon^{ADC}}\right) \times \frac{V^{tumor}}{BW} \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{ADC}}{R_{Tumor}^2}\right)$$

To tumor extracellular space

$$+K_{on}^{Ab,Drug} \times ADC_{m1}^{C1} \times Drug_f^{C1} - K_{off}^{Ab,Drug} \times ADC_{b1,m1}^{C1}$$

From binding to drug   To unbinding of drug

$$+K_{on}^{Ab,Meta} \times ADC_{b1}^{C1} \times Meta1_f^{C1} - K_{off}^{Ab,Meta} \times ADC_{b1,m1}^{C1}$$

From binding to metabolite   To unbinding of metabolite

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

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

$$\boxed{\text{Amount (nmol/kg) of Antibody bound to i Protacs in central compartment/plasma, i = 1,2,3}}$$

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

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

$$\underbrace{+K_{on}^{Ab,Drug} \times (max-i+1) \times Ab_{bi-1}^{C1} \times Drug_f^{C1}}_{\text{From binding to drug}} \underbrace{- K_{off}^{Ab,Drug} \times Ab_{bi}^{C1}}_{\text{To unbinding of drug}} \underbrace{- K_{on}^{Ab,Meta} \times (max-i) \times Ab_{bi}^{C1} \times Meta1_f^{C1}}_{\text{To binding to metabolite}} + \underbrace{K_{off}^{Ab,}}_{\text{From unbin}}$$

$$\boxed{\begin{aligned} \text{Units:}\quad & \frac{nmol}{kg \times h} = \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{kg} - \frac{\frac{l}{h}/kg}{l/kg} \times nmol/kg + \frac{\frac{l}{h}/kg}{l/kg} \times nmol/kg - \left(\frac{nmol/kg}{l/kg} - \frac{nmol/l}{1}\right) \times \frac{l}{kg} \times \left(\frac{\frac{um}{h} \times um}{um^2} + \frac{cm^2/h}{cm^2}\right) \\ & - \frac{l}{h} \times \left(\frac{1}{l/kg \times kg}\right) \times \frac{nmol}{kg} - \frac{1}{\frac{nmol}{l} \times h} \times \frac{nmol}{kg} \times (1-1-1) \times 1 \times \frac{nmol}{kg \times \frac{l}{kg}} + \frac{1}{h} \times 1 \times 1 \times \frac{nmol}{kg} - \frac{1}{\frac{nmol}{l} \times h} \times \frac{nmol}{kg} \times \frac{nmol}{kg \times \frac{l}{kg}} + \frac{1}{h} \times \frac{nmol}{kg} \end{aligned}}$$

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

$$\frac{d(Ab_{b4}^{C1})}{dt} = -\frac{CL_{ADC}}{V_{ADC}^{C1}} \times Ab_{b4}^{C1} - \frac{CLD_{ADC}}{V_{ADC}^{C1}} \times Ab_{b4}^{C1} + \frac{CLD_{ADC}}{V_{ADC}^{C2}} \times Ab_{b4}^{C2}$$

To clearance of ADC   To peripheral space   From peripheral space

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

To tumor extracellular space

$$+K_{on}^{Ab,Drug} \times Ab_{b3}^{C1} \times Drug_f^{C1} - K_{off}^{Ab,Drug} \times Ab_{b4}^{C1}$$

From binding to drug   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

$$\frac{d(Ab_{mj}^{C1})}{dt} = -\frac{CL_{ADC}}{V_{ADC}^{C1}} \times Ab_{mj}^{C1} - \frac{CLD_{ADC}}{V_{ADC}^{C1}} \times Ab_{mj}^{C1} + \frac{CLD_{ADC}}{V_{ADC}^{C2}} \times Ab_{mj}^{C2}$$

$$\underbrace{\hphantom{-\frac{CL_{ADC}}{V_{ADC}^{C1}} \times Ab_{mj}^{C1}}}_{\text{To clearance of ADC}} \quad \underbrace{\hphantom{-\frac{CLD_{ADC}}{V_{ADC}^{C1}} \times Ab_{mj}^{C1}}}_{\text{To peripheral space}} \quad \underbrace{\hphantom{\frac{CLD_{ADC}}{V_{ADC}^{C2}} \times Ab_{mj}^{C2}}}_{\text{From peripheral space}}$$

$$-\left(\frac{Ab_{mj}^{C1}}{V_{ADC}^{C1}} - \frac{Ab_{mj}^{ex}}{\varepsilon^{ADC}}\right) \times \frac{V^{tumor}}{BW} \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{ADC}}{R_{Tumor}^2}\right) - K_{on}^{Ab,Drug} \times (max - j) \times Ab_{mj}^{C1} \times Drug_f^{C1} + K_{off}^{Ab,Drug} \times Ab_{b1,mj}^{C1}$$

$$\underbrace{\hphantom{-\left(\frac{Ab_{mj}^{C1}}{V_{ADC}^{C1}} - \frac{Ab_{mj}^{ex}}{\varepsilon^{ADC}}\right) \times \frac{V^{tumor}}{BW}}}_{\text{To tumor extracellular space}} \quad \underbrace{\hphantom{-K_{on}^{Ab,Drug} \times (max - j) \times Ab_{mj}^{C1}}}_{\text{To binding to drug}} \quad \underbrace{\hphantom{+ K_{off}^{Ab,Drug} \times Ab_{b1,mj}^{C1}}}_{\text{From unbinding of drug}}$$

$$+K_{on}^{Ab,Meta} \times (max - j + 1) \times Ab_{mj-1}^{C1} \times Meta1_f^{C1} - K_{off}^{Ab,Meta} \times Ab_{mj}^{C1} - K_{on}^{Ab,Meta} \times (max - j) \times Ab_{mj}^{C1} \times Meta1_f^{C1} + K_o^{A}$$

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

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

$$\frac{d(Ab_{m4}^{C1})}{dt} = -\frac{CL_{ADC}}{V_{ADC}^{C1}} \times Ab_{m4}^{C1} - \frac{CLD_{ADC}}{V_{ADC}^{C1}} \times Ab_{m4}^{C1} + \frac{CLD_{ADC}}{V_{ADC}^{C2}} \times Ab_{m4}^{C2}$$

To clearance of ADC   To peripheral space   From peripheral space

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

To tumor extracellular space

$$+K_{on}^{Ab,Meta} \times Ab_{m3}^{C1} \times Meta1_f^{C1} - K_{off}^{Ab,Meta} \times Ab_{m4}^{C1}$$

From binding to metabolite   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 with i + j < max

$$\frac{d(Ab_{bi,mj}^{C1})}{dt} = -\frac{CL_{ADC}}{V_{ADC}^{C1}} \times Ab_{bi,mj}^{C1} - \frac{CLD_{ADC}}{V_{ADC}^{C1}} \times Ab_{bi,mj}^{C1} + \frac{CLD_{ADC}}{V_{ADC}^{C2}} \times Ab_{bi,mj}^{C2}$$

To clearance of ADC   To peripheral space   From peripheral space

$$-\left(\frac{Ab_{bi,mj}^{C1}}{V_{ADC}^{C1}} - \frac{Ab_{bi,mj}^{ex}}{\varepsilon^{ADC}}\right) \times \frac{V^{tumor}}{BW} \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{ADC}}{R_{Tumor}^2}\right) - K_{on}^{Ab,Drug} \times (max - i - j) \times Ab_{bi,mj}^{C1} \times Drug_f^{C1} + K_{off}^{Ab,Drug} \times A$$

To tumor extracellular space   To binding to drug   From unbinding of

$$+K_{on}^{Ab,Drug} \times (max - i + 1 - j) \times Ab_{bi-1,mj}^{C1} \times Drug_f^{C1} - K_{off}^{Ab,Drug} \times Ab_{bi,mj}^{C1} - K_{on}^{Ab,Meta} \times (max - i - j) \times Ab_{bi,mj}^{C1} \times M$$

From binding to drug   To unbinding of drug   To binding to metabolite

$$+K_{off}^{Ab,Meta} \times Ab_{bi,mj+1}^{C1} + K_{on}^{Ab,Meta} \times (max - i - j + 1) \times Ab_{bi,mj-1}^{C1} \times Meta1_f^{C1} - K_{off}^{Ab,Meta} \times Ab_{bi,mj}^{C1}$$

From unbinding of metabolite   From binding to metabolite   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

$$\frac{d(Drug_f^{C1})}{dt} = -\frac{CL_{Drug}}{V_{Drug}^{C1}} \times Drug_f^{C1} - \frac{CLD_{Drug}}{V_{Drug}^{C1}} \times Drug_f^{C1} + \frac{CLD_{Drug}}{V_{Drug}^{C1}} \times Drug_f^{C2} + \frac{\sum_{i=1,j=0}^{max} CL_{ADC} \times i \times \frac{Ab_{bi,mj}^{C1}}{V_{ADC}^{C1}}}{V_{Drug}^{C1}}$$

To clearance of drug   To peripheral space   From peripheral space   From clearance of Ab bound to i Protacs

$$-\left(Drug_f^{C1} - \frac{Drug_f^{ex}}{V^{tumor} \times \varepsilon^{Drug}}\right) \times \frac{V^{tumor}}{V_{Drug}^{C1} \times BW} \times \left(\frac{2 \times P_{Drug} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{Drug}}{R_{Tumor}^2}\right) + \frac{K_{dec}^{ADC} \times \left(\sum_{i=0}^{2} ADC_{bi}^{C1} + \sum_{j=1}^{2} ADC_{mj}^{C1} + ADC_{b1,m}^{C1}\right)}{V_{Drug}^{C1}}$$

To tumor extracellular space   From non-specific deconjugation of ADC

$$-K_{on,off}^{Drug,ex,ntp} \times (1 - f_{ub}^{ex}) \times Drug_f^{C1} + K_{on,off}^{Drug,ex,ntp} \times f_{ub}^{ex} \times Drug_{b,ntp}^{C1} - K_{met}^{Drug,C1} \times Drug_f^{C1} + \frac{CL_{ADC} \times \overline{DAR} \times \frac{\sum_{i=0}^{2} ADC_{bi}^{C1} + \sum_{j=1}^{2} A\cdots}{V_{ADC}^{C1}}}{V_{Drug}^{C1}}$$

To and from protein binding   To metabolism   From clearance of ADC

$$-\sum_{i,j=0,i+j<max}^{max-1} K_{on}^{Ab,Drug} \times (max - i - j) \times \frac{Ab_{bi,mj}^{C1}}{V_{Drug}^{C1}} \times Drug_f^{C1} + \sum_{i=1,j=0,i+j\leq max}^{max} K_{off}^{Ab,Drug} \times \frac{Ab_{bi,mj}^{C1}}{V_{Drug}^{C1}}$$

To binding to antibody   From unbinding of antibody

$$-K_{on}^{Ab,Drug} \times \left(2 \times \frac{ADC_f^{C1}}{V_{Drug}^{C1}} + \frac{ADC_{b1}^{C1}}{V_{Drug}^{C1}} + \frac{ADC_{m1}^{C1}}{V_{Drug}^{C1}}\right) \times Drug_f^{C1} + K_{off}^{Ab,Drug} \times \left(\frac{ADC_{b1}^{C1}}{V_{Drug}^{C1}} + \frac{ADC_{b2}^{C1}}{V_{Drug}^{C1}} + \frac{ADC_{b1,m1}^{C1}}{V_{Drug}^{C1}}\right)$$

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

$$\frac{d(Drug_{b,ntp}^{C1})}{dt} = K_{on,off}^{Drug,ex,ntp} \times (1 - f_{ub}^{ex}) \times Drug_f^{C1} - K_{on,off}^{Drug,ex,ntp} \times f_{ub}^{ex} \times Drug_{b,ntp}^{C1}$$

$\underbrace{\qquad\qquad}_{\text{To unspecific protein binding}}$ $\underbrace{\qquad\qquad}_{\text{To unspecific protein unbinding}}$

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

$$\frac{d(Meta1_f^{C1})}{dt} = -\frac{CL_{Meta}}{V_{Meta}^{C1}} \times Meta1_f^{C1} + \frac{\sum_{i=0,j=1}^{max} CL_{ADC} \times j \times \frac{Ab_{bi,mj}^{C1}}{V_{ADC}^{C1}}}{V_{Meta}^{C1}} + K_{met}^{Drug,C1} \times Drug_f^{C1}$$

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

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

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

$$-\sum_{i,j=0,i+j<max}^{max-1} K_{on}^{Ab,Meta} \times (max-i-j) \times \frac{Ab_{bi,mj}^{C1}}{V_{Meta}^{C1}} \times Meta1_f^{C1} + \sum_{i=0,j=1,i+j\leq max}^{max} K_{off}^{Ab,Meta} \times \frac{Ab_{bi,mj}^{C1}}{V_{Meta}^{C1}}$$

$$\underbrace{\phantom{-\sum_{i,j=0,i+j<max}^{max-1} K_{on}^{Ab,Meta} \times (max-i-j) \times \frac{Ab_{bi,mj}^{C1}}{V_{Meta}^{C1}} \times Meta1_f^{C1}}}_{\text{To binding to antibody}} \quad \underbrace{\phantom{\sum_{i=0,j=1,i+j\leq max}^{max} K_{off}^{Ab,Meta} \times \frac{Ab_{bi,mj}^{C1}}{V_{Meta}^{C1}}}}_{\text{From unbinding of antibody}}$$

$$-K_{on}^{Ab,Meta} \times \left(2 \times \frac{ADC_f^{C1}}{V_{Meta}^{C1}} + \frac{ADC_{b1}^{C1}}{V_{Meta}^{C1}} + \frac{ADC_{m1}^{C1}}{V_{Meta}^{C1}}\right) \times Meta1_f^{C1} + K_{off}^{Ab,Meta} \times \left(\frac{ADC_{m1}^{C1}}{V_{Meta}^{C1}} + \frac{ADC_{m2}^{C1}}{V_{Meta}^{C1}} + \frac{ADC_{b1,m1}^{C1}}{V_{Meta}^{C1}}\right)$$

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

$$\frac{d(Meta2_f^{C1})}{dt} = -\frac{CL_{Meta}}{V_{Meta}^{C1}} \times Meta2_f^{C1} + K_{met}^{Drug,C1} \times Drug_f^{C1}$$

$\underbrace{\phantom{-\frac{CL_{Meta}}{V_{Meta}^{C1}} \times Meta2_f^{C1}}}_{\text{To clearance}}$ $\underbrace{\phantom{K_{met}^{Drug,C1} \times Drug_f^{C1}}}_{\text{From metabolism}}$

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

$\underbrace{\phantom{-\left(Meta2_f^{C1} - \frac{Meta2_f^{ex}}{V^{tumor} \times \varepsilon^{Meta}}\right) \times \frac{V^{tumor}}{V_{Meta}^{C1} \times BW}}}_{\text{To tumor extracellular space}}$

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 ADC (bound to 0 Protacs) in peripheral compartment

$$\frac{d\,(ADC_f^{C2})}{dt} = \frac{CLD_{ADC}}{V_{ADC}^{C1}} \times ADC_f^{C1} - \frac{CLD_{ADC}}{V_{ADC}^{C2}} \times ADC_f^{C2}$$

From central space   To central space

$$-K_{on}^{Ab,Drug} \times 2 \times ADC_f^{C2} \times Drug_f^{C2} + K_{off}^{Ab,Drug} \times ADC_{b1}^{C2}$$

To binding to drug   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 ADC bound to 1 Protac in peripheral compartment

$$\frac{d\left(ADC_{b1}^{C2}\right)}{dt} = \frac{CLD_{ADC}}{V_{ADC}^{C1}} \times ADC_{b1}^{C1} - \frac{CLD_{ADC}}{V_{ADC}^{C2}} \times ADC_{b1}^{C2}$$

From central space   To central space

$$-K_{on}^{Ab,Drug} \times ADC_{b1}^{C2} \times Drug_f^{C2} + K_{off}^{Ab,Drug} \times ADC_{b2}^{C2}$$

To binding to drug   From unbinding of drug

$$+K_{on}^{Ab,Drug} \times 2 \times ADC_f^{C2} \times Drug_f^{C2} - K_{off}^{Ab,Drug} \times ADC_{b1}^{C2}$$

From binding to drug   To 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 ADC bound to 2 Protacs in peripheral compartment

$$\frac{d\,(ADC_{b2}^{C2})}{dt} = \underbrace{\frac{CLD_{ADC}}{V_{ADC}^{C1}} \times ADC_{b2}^{C1}}_{\text{From central space}} - \underbrace{\frac{CLD_{ADC}}{V_{ADC}^{C2}} \times ADC_{b2}^{C2}}_{\text{To central space}}$$

$$+ \underbrace{K_{on}^{Ab,Drug} \times ADC_{b1}^{C2} \times Drug_{f}^{C2}}_{\text{From binding to drug}} - \underbrace{K_{off}^{Ab,Drug} \times ADC_{b2}^{C2}}_{\text{To unbinding of drug}}$$

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 ADC bound to 1 Metabolite1 in peripheral compartment

$$\frac{d\left(ADC_{m1}^{C2}\right)}{dt} = \underbrace{\frac{CLD_{ADC}}{V_{ADC}^{C1}} \times ADC_{m1}^{C1}}_{\text{From central space}} - \underbrace{\frac{CLD_{ADC}}{V_{ADC}^{C2}} \times ADC_{m1}^{C2}}_{\text{To central space}}$$

$$\underbrace{-K_{on}^{Ab,Drug} \times ADC_{m1}^{C2} \times Drug_{f}^{C2}}_{\text{To binding to drug}} + \underbrace{K_{off}^{Ab,Drug} \times ADC_{b1,m1}^{C2}}_{\text{From unbinding of drug}}$$

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 ADC bound to 2 Metabolites1 in peripheral compartment

$$\frac{d\ (ADC_{m2}^{C2})}{dt} = \underbrace{\frac{CLD_{ADC}}{V_{ADC}^{C1}} \times ADC_{m2}^{C1}}_{\text{From central space}} - \underbrace{\frac{CLD_{ADC}}{V_{ADC}^{C2}} \times ADC_{m2}^{C2}}_{\text{To central space}}$$

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 ADC bound to 1 Protac and 1 Metabolite1 in peripheral compartment

$$\frac{d(ADC_{b1,m1}^{C2})}{dt} = \underbrace{\frac{CLD_{ADC}}{V_{ADC}^{C1}} \times ADC_{b1,m1}^{C1}}_{\text{From central space}} - \underbrace{\frac{CLD_{ADC}}{V_{ADC}^{C2}} \times ADC_{b1,m1}^{C2}}_{\text{To central space}}$$

$$\underbrace{+K_{on}^{Ab,Drug} \times ADC_{m1}^{C2} \times Drug_{f}^{C2}}_{\text{From binding to drug}} - \underbrace{K_{off}^{Ab,Drug} \times ADC_{b1,m1}^{C2}}_{\text{To unbinding of drug}}$$

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

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

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

Units:

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

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

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

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

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

Units:

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

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:

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

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

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

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

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

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

From central space   To central space

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 Protac and j Metabolites1 in peripheral compartment, i = 1,2 and j = 1,2 with i + j < max

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

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

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

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

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

$$- \underbrace{\sum_{i,j=0,i+j<max}^{max-1} K_{on}^{Ab,Drug} \times (max-i-j) \times \frac{Ab_{bi,mj}^{C2}}{V_{Drug}^{C2}} \times Drug_f^{C2}}_{\text{To binding to antibody}} + \underbrace{\sum_{i=1,j=0,i+j\leq max}^{max} K_{off}^{Ab,Drug} \times \frac{Ab_{bi,mj}^{C2}}{V_{Drug}^{C2}}}_{\text{From unbinding of antibody}}$$

$$- K_{on}^{Ab,Drug} \times \left(2 \times \frac{ADC_f^{C2}}{V_{Drug}^{C2}} + \frac{ADC_{b1}^{C2}}{V_{Drug}^{C2}} + \frac{ADC_{m1}^{C2}}{V_{Drug}^{C2}} \right) \times Drug_f^{C2} + K_{off}^{Ab,Drug} \times \left(\frac{ADC_{b1}^{C2}}{V_{Drug}^{C2}} + \frac{ADC_{b2}^{C2}}{V_{Drug}^{C2}} + \frac{ADC_{b1,m1}^{C2}}{V_{Drug}^{C2}} \right)$$

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 ADC (bound to 0 Protacs) in tumor extracellular space

$$\frac{d(ADC_f^{ex})}{dt} = \left(\frac{ADC_f^{C1}}{V_{ADC}^{C1}} - \frac{ADC_f^{ex}}{\varepsilon^{ADC}}\right) \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{ADC}}{R_{Tumor}^2}\right) + K_{off}^{ADC,cell,ag} \times ADC_{f,b,ag}^{cell} \times \frac{NC^{tumor} \times SF}{V^{tumor}}$$

<u>From central space</u>   <u>From unbinding of ADC to receptors on tumor cell</u>

$$-K_{on}^{ADC,cell,ag} \times \frac{ADC_f^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - \sum_{i=0}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j\leq max} Ab_{bi,mj,b,ag}^{cell} - \sum_{i=0}^{2} ADC_{bi,b,ag}^{cell} - \sum_{j=1}^{2} ADC_{mj,b,ag}^{cell} - ADC_{b1,m1,b,ag}^{cell}\right)$$

<u>To binding of ADC to receptors on tumor cell</u>

$$\times \frac{NC^{tumor} \times SF}{V^{tumor}} + \frac{1}{\tau} \times V_{dyi,3,mm3}^{tumor} \times 10^5 \times \left(ADC_{f,b,ag}^{cell}\right) \times \frac{SF}{V^{tumor}} - K_{pino}^{ADC,cell,lyso} \times \left(\frac{NCL^{tumor}}{\varepsilon^{ADC}}\right) \times ADC_f^{ex}$$

<u>From intracellular content of dying cells</u>   <u>To pinocytosis</u>

$$-K_{on}^{Ab,Drug} \times 2 \times \frac{ADC_f^{ex}}{\varepsilon^{ADC}} \times \frac{Drug_f^{ex}}{V^{tumor} \times \varepsilon^{Drug}} + K_{off}^{Ab,Drug} \times \frac{ADC_{b1}^{ex}}{\varepsilon^{ADC}} - K_{on}^{Ab,Meta} \times 2 \times \frac{ADC_f^{ex}}{\varepsilon^{ADC}} \times \frac{Meta1_f^{ex}}{V^{tumor} \times \varepsilon^{Meta}} + K_{off}^{Ab,Meta} \times \frac{ADC_{m1}^{ex}}{\varepsilon^{ADC}}$$

<u>To binding to drug</u>   <u>From unbinding of drug</u>   <u>To binding to metabolite</u>   <u>From unbinding of metabolite</u>

Concentration (nM) of ADC bound to 1 Protac in tumor extracellular space

$$\frac{d(ADC_{b1}^{ex})}{dt} = \left(\frac{ADC_{b1}^{C1}}{V_{ADC}^{C1}} - \frac{ADC_{b1}^{ex}}{\varepsilon^{ADC}}\right) \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{ADC}}{R_{Tumor}^2}\right) + K_{off}^{ADC,cell,ag} \times ADC_{b1,b,ag}^{cell} \times \frac{NC^{tumor} \times SF}{V^{tumor}}$$

From central space

$$+ \left(-K_{on}^{ADC,cell,ag} \times \frac{ADC_{b1}^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - \sum_{i=0}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j \leq max} Ab_{bi,mj,b,ag}^{cell} - \sum_{i=0}^{2} ADC_{bi,b,ag}^{cell} - \sum_{j=1}^{2} ADC_{mj,b,ag}^{cell} - ADC_{b1,m1,b,a}^{cell}\right.\right.$$

Binding and unbinding of ADC to receptors on tumor cell

$$\times \frac{NC^{tumor} \times SF}{V^{tumor}} + \frac{1}{\tau} \times V_{dyi,3,mm3}^{tumor} \times 10^5 \times \left(ADC_{b1,b,ag}^{cell} + ADC_{b1}^{cell,lyso}\right) \times \frac{SF}{V^{tumor}} - K_{pino}^{ADC,cell,lyso} \times \left(\frac{NCL^{tumor}}{\varepsilon^{ADC}}\right) \times ADC_{b1}^{ex}$$

From intracellular content of dying cells · · · · · · · · To pinocytosis

$$-K_{on}^{Ab,Drug} \times \frac{ADC_{b1}^{ex}}{\varepsilon^{ADC}} \times \frac{Drug_f^{ex}}{V^{tumor} \times \varepsilon^{Drug}} + K_{off}^{Ab,Drug} \times \frac{ADC_{b2}^{ex}}{\varepsilon^{ADC}} + K_{on}^{Ab,Drug} \times 2 \times \frac{ADC_f^{ex}}{\varepsilon^{ADC}} \times \frac{Drug_f^{ex}}{V^{tumor} \times \varepsilon^{Drug}}$$

To binding to drug · · · From unbinding of drug · · · From binding to drug

$$-K_{off}^{Ab,Drug} \times \frac{ADC_{b1}^{ex}}{\varepsilon^{ADC}} - K_{on}^{Ab,Meta} \times \frac{ADC_{b1}^{ex}}{\varepsilon^{ADC}} \times \frac{Meta1_f^{ex}}{V^{tumor} \times \varepsilon^{Meta}} + K_{off}^{Ab,Meta} \times \frac{ADC_{b1,m1}^{ex}}{\varepsilon^{ADC}}$$

To unbinding of drug · · · To binding to metabolite · · · From unbinding of metabolite

$$\frac{d(ADC_{b2}^{ex})}{dt} = \left(\frac{ADC_{b2}^{C1}}{V_{ADC}^{C1}} - \frac{ADC_{b2}^{ex}}{\varepsilon^{ADC}}\right) \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{ADC}}{R_{Tumor}^2}\right) + K_{off}^{ADC,cell,ag} \times ADC_{b2,b,ag}^{cell} \times \frac{NC^{tumor} \times SF}{V^{tumor}}$$

From central space

$$+ \left(-K_{on}^{ADC,cell,ag} \times \frac{ADC_{b2}^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - \sum_{i=0}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j\leq max} Ab_{bi,mj,b,ag}^{cell} - \sum_{i=0}^{2} ADC_{bi,b,ag}^{cell} - \sum_{j=1}^{2} ADC_{mj,b,ag}^{cell} - ADC_{b1,m1,b,a}^{cell}\right.\right.$$

Binding and unbinding of ADC to receptors on tumor cell

$$\times \frac{NC^{tumor} \times SF}{V^{tumor}} + \frac{1}{\tau} \times V_{dyi,3,mm3}^{tumor} \times 10^5 \times \left(ADC_{b2,b,ag}^{cell} + ADC_{b2}^{cell,lyso}\right) \times \frac{SF}{V^{tumor}} - K_{pino}^{ADC,cell,lyso} \times \left(\frac{NCL^{tumor}}{\varepsilon^{ADC}}\right) \times ADC_{b2}^{ex}$$

From intracellular content of dying cells   To pinocytosis

$$+ K_{on}^{Ab,Drug} \times \frac{ADC_{b1}^{ex}}{\varepsilon^{ADC}} \times \frac{Drug_f^{ex}}{V^{tumor} \times \varepsilon^{Drug}} - K_{off}^{Ab,Drug} \times \frac{ADC_{b2}^{ex}}{\varepsilon^{ADC}}$$

From binding to drug   To unbinding of drug

Concentration (nM) of ADC bound to 1 Metabolite1 in tumor extracellular space

$$\frac{d(ADC_{m1}^{ex})}{dt} = \left(\frac{ADC_{m1}^{C1}}{V_{ADC}^{C1}} - \frac{ADC_{m1}^{ex}}{\varepsilon^{ADC}} \right) \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{ADC}}{R_{Tumor}^2} \right)$$

From central space

$$+ \left(-K_{on}^{ADC,cell,ag} \times \frac{ADC_{m1}^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - \sum_{i=0}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j \leq max} Ab_{bi,mj,b,ag}^{cell} - \sum_{i=0}^{2} ADC_{bi,b,ag}^{cell} - \sum_{j=1}^{2} ADC_{m,}^{ce} \right. \right.$$

Binding and unbinding of ADC to receptors on tumor cell

$$\times \frac{NC^{tumor} \times SF}{V^{tumor}} + \frac{1}{\tau} \times V_{dyi,3,mm3}^{tumor} \times 10^5 \times \left(ADC_{m1,b,ag}^{cell} + ADC_{m1}^{cell,lyso} \right) \times \frac{SF}{V^{tumor}} - K_{pino}^{ADC,cell,lyso} \times \left(\frac{NCL^{tumor}}{\varepsilon^{ADC}} - \right) \times ADC_{m1}^{ex}$$

From intracellular content of dying cells   To pinocytosis

$$-K_{on}^{Ab,Drug} \times \frac{ADC_{m1}^{ex}}{\varepsilon^{ADC}} \times \frac{Drug_f^{ex}}{V^{tumor} \times \varepsilon^{Drug}} + K_{off}^{Ab,Drug} \times \frac{ADC_{b1,m1}^{ex}}{\varepsilon^{ADC}} + K_{on}^{Ab,Meta} \times 2 \times \frac{ADC_f^{ex}}{\varepsilon^{ADC}} \times \frac{Meta1_f^{ex}}{V^{tumor} \times \varepsilon^{Meta}}$$

To binding to drug   From unbinding of drug   From binding to metabolite

$$-K_{off}^{Ab,Meta} \times \frac{ADC_{m1}^{ex}}{\varepsilon^{ADC}} - K_{on}^{Ab,Meta} \times \frac{ADC_{m1}^{ex}}{\varepsilon^{ADC}} \times \frac{Meta1_f^{ex}}{V^{tumor} \times \varepsilon^{Meta}} + K_{off}^{Ab,Meta} \times \frac{ADC_{m2}^{ex}}{\varepsilon^{ADC}}$$

To unbinding of metabolite   To binding to metabolite   From unbinding of metabolite

Concentration (nM) of ADC bound to 2 Metabolites1 in tumor extracellular space

$$\frac{d(ADC_{m2}^{ex})}{dt} = \left(\frac{ADC_{m2}^{C1}}{V_{ADC}^{C1}} - \frac{ADC_{m2}^{ex}}{\varepsilon^{ADC}}\right) \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{ADC}}{R_{Tumor}^2}\right)$$

From central space

$$+ \left(-K_{on}^{ADC,cell,ag} \times \frac{ADC_{m2}^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - \sum_{i=0}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j\leq max} Ab_{bi,mj,b,ag}^{cell} - \sum_{i=0}^{2} ADC_{bi,b,ag}^{cell} - \sum_{j=1}^{2} ADC_{m}^{ce}\right.\right.$$

Binding and unbinding of ADC to receptors on tumor cell

$$\times \frac{NC^{tumor} \times SF}{V^{tumor}} + \frac{1}{\tau} \times V_{dyi,3,mm3}^{tumor} \times 10^5 \times \left(ADC_{m2,b,ag}^{cell} + ADC_{m2}^{cell,lyso}\right) \times \frac{SF}{V^{tumor}} - K_{pino}^{ADC,cell,lyso} \times \left(\frac{NCL^{tumor}}{\varepsilon^{ADC}} + \right) \times ADC_{m2}^{ex}$$

From intracellular content of dying cells **To pinocytosis**

$$+ K_{on}^{Ab,Meta} \times \frac{ADC_{m1}^{ex}}{\varepsilon^{ADC}} \times \frac{Meta1_f^{ex}}{V^{tumor} \times \varepsilon^{Meta}} - K_{off}^{Ab,Meta} \times \frac{ADC_{m2}^{ex}}{\varepsilon^{ADC}}$$

From binding to metabolite **To unbinding of metabolite**

Concentration (nM) of ADC bound to 1 Protac and 1 Metabolite1 in tumor extracellular space

$$\frac{d(ADC_{b1,m1}^{ex})}{dt} = \underbrace{\left(\frac{ADC_{b1,m1}^{C1}}{V_{ADC}^{C1}} - \frac{ADC_{b1,m1}^{ex}}{\varepsilon^{ADC}}\right) \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{ADC}}{R_{Tumor}^2}\right)}_{\text{From central space}}$$

$$+ \underbrace{\left(-K_{on}^{ADC,cell,ag} \times \frac{ADC_{b1,m1}^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - \sum_{i=0}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j\leq max} Ab_{bi,mj,b,ag}^{cell} - \sum_{i=0}^{2} ADC_{bi,b,ag}^{cell} - \sum_{j=1}^{2} AD\right.\right.}_{\text{Binding and unbinding of ADC to receptors on tumor cell}}$$

$$\underbrace{\times \frac{NC^{tumor} \times SF}{V^{tumor}} + \frac{1}{\tau} \times V_{dyi,3,mm3}^{tumor} \times 10^5 \times \left(ADC_{b1,m1,b,ag}^{cell} + ADC_{b1,m1}^{cell,lyso}\right) \times \frac{SF}{V^{tumor}}}_{\text{From intracellular content of dying cells}} \underbrace{- K_{pino}^{ADC,cell,lyso} \times \left(\frac{NCL^{tumor}}{\varepsilon^{ADC}}\right) \times AD}_{\text{To pinocytosis}}$$

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

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

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

$$\frac{d(Ab_f^{ex})}{dt} = \left(\frac{Ab_f^{C1}}{V_{ADC}^{C1}} - \frac{Ab_f^{ex}}{\varepsilon^{ADC}}\right) \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{ADC}}{R_{Tumor}^2}\right)$$

From central space

$$+ \left(-K_{on}^{ADC,cell,ag} \times \frac{Ab_f^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - \sum_{i=0}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j \leq max} Ab_{bi,mj,b,ag}^{cell} - \sum_{i=0}^{2} ADC_{bi,b,ag}^{cell} - \sum_{j=1}^{2} ADC_{mj,b,ag}^{cell} - ADC_{b1,m1,b,ag}^{cell}\right.\right.$$

$$\left.+ K_{off}^{ADC,cell,ag} \times Ab_{f,b,ag}^{cell}\right)$$

Binding and unbinding of ADC to receptors on tumor cell

$$\times \frac{NC^{tumor} \times SF}{V^{tumor}} + \frac{1}{\tau} \times V_{dyi,3,mm3}^{tumor} \times 10^5 \times \left(Ab_{f,b,ag}^{cell}\right) \times \frac{SF}{V^{tumor}} - K_{pino}^{ADC,cell,lyso} \times \left(\frac{NCL^{tumor}}{\varepsilon^{ADC}}\right) \times Ab_f^{ex}$$

From intracellular content of dying cells

To pinocytosis

$$-K_{on}^{Ab,Drug} \times max \times \frac{Ab_f^{ex}}{\varepsilon^{ADC}} \times \frac{Drug_f^{ex}}{V^{tumor} \times \varepsilon^{Drug}} + K_{off}^{Ab,Drug} \times \frac{Ab_{b1}^{ex}}{\varepsilon^{ADC}} - K_{on}^{Ab,Meta} \times max \times \frac{Ab_f^{ex}}{\varepsilon^{ADC}} \times \frac{Meta1_f^{ex}}{V^{tumor} \times \varepsilon^{Meta}} + K_{off}^{Ab,Meta} \times \frac{Ab_{m1}^{ex}}{\varepsilon^{ADC}}$$

To binding to drug

From unbinding of drug

To binding to metabolite

From unbinding of metabolite

$$\boxed{\text{Concentration (nM) of Antibody bound to i Protacs in tumor extracellular space, i = 1,2,3}}$$

$$\frac{d(Ab_{bi}^{ex})}{dt} = \underbrace{\left(\frac{Ab_{bi}^{C1}}{V_{ADC}^{C1}} - \frac{Ab_{bi}^{ex}}{\varepsilon^{ADC}}\right) \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{ADC}}{R_{Tumor}^2}\right)}_{\text{From central space}} + K_{off}^{ADC,cell,ag} \times Ab_{bi,b,ag}^{cell} \times \frac{NC^{tumor} \times SF}{V^{tumor}}$$

$$+ \underbrace{\left(-K_{on}^{ADC,cell,ag} \times \frac{Ab_{bi}^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - \sum_{i=0}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j\leq max} Ab_{bi,mj,b,ag}^{cell} - \sum_{i=0}^{2} ADC_{bi,b,ag}^{cell} - \sum_{j=1}^{2} ADC_{mj,b,ag}^{cell} - ADC_{b1,m1,b,ag}^{cell}\right.}_{\text{Binding and unbinding of ADC to receptors on tumor cell}}$$

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

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

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

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

$$\frac{d(Ab_{b4}^{ex})}{dt} = \left(\frac{Ab_{b4}^{C1}}{V_{ADC}^{C1}} - \frac{Ab_{b4}^{ex}}{\varepsilon^{ADC}}\right) \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{ADC}}{R_{Tumor}^2}\right)$$

From central space

$$+ \left(-K_{on}^{ADC,cell,ag} \times \frac{Ab_{b4}^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - \sum_{i=0}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j\leq max} Ab_{bi,mj,b,ag}^{cell} - \sum_{i=0}^{2} ADC_{bi,b,ag}^{cell} - \sum_{j=1}^{2} ADC_{mj,b,ag}^{cell} - ADC_{b1,m1,b,ag}^{cell} \right) \right.$$

Binding and unbinding of ADC to receptors on tumor cell

$$\left. + K_{off}^{ADC,cell,ag} \times Ab_{b4,b,ag}^{cell} \right)$$

$$\times \frac{NC^{tumor} \times SF}{V^{tumor}} + \frac{1}{\tau} \times V_{dyi,3,mm3}^{tumor} \times 10^5 \times \left(Ab_{b4,b,ag}^{cell} + Ab_{b4}^{cell,lyso} \right) \times \frac{SF}{V^{tumor}} - K_{pino}^{ADC,cell,lyso} \times \left(\frac{NCL^{tumor}}{\varepsilon^{ADC}} \right) \times Ab_{b4}^{ex}$$

From intracellular content of dying cells

To pinocytosis

$$+ K_{on}^{Ab,Drug} \times \frac{Ab_{b3}^{ex}}{\varepsilon^{ADC}} \times \frac{Drug_f^{ex}}{V^{tumor} \times \varepsilon^{Drug}} - K_{off}^{Ab,Drug} \times \frac{Ab_{b4}^{ex}}{\varepsilon^{ADC}}$$

From binding to drug   To unbinding of drug

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

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

From central space

$$+ \left(-K_{on}^{ADC,cell,ag} \times \frac{Ab_{mj}^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - \sum_{i=0}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j \leq max} Ab_{bi,mj,b,ag}^{cell} - \sum_{i=0}^{2} ADC_{bi,b,ag}^{cell} - \sum_{j=1}^{2} ADC_{mj}^{ce}\right)\right.$$

Binding and unbinding of ADC to receptors on tumor cell

$$\times \frac{NC^{tumor} \times SF}{V^{tumor}} + \frac{1}{\tau} \times V_{dyi,3,mm3}^{tumor} \times 10^5 \times \left(Ab_{mj,b,ag}^{cell} + Ab_{mj}^{cell,lyso}\right) \times \frac{SF}{V^{tumor}} - K_{pino}^{ADC,cell,lyso} \times \left(\frac{NCL^{tumor}}{\varepsilon^{ADC}}\right) \times Ab_{mj}^{ex}$$

From intracellular content of dying cells   To pinocytosis

$$-K_{on}^{Ab,Drug} \times (max - j) \times \frac{Ab_{mj}^{ex}}{\varepsilon^{ADC}} \times \frac{Drug_f^{ex}}{V^{tumor} \times \varepsilon^{Drug}} + K_{off}^{Ab,Drug} \times \frac{Ab_{b1,mj}^{ex}}{\varepsilon^{ADC}} + K_{on}^{Ab,Meta} \times (max - j + 1) \times \frac{Ab_{mj-1}^{ex}}{\varepsilon^{ADC}} \times \frac{M}{V^{tum}}$$

To binding to drug   From unbinding of drug   From binding to metabolite

$$-K_{off}^{Ab,Meta} \times \frac{Ab_{mj}^{ex}}{\varepsilon^{ADC}} - K_{on}^{Ab,Meta} \times (max - j) \times \frac{Ab_{mj}^{ex}}{\varepsilon^{ADC}} \times \frac{Meta1_f^{ex}}{V^{tumor} \times \varepsilon^{Meta}} + K_{off}^{Ab,Meta} \times \frac{Ab_{mj+1}^{ex}}{\varepsilon^{ADC}}$$

To unbinding of metabolite   To binding to metabolite   From unbinding of metabolite

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

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

From central space

$$+ \left(-K_{on}^{ADC,cell,ag} \times \frac{Ab_{m4}^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - \sum_{i=0}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j \leq max} Ab_{bi,mj,b,ag}^{cell} - \sum_{i=0}^{2} ADC_{bi,b,ag}^{cell} - \sum_{j=1}^{2} ADC_{mj}^{ce} \right. \right.$$

Binding and unbinding of ADC to receptors on tumor cell

$$\times \frac{NC^{tumor} \times SF}{V^{tumor}} + \frac{1}{\tau} \times V_{dyi,3,mm3}^{tumor} \times 10^5 \times \left(Ab_{m4,b,ag}^{cell} + Ab_{m4}^{cell,lyso} \right) \times \frac{SF}{V^{tumor}} - K_{pino}^{ADC,cell,lyso} \times \left(\frac{NCL^{tumor}}{\varepsilon^{ADC}} \right) \times Ab_{m4}^{ex}$$

From intracellular content of dying cells   To pinocytosis

$$+ K_{on}^{Ab,Meta} \times \frac{Ab_{m3}^{ex}}{\varepsilon^{ADC}} \times \frac{Meta1_f^{ex}}{V^{tumor} \times \varepsilon^{Meta}} - K_{off}^{Ab,Meta} \times \frac{Ab_{m4}^{ex}}{\varepsilon^{ADC}}$$

From binding to metabolite   To unbinding of metabolite

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

From central space

$$+ \left(-K_{on}^{ADC,cell,ag} \times \frac{Ab_{bi,mj}^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - \sum_{i=0}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j \leq max} Ab_{bi,mj,b,ag}^{cell} - \sum_{i=0}^{2} ADC_{bi,b,ag}^{cell} - \sum_{j=1}^{2} ADC_{1}^{c} \right.\right.$$

Binding and unbinding of ADC to receptors on tumor cell

$$\times \frac{NC^{tumor} \times SF}{V^{tumor}} + \frac{1}{\tau} \times V_{dyi,3,mm3}^{tumor} \times 10^5 \times \left(Ab_{bi,mj,b,ag}^{cell} + Ab_{bi,mj}^{cell,lyso}\right) \times \frac{SF}{V^{tumor}} - K_{pino}^{ADC,cell,lyso} \times \left(\frac{NCL^{tumor}}{\varepsilon^{ADC}}\right) \times Ab_{bi,m}^{ex}$$

From intracellular content of dying cells   To pinocytosis

$$-K_{on}^{Ab,Drug} \times (max - i - j) \times \frac{Ab_{bi,mj}^{ex}}{\varepsilon^{ADC}} \times \frac{Drug_f^{ex}}{V^{tumor} \times \varepsilon^{Drug}} + K_{off}^{Ab,Drug} \times \frac{Ab_{bi+1,mj}^{ex}}{\varepsilon^{ADC}}$$

To binding to drug   From unbinding of drug

$$+K_{on}^{Ab,Drug} \times (max - i + 1 - j) \times \frac{Ab_{bi-1,mj}^{ex}}{\varepsilon^{ADC}} \times \frac{Drug_f^{ex}}{V^{tumor} \times \varepsilon^{Drug}} - K_{off}^{Ab,Drug} \times \frac{Ab_{bi,mj}^{ex}}{\varepsilon^{ADC}} - K_{on}^{Ab,Meta} \times (max - i - j) \times \frac{Ab_{bi}^{ex}}{\varepsilon^{AL}}$$

From binding to drug   To unbinding of drug   To binding to metabolite

$$+K_{off}^{Ab,Meta} \times \frac{Ab_{bi,mj+1}^{ex}}{\varepsilon^{ADC}} + K_{on}^{Ab,Meta} \times (max - i - j + 1) \times \frac{Ab_{bi,mj-1}^{ex}}{\varepsilon^{ADC}} \times \frac{Meta1_f^{ex}}{V^{tumor} \times \varepsilon^{Meta}} - K_{off}^{Ab,Meta} \times \frac{Ab_{bi,mj}^{ex}}{\varepsilon^{ADC}}$$

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

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

From central space

$$+ \left(-K_{on}^{ADC,cell,ag} \times \frac{Ab_{bi,mj}^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - \sum_{i=0}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j \leq max} Ab_{bi,mj,b,ag}^{cell} - \sum_{i=0}^{2} ADC_{bi,b,ag}^{cell} - \sum_{j=1}^{2} ADC_{n}^{c}\right)\right.$$

Binding and unbinding of ADC to receptors on tumor cell

$$\times \frac{NC^{tumor} \times SF}{V^{tumor}} + \frac{1}{\tau} \times V_{dyi,3,mm3}^{tumor} \times 10^5 \times \left(Ab_{bi,mj,b,ag}^{cell} + Ab_{bi,mj}^{cell,lyso}\right) \times \frac{SF}{V^{tumor}} - K_{pino}^{ADC,cell,lyso} \times \left(\frac{NCL^{tumor}}{\varepsilon^{ADC}}\right) \times Ab_{bi,mj}^{ex}$$

From intracellular content of dying cells   To pinocytosis

$$+K_{on}^{Ab,Drug} \times (max - i + 1 - j) \times \frac{Ab_{bi-1,mj}^{ex}}{\varepsilon^{ADC}} \times \frac{Drug_f^{ex}}{V^{tumor} \times \varepsilon^{Drug}} - K_{off}^{Ab,Drug} \times \frac{Ab_{bi,mj}^{ex}}{\varepsilon^{ADC}}$$

From binding to drug   To unbinding of drug

$$+K_{on}^{Ab,Meta} \times (max - i - j + 1) \times \frac{Ab_{bi,mj-1}^{ex}}{\varepsilon^{ADC}} \times \frac{Meta1_f^{ex}}{V^{tumor} \times \varepsilon^{Meta}} - K_{off}^{Ab,Meta} \times \frac{Ab_{bi,mj}^{ex}}{\varepsilon^{ADC}}$$

From binding to metabolite   To unbinding of metabolite

$$\boxed{\text{Amount (nmol) of drug in tumor extracellular space}}$$

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

$$+ \left(\underbrace{K_{dec}^{ADC} \times \left(\sum_{i=0}^{2} ADC_{bi,b,ag}^{cell} + \sum_{j=1}^{2} ADC_{mj,b,ag}^{cell} + ADC_{b1,m1,b,ag}^{cell}\right) \times \overline{DAR}}_{\text{Non-specific deconj. of ADC}} + \underbrace{K_{out}^{Drug,ex} \times Drug_f^{cell,cyto}}_{\text{Efflux of drug from the cell}}\right) \times NC^{tumor} \times SF$$

$$\underbrace{- K_{in}^{Drug,ex} \times NC^{tumor} \times \left(\frac{V^{cell}}{V^{tumor} \times \varepsilon^{Drug}}\right) \times Drug_f^{ex}}_{\text{To influx into cells}} \underbrace{- K_{met}^{Drug,ex} \times \frac{Drug_f^{ex}}{\varepsilon^{Drug}}}_{\text{To metabolism}} \underbrace{+ K_{dec}^{ADC} \times \frac{\left(\sum_{i=0}^{2} ADC_{bi}^{ex} + \sum_{j=1}^{2} ADC_{mj}^{ex} + ADC_{b1,m1}^{ex}\right)}{\varepsilon^{ADC}} \times \overline{DAR} \times V^{tu}}_{\text{From non-specific deconjugation of ADC}}$$

$$\underbrace{+ \frac{1}{\tau} \times V_{dyi,3,mm3}^{tumor} \times 10^5 \times \left(\text{Drug}_f^{cell,cyto} + \text{Drug}_{b,dt}^{cell,cyto} + \text{Drug}_f^{cell,lyso}\right) \times SF}_{\text{From intracellular content of dying cells}} \underbrace{- \sum_{i,j=0,i+j<max}^{max-1} K_{on}^{Ab,Drug} \times (max - i - j) \times \frac{Ab_{bi,mj}^{ex}}{\varepsilon^{ADC}} \times \frac{Drug_f^{ex}}{\varepsilon^{Drug}}}_{\text{To binding to antibody}}$$

$$\underbrace{+ \sum_{i=1,j=0,i+j\leq max}^{max} K_{off}^{Ab,Drug} \times \frac{Ab_{bi,mj}^{ex}}{\varepsilon^{ADC}} \times V^{tumor}}_{\text{From unbinding of antibody}} \underbrace{- \sum_{i,j=0,i+j<max}^{max-1} K_{on}^{Ab,Drug} \times (max - i - j) \times Ab_{bi,mj,b,ag}^{cell} \times NC^{tumor} \times \frac{Drug_f^{ex}}{V^{tumor} \times \varepsilon^{Drug}} \times SF}_{\text{To binding to antibody bound to binding target on a single cell}}$$

$$+ \underbrace{\sum_{i=1,j=0,i+j\leq max}^{max} K_{off}^{Ab,Drug} \times Ab_{bi,mj,b,ag}^{cell} \times NC^{tumor} \times SF}_{\text{From unbinding of antibody bound to binding target on a single cell}} - K_{on}^{Ab,Drug} \times \left(2 \times \frac{ADC_f^{ex}}{\varepsilon^{ADC}} + \frac{ADC_{b1}^{ex}}{\varepsilon^{ADC}} + \frac{ADC_{m1}^{ex}}{\varepsilon^{ADC}}\right) \times \frac{Drug_f^{ex}}{\varepsilon^{Drug}}$$

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

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

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

$$+ \underbrace{\frac{1}{\tau} \times V_{dyi,3,mm3}^{tumor} \times 10^5 \times \left(Meta1_f^{cell,cyto} + Meta1_f^{cell,lyso}\right) \times SF}_{\text{From intracellular content of dying cells}} - \underbrace{\sum_{i,j=0,i+j<max}^{max-1} K_{on}^{Ab,Meta} \times (max - i - j) \times \frac{Ab_{bi,mj}^{ex}}{\varepsilon^{ADC}} \times \frac{Meta1_f^{ex}}{\varepsilon^{Meta}}}_{\text{To binding to antibody}}$$

$$+ \underbrace{\sum_{i=0,j=1,i+j\leq max}^{max} K_{off}^{Ab,Meta} \times \frac{Ab_{bi,mj}^{ex}}{\varepsilon^{ADC}} \times V^{tumor}}_{\text{From unbinding of antibody}} - \underbrace{\sum_{i,j=0,i+j<max}^{max-1} K_{on}^{Ab,Meta} \times (max - i - j) \times Ab_{bi,mj,b,ag}^{cell} \times NC^{tumor} \times \frac{Meta1_f^{ex}}{V^{tumor} \times \varepsilon^{Meta}} \times SF}_{\text{To binding to antibody bound to binding target on a single cell}}$$

$$+ \underbrace{\sum_{i=0,j=1,i+j\leq max}^{max} K_{off}^{Ab,Meta} \times Ab_{bi,mj,b,ag}^{cell} \times NC^{tumor} \times SF}_{\text{From unbinding of antibody bound to binding target on a single cell}} - K_{on}^{Ab,Meta} \times \left(2 \times \frac{ADC_f^{ex}}{\varepsilon^{ADC}} + \frac{ADC_{b1}^{ex}}{\varepsilon^{ADC}} + \frac{ADC_{m1}^{ex}}{\varepsilon^{ADC}}\right) \times \frac{Meta1_f^{ex}}{\varepsilon^{Meta}}$$

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

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

From metabolism

From central space

$$+K_{out}^{Meta,ex} \times Meta2_f^{cell,cyto} \times NC^{tumor} \times SF - K_{in}^{Meta,ex} \times NC^{tumor} \times \left(\frac{V^{cell}}{V^{tumor} \times \varepsilon^{Meta}}\right) \times Meta2_f^{ex}$$

Fromm efflux of drug from the cell

To influx into cells

$$+\frac{1}{\tau} \times V_{dyi,3,mm3}^{tumor} \times 10^5 \times \left(Meta2_f^{cell,cyto} + Meta2_{b,dt}^{cell,cyto} + Meta2_f^{cell,lyso}\right) \times SF$$

From intracellular content of dying cells

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

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

$$\frac{d(ADC_{f,b,ag}^{cell})}{dt} = K_{on}^{ADC,cell,ag} \times \frac{ADC_f^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - \sum_{i=0}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j\leq max} Ab_{bi,mj,b,ag}^{cell} - \sum_{i=0}^{2} ADC_{bi,b,ag}^{cell} - \sum_{j=1}^{2} A \right.$$

From binding to receptor

$$-K_{off}^{ADC,cell,ag} \times ADC_{f,b,ag}^{cell} - K_{int}^{ADC,cell} \times ADC_{f,b,ag}^{cell} - \frac{\ln(2)}{DT^{tumor}} \times ADC_{f,b,ag}^{cell} - K_{on}^{Ab,Drug} \times 2 \times ADC_{f,b,ag}^{cell} \times \frac{Drug_f^{ex}}{V^{tumor} \times \varepsilon^{Drug}}$$

To unbinding from receptor   To internalization into cell   To dilution as cells grow and divide   To binding to drug

$$+K_{off}^{Ab,Drug} \times ADC_{b1,b,ag}^{cell} - K_{on}^{Ab,Meta} \times 2 \times ADC_{f,b,ag}^{cell} \times \frac{Meta1_f^{ex}}{V^{tumor} \times \varepsilon^{Meta}} + K_{off}^{Ab,Meta} \times ADC_{m1,b,ag}^{cell}$$

From unbinding of drug   To binding to metabolite   From unbinding of metabolite

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

Number of ADC molecules bound to 1 Protac bound to binding target on a single cell

$$\frac{d(ADC_{b1,b,ag}^{cell})}{dt} = K_{on}^{ADC,cell,ag} \times \frac{ADC_{b1}^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - \sum_{i=0}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j \leq max} Ab_{bi,mj,b,ag}^{cell} - \sum_{i=0}^{2} ADC_{bi,b,ag}^{cell} - \sum_{j=1}^{2} \right.$$

From binding to receptor

$$-K_{off}^{ADC,cell,ag} \times ADC_{b1,b,ag}^{cell} - K_{int}^{ADC,cell} \times ADC_{b1,b,ag}^{cell} - \frac{\ln(2)}{DT^{tumor}} \times ADC_{b1,b,ag}^{cell} - K_{on}^{Ab,Drug} \times ADC_{b1,b,ag}^{cell} \times \frac{Drug_f^{ex}}{V^{tumor} \times \varepsilon^{Drug}}$$

To unbinding from receptor

To internalization into cell

To dilution as cells grow and divide

To binding to drug

$$+K_{off}^{Ab,Drug} \times ADC_{b2,b,ag}^{cell} + K_{on}^{Ab,Drug} \times 2 \times ADC_{f,b,ag}^{cell} \times \frac{Drug_f}{V^{tumor} \times \varepsilon^{Drug}} - K_{off}^{Ab,Drug} \times ADC_{b1,b,ag}^{cell}$$

From unbinding of drug

From binding to drug

To unbinding of drug

$$-K_{on}^{Ab,Meta} \times ADC_{b1,b,ag}^{cell} \times \frac{Meta1_f^{ex}}{V^{tumor} \times \varepsilon^{Meta}} + K_{off}^{Ab,Meta} \times ADC_{b1,m1,b,ag}^{cell}$$

To binding to metabolite

From unbinding of metabolite

Number of ADC molecules bound to 2 Protacs bound to binding target on a single cell

$$\frac{d(ADC_{b2,b,ag}^{cell})}{dt} = K_{on}^{ADC,cell,ag} \times \frac{ADC_{b2}^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - \sum_{i=0}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j\leq max} Ab_{bi,mj,b,ag}^{cell} - \sum_{i=0}^{2} ADC_{bi,b,ag}^{cell} - \sum_{j=1}^{2} \right.$$

From binding to receptor

$$-K_{off}^{ADC,cell,ag} \times ADC_{b2,b,ag}^{cell} - K_{int}^{ADC,cell} \times ADC_{b2,b,ag}^{cell} - \frac{\ln(2)}{DT^{tumor}} \times ADC_{b2,b,ag}^{cell}$$

To unbinding from receptor   To internalization into cell   To dilution as cells grow and divide

$$+K_{on}^{Ab,Drug} \times ADC_{b1,b,ag}^{cell} \times \frac{Drug_f^{ex}}{V^{tumor} \times \varepsilon^{Drug}} - K_{off}^{Ab,Drug} \times ADC_{b2,b,ag}^{cell}$$

From binding to drug   To unbinding of drug

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

Number of ADC molecules bound to 1 Metabolite1 bound to binding target on a single cell

$$\frac{d(ADC_{m1,b,ag}^{cell})}{dt} = K_{on}^{ADC,cell,ag} \times \frac{ADC_{m1}^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - \sum_{i=0}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j\leq max} Ab_{bi,mj,b,ag}^{cell} - \sum_{i=0}^{2} ADC_{bi,b,ag}^{cell} - \sum_{j=1}^{2} \right.$$

From binding to receptor

$$-K_{off}^{ADC,cell,ag} \times ADC_{m1,b,ag}^{cell} - K_{int}^{ADC,cell} \times ADC_{m1,b,ag}^{cell} - \frac{\ln(2)}{DT^{tumor}} \times ADC_{m1,b,ag}^{cell} - K_{on}^{Ab,Drug} \times ADC_{m1,b,ag}^{cell} \times \frac{Drug_f^{ex}}{V^{tumor} \times \varepsilon^{Drug}}$$

To unbinding from receptor   To internalization into cell   To dilution as cells grow and divide   From binding to drug

$$+K_{off}^{Ab,Drug} \times ADC_{b1,m1,b,ag}^{cell} + K_{on}^{Ab,Meta} \times 2 \times ADC_{f,b,ag}^{cell} \times \frac{Meta1_f^{ex}}{V^{tumor} \times \varepsilon^{Meta}}$$

To unbinding of drug   From binding to metabolite

$$-K_{off}^{Ab,Meta} \times ADC_{m1,b,ag}^{cell} - K_{on}^{Ab,Meta} \times ADC_{m1,b,ag}^{cell} \times \frac{Meta1_f^{ex}}{V^{tumor} \times \varepsilon^{Meta}} + K_{off}^{Ab,Meta} \times ADC_{m2,b,ag}^{cell}$$

To unbinding of metabolite   To binding to metabolite   From unbinding of metabolite

Number of ADC molecules bound to 2 Metabolites1 bound to binding target on a single cell

$$\frac{d(ADC_{m2,b,ag}^{cell})}{dt} = K_{on}^{ADC,cell,ag} \times \frac{ADC_{m2}^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - \sum_{i=0}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j\leq max} Ab_{bi,mj,b,ag}^{cell} - \sum_{i=0}^{2} ADC_{bi,b,ag}^{cell} - \sum_{j=}^{} \right.$$

From binding to receptor

$$-K_{off}^{ADC,cell,ag} \times ADC_{m2,b,ag}^{cell} - K_{int}^{ADC,cell} \times ADC_{m2,b,ag}^{cell} - \frac{\ln(2)}{DT^{tumor}} \times ADC_{m2,b,ag}^{cell}$$

To unbinding from receptor   To internalization into cell   To dilution as cells grow and divide

$$+K_{on}^{Ab,Meta} \times ADC_{m1,b,ag}^{cell} \times \frac{Meta1_f^{ex}}{V^{tumor} \times \varepsilon^{Meta}} - K_{off}^{Ab,Meta} \times ADC_{m2,b,ag}^{cell}$$

From binding to metabolite   To unbinding of metabolite

Number of ADC molecules bound 1 Protac and 1 Metabolite1 bound to binding target on a single cell

$$\frac{d(ADC_{b1,m1,b,ag}^{cell})}{dt} = K_{on}^{ADC,cell,ag} \times \frac{ADC_{b1,m1}^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - \sum_{i=0}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j \leq max} Ab_{bi,mj,b,ag}^{cell} - \sum_{i=0}^{2} ADC_{bi,b,ag}^{cell} \right)$$

From binding to receptor

$$-K_{off}^{ADC,cell,ag} \times ADC_{b1,m1,b,ag}^{cell} - K_{int}^{ADC,cell} \times ADC_{b1,m1,b,ag}^{cell} - \frac{\ln(2)}{DT^{tumor}} \times ADC_{b1,m1,b,ag}^{cell}$$

To unbinding from receptor   To internalization into cell   To dilution as cells grow and divide

$$+K_{on}^{Ab,Drug} \times ADC_{m1,b,ag}^{cell} \times \frac{Drug_f^{ex}}{V^{tumor} \times \varepsilon^{Drug}} - K_{off}^{Ab,Drug} \times ADC_{b1,m1,b,ag}^{cell}$$

From binding to drug   To unbinding of drug

$$+K_{on}^{Ab,Meta} \times ADC_{b1,b,ag}^{cell} \times \frac{Meta1_f^{ex}}{V^{tumor} \times \varepsilon^{Meta}} - K_{off}^{Ab,Meta} \times ADC_{b1,m1,b,ag}^{cell}$$

From binding to metabolite   To unbinding of metabolite

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

$$\frac{d(Ab_{f,b,ag}^{cell})}{dt} = K_{on}^{ADC,cell,ag} \times \frac{Ab_f^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - \sum_{i=0}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j\leq max} Ab_{bi,mj,b,ag}^{cell} - \sum_{i=0}^{2} ADC_{bi,b,ag}^{cell} - \sum_{j=1}^{2} ADC_{...} \right)$$

From binding to receptor

$$-K_{off}^{ADC,cell,ag} \times Ab_{f,b,ag}^{cell} - K_{int}^{ADC,cell} \times Ab_{f,b,ag}^{cell} - \frac{\ln(2)}{DT^{tumor}} \times Ab_{f,b,ag}^{cell} - K_{on}^{Ab,Drug} \times max \times Ab_{f,b,ag}^{cell} \times \frac{Drug_f^{ex}}{V^{tumor} \times \varepsilon^{Drug}}$$

To unbinding from receptor   To internalization into cell   To dilution as cells grow and divide   To binding to drug

$$+K_{off}^{Ab,Drug} \times Ab_{b1,b,ag}^{cell} - K_{on}^{Ab,Meta} \times max \times Ab_{f,b,ag}^{cell} \times \frac{Meta1_f^{ex}}{V^{tumor} \times \varepsilon^{Meta}} + K_{off}^{Ab,Meta} \times Ab_{m1,b,ag}^{cell}$$

From unbinding of drug   To binding to metabolite   From unbinding of metabolite

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

$$\frac{d(Ab_{bi,b,ag}^{cell})}{dt} = K_{on}^{ADC,cell,ag} \times \frac{Ab_{bi}^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - \sum_{i=0}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j\leq max} Ab_{bi,mj,b,ag}^{cell} - \sum_{i=0}^{2} ADC_{bi,b,ag}^{cell} - \sum_{j=1}^{2} ADC \right.$$

From binding to receptor

$$-K_{off}^{ADC,cell,ag} \times Ab_{bi,b,ag}^{cell} - K_{int}^{ADC,cell} \times Ab_{bi,b,ag}^{cell} - \frac{\ln(2)}{DT^{tumor}} \times Ab_{bi,b,ag}^{cell} - K_{on}^{Ab,Drug} \times (max - i) \times Ab_{bi,b,ag}^{cell} \times \frac{Drug_f^{ex}}{V^{tumor} \times \varepsilon^{Drug}}$$

To unbinding from receptor

To internalization into cell

To dilution as cells grow and divide

To binding to drug

$$+K_{off}^{Ab,Drug} \times Ab_{bi+1,b,ag}^{cell} + K_{on}^{Ab,Drug} \times (max - i + 1) \times Ab_{bi-1,b,ag}^{cell} \times \frac{Drug_f^{ex}}{V^{tumor} \times \varepsilon^{Drug}} - K_{off}^{Ab,Drug} \times Ab_{bi,b,ag}^{cell}$$

From unbinding of drug

From binding to drug

To unbinding of drug

$$-K_{on}^{Ab,Meta} \times (max - i) \times Ab_{bi,b,ag}^{cell} \times \frac{Meta1_f^{ex}}{V^{tumor} \times \varepsilon^{Meta}} + K_{off}^{Ab,Meta} \times Ab_{bi,m1,b,ag}^{cell}$$

To binding to metabolite

From unbinding of metabolite

Units:

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

$$\frac{d(Ab_{b4,b,ag}^{cell})}{dt} = K_{on}^{ADC,cell,ag} \times \frac{Ab_{b4}^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - \sum_{i=0}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j\leq max} Ab_{bi,mj,b,ag}^{cell} - \sum_{i=0}^{2} ADC_{bi,b,ag}^{cell} - \sum_{j=1}^{2} AD \right.$$

From binding to receptor

$$- K_{off}^{ADC,cell,ag} \times Ab_{b4,b,ag}^{cell} - K_{int}^{ADC,cell} \times Ab_{b4,b,ag}^{cell} - \frac{\ln(2)}{DT^{tumor}} \times Ab_{b4,b,ag}^{cell}$$

To unbinding from receptor   To internalization into cell   To dilution as cells grow and divide

$$+ K_{on}^{Ab,Drug} \times Ab_{b3,b,ag}^{cell} \times \frac{Drug_f^{ex}}{V^{tumor} \times \varepsilon^{Drug}} - K_{off}^{Ab,Drug} \times Ab_{b4,b,ag}^{cell}$$

From binding to drug   To unbinding of drug

Units:

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

$$\frac{d(Ab^{cell}_{mj,b,ag})}{dt} = K^{ADC,cell,ag}_{on} \times \frac{Ab^{ex}_{mj}}{\varepsilon^{ADC}} \times \left(Ag^{cell}_t - \sum_{i=0}^{max} Ab^{cell}_{bi,b,ag} - \sum_{j=1}^{max} Ab^{cell}_{mj,b,ag} - \sum_{i,j=1}^{i+j \leq max} Ab^{cell}_{bi,mj,b,ag} - \sum_{i=0}^{2} ADC^{cell}_{bi,b,ag} - \sum_{j=1}^{2} A \right.$$

From binding to receptor

$$-K^{ADC,cell,ag}_{off} \times Ab^{cell}_{mj,b,ag} - K^{ADC,cell}_{int} \times Ab^{cell}_{mj,b,ag} - \frac{\ln(2)}{DT^{tumor}} \times Ab^{cell}_{mj,b,ag} - K^{Ab,Drug}_{on} \times (max - j) \times Ab^{cell}_{mj,b,ag} \times \frac{Drug^{ex}_f}{V^{tumor} \times \varepsilon^{D}}$$

To unbinding from receptor   To internalization into cell   To dilution as cells grow and divide   From binding to drug

$$+K^{Ab,Drug}_{off} \times Ab^{cell}_{b1,mj,b,ag} + K^{Ab,Meta}_{on} \times (max - j + 1) \times Ab^{cell}_{mj-1,b,ag} \times \frac{Meta1^{ex}_f}{V^{tumor} \times \varepsilon^{Meta}}$$

To unbinding of drug   From binding to metabolite

$$-K^{Ab,Meta}_{off} \times Ab^{cell}_{mj,b,ag} - K^{Ab,Meta}_{on} \times (max - j) \times Ab^{cell}_{mj,b,ag} \times \frac{Meta1^{ex}_f}{V^{tumor} \times \varepsilon^{Meta}} + K^{Ab,Meta}_{off} \times Ab^{cell}_{mj+1,b,ag}$$

To unbinding of metabolite   To binding to metabolite   From unbinding of metabolite

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

$$\frac{d(Ab_{m4,b,ag}^{cell})}{dt} = K_{on}^{ADC,cell,ag} \times \frac{Ab_{m4}^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - \sum_{i=0}^{max} Ab_{bi,b,ag}^{cell} - \sum_{j=1}^{max} Ab_{mj,b,ag}^{cell} - \sum_{i,j=1}^{i+j\leq max} Ab_{bi,mj,b,ag}^{cell} - \sum_{i=0}^{2} ADC_{bi,b,ag}^{cell} - \sum_{j=1}^{2} Al \right.$$

From binding to receptor

$$-K_{off}^{ADC,cell,ag} \times Ab_{m4,b,ag}^{cell} - K_{int}^{ADC,cell} \times Ab_{m4,b,ag}^{cell} - \frac{\ln(2)}{DT^{tumor}} \times Ab_{m4,b,ag}^{cell}$$

To unbinding from receptor   To internalization into cell   To dilution as cells grow and divide

$$+K_{on}^{Ab,Meta} \times Ab_{m3,b,ag}^{cell} \times \frac{Meta1_f^{ex}}{V^{tumor} \times \varepsilon^{Meta}} - K_{off}^{Ab,Meta} \times Ab_{m4,b,ag}^{cell}$$

From binding to metabolite   To unbinding of metabolite

$$\frac{d(Ab^{cell}_{bi,mj,b,ag})}{dt} = K^{ADC,cell,ag}_{on} \times \frac{Ab^{ex}_{bi,mj}}{\varepsilon^{ADC}} \times \left(Ag^{cell}_t - \sum_{i=0}^{max} Ab^{cell}_{bi,b,ag} - \sum_{j=1}^{max} Ab^{cell}_{mj,b,ag} - \sum_{i,j=1}^{i+j\leq max} Ab^{cell}_{bi,mj,b,ag} - \sum_{i=0}^{2} ADC^{cell}_{bi,b,ag} - \right.$$

From binding to receptor

$$-K^{ADC,cell,ag}_{off} \times Ab^{cell}_{bi,mj,b,ag} - K^{ADC,cell}_{int} \times Ab^{cell}_{bi,mj,b,ag} - \frac{\ln(2)}{DT^{tumor}} \times Ab^{cell}_{bi,mj,b,ag}$$

To unbinding from receptor   To internalization into cell   To dilution as cells grow and divide

$$-K^{Ab,Drug}_{on} \times (max - i - j) \times Ab^{cell}_{bi,mj,b,ag} \times \frac{Drug^{ex}_f}{V^{tumor} \times \varepsilon^{Drug}} + K^{Ab,Drug}_{off} \times Ab^{cell}_{bi+1,mj,b,ag} - K^{Ab,Drug}_{off} \times Ab^{cell}_{bi,mj,b,ag}$$

To binding to drug   From unbinding of drug   To unbinding of drug

$$+K^{Ab,Drug}_{on} \times (max - i + 1 - j) \times Ab^{cell}_{bi-1,mj,b,ag} \times \frac{Drug^{ex}_f}{V^{tumor} \times \varepsilon^{Drug}} - K^{Ab,Meta}_{on} \times (max - i - j) \times Ab^{cell}_{bi,mj,b,ag} \times \frac{Meta1^{ex}_f}{V^{tumor} \times \varepsilon^{Me}}$$

From binding to drug   To binding to metabolite

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

From unbinding of metabolite   From binding to metabolite   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

$$\frac{d(Ab^{cell}_{bi,mj,b,ag})}{dt} = K^{ADC,cell,ag}_{on} \times \frac{Ab^{ex}_{bi,mj}}{\varepsilon^{ADC}} \times \left(Ag^{cell}_t - \sum_{i=0}^{max} Ab^{cell}_{bi,b,ag} - \sum_{j=1}^{max} Ab^{cell}_{mj,b,ag} - \sum_{i,j=1}^{i+j\leq max} Ab^{cell}_{bi,mj,b,ag} - \sum_{i=0}^{2} ADC^{cell}_{bi,b,ag} - \sum_{j=}^{2} \right.$$

From binding to receptor

$$-K^{ADC,cell,ag}_{off} \times Ab^{cell}_{bi,mj,b,ag} - K^{ADC,cell}_{int} \times Ab^{cell}_{bi,mj,b,ag} - \frac{\ln(2)}{DT^{tumor}} \times Ab^{cell}_{bi,mj,b,ag}$$

To unbinding from receptor   To internalization into cell   To dilution as cells grow and divide

$$+K^{Ab,Drug}_{on} \times (max - i + 1 - j) \times Ab^{cell}_{bi-1,mj,b,ag} \times \frac{Drug^{ex}_f}{V^{tumor} \times \varepsilon^{Drug}} - K^{Ab,Drug}_{off} \times Ab^{cell}_{bi,mj,b,ag}$$

From binding to drug   To unbinding of drug

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

From binding to metabolite   To unbinding of metabolite

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

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

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

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 ADC molecules bound to j Metabolites1 internalized in endosomal/lysosomal space on a single cell, j = 1,2

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

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

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

Number of ADC molecules bound to 1 Protac and 1 Metabolite1 internalized in endosomal/lysosomal space on a single cell

$$\frac{d(ADC_{b1,m1}^{cell,lyso})}{dt} = \underbrace{K_{int}^{ADC,cell} \times ADC_{b1,m1,b,ag}^{cell}}_{\text{From internalization into cell}}$$

$$\underbrace{-K_{deg}^{ADC} \times ADC_{b1,m1}^{cell,lyso}}_{\text{To degradation}} \underbrace{+ K_{pino}^{ADC,cell,lyso} \times \frac{ADC_{b1,m1}^{ex}}{\varepsilon^{ADC} \times SF}}_{\text{From pinocytosis}} \underbrace{- \frac{\ln(2)}{DT^{tumor}} \times ADC_{b1,m1}^{cell,lyso}}_{\substack{\text{To dilution as cells grow} \\ \text{and divide}}}$$

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

From degradation of Shuttle   To cytosol

$$+K_{in}^{Drug,lyso} \times Drug_f^{cell,cyto} - \frac{\ln(2)}{DT^{tumor}} \times Drug_f^{cell,lyso} - K_{met}^{Drug,cell} \times Drug_f^{cell,lyso}$$

From cytosol   To dilution as cells grow and divide   To metabolism

$$+K_{deg}^{ADC} \times \left(ADC_{b1}^{cell,lyso} + ADC_{b2}^{cell,lyso} \times 2 + ADC_{b1,m1}^{cell,lyso}\right) + K_{deg}^{ADC} \times \left(\sum_{i=1}^{2} ADC_{bi}^{cell,lyso} + \sum_{j=1}^{2} ADC_{mj}^{cell,lyso} + ADC_{b1,m1}^{cell,lyso}\right) \times \overline{DAR}$$

From degradation of non-covalent bound Protac of ADC   From degradation of ADC

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

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

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

$$\underbrace{+ K_{deg}^{ADC} \times \left(ADC_{m1}^{cell,lyso} + ADC_{m2}^{cell,lyso} \times 2 + ADC_{b1,m1}^{cell,lyso}\right)}_{\text{From degradation of non-covalent bound Meta1 of ADC}}$$

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

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

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

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

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

$$\frac{d(Drug_f^{cell,cyto})}{dt} = +K_{out}^{Drug,lyso} \times \left(\frac{V^{cell}}{V^{cell,lyso}}\right) \times Drug_f^{cell,lyso} - K_{in}^{Drug,lyso} \times Drug_f^{cell,cyto} - K_{out}^{Drug,ex} \times Drug_f^{cell,cyto}$$

From and to lysosome   To efflux

$$-K_{met}^{Drug,cell} \times Drug_f^{cell,cyto} + K_{in}^{Drug,ex} \times \left(\frac{V^{cell}}{V^{tumor} \times \varepsilon^{Drug}}\right) \times \frac{Drug_f^{ex}}{SF} - \frac{\ln(2)}{DT^{tumor}} \times Drug_f^{cell,cyto}$$

To metabolism   From influx   To dilution as cells grow and divide

$$-K_{met}^{Drug} \times Drug_f^{cell,cyto} + K_{off}^{Drug,E3} \times Drug\_E3_b^{cell,cyto} + K_{off}^{Drug,Target} \times Drug\_DrugTarget_b^{cell,cyto}$$

To metabolism   From unbinding from E3-ligase   From unbinding from drug target

$$-\frac{K_{on}^{Drug,E3} \times SF}{V^{cell}} \times Drug_f^{cell,cyto} \times \left(E3_f^{cell,cyto} - Drug\_E3_b^{cell,cyto} - Drug_{b,dt}^{cell,cyto} - Meta1\_E3_b^{cell,cyto}\right)$$

To binding to E3-ligase

$$-\frac{K_{on}^{Drug,Target} \times SF}{V^{cell}} \times Drug_f^{cell,cyto} \times \left(\begin{array}{l} DrugTarget_f^{cell,cyto} - Drug\_DrugTarget_b^{cell,cyto} - Drug_{b,dt}^{cell,cyto} \\ -Meta2\_DrugTarget_b^{cell,cyto} \end{array}\right)$$

To binding to drug target

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

$$\frac{d(Meta1_f^{cell,cyto})}{dt} = +K_{out}^{Meta,lyso} \times \left(\frac{V^{cell}}{V^{cell,lyso}}\right) \times Meta1_f^{cell,lyso} - K_{in}^{Meta,lyso} \times Meta1_f^{cell,cyto}$$

From and to lysosome

$$-K_{out}^{Meta,ex} \times Meta1_f^{cell,cyto} + K_{in}^{Meta,ex} \times \left(\frac{V^{cell}}{V^{tumor} \times \varepsilon^{Meta}}\right) \times \frac{Meta1_f^{ex}}{SF} - \frac{\ln(2)}{DT^{tumor}} \times Meta1_f^{cell,cyto}$$

To efflux   From influx   To dilution as cells grow and divide

$$+K_{met}^{Drug,cell} \times Drug_f^{cell,cyto} + K_{off}^{Meta,E3} \times Meta1\_E3_b^{cell,cyto}$$

From metabolism   From unbinding from E3-ligase

$$-\frac{K_{on}^{Meta,E3} \times SF}{V^{cell}} \times Meta1_f^{cell,cyto} \times \left(E3_f^{cell,cyto} - Drug\_E3_b^{cell,cyto} - Drug_{b,dt}^{cell,cyto} - Meta1\_E3_b^{cell,cyto}\right)$$

To binding to E3-ligase

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

$$\frac{d(Meta2_f^{cell,cyto})}{dt} = +K_{out}^{Meta,lyso} \times \left(\frac{V^{cell}}{V^{cell,lyso}}\right) \times Meta2_f^{cell,lyso} - K_{in}^{Meta,lyso} \times Meta2_f^{cell,cyto} - \frac{\ln(2)}{DT^{tumor}} \times Meta2_f^{cell,cyto}$$

From and to lysosome   To dilution as cells grow and divide

$$+K_{met}^{Drug,cell} \times Drug_f^{cell,cyto} - K_{out}^{Meta,ex} \times Meta2_f^{cell,cyto} + K_{in}^{Meta,ex} \times \left(\frac{V^{cell}}{V^{tumor} \times \varepsilon^{Meta}}\right) \times \frac{Meta2_f^{ex}}{SF}$$

From metabolism   To efflux   From influx

$$-\frac{K_{on}^{Meta,Target} \times SF}{V^{cell}} \times Meta2_f^{cell,cyto} \times \left(DrugTarget_f^{cell,cyto} - Drug\_DrugTarget_b^{cell,cyto} - Drug_{b,dt}^{cell,cyto} \right.$$
$$\left. -Meta2\_DrugTarget_b^{cell,cyto} \right)$$

To binding to drug target

$$+K_{off}^{Meta,Target} \times Meta2\_DrugTarget_b^{cell,cyto}$$

From unbinding from drug target

Number of target and E3-ligase-bound drug molecules in cytosol on a single cell

$$\frac{d(Drug_{b,dt}^{cell,cyto})}{dt} = -\underbrace{\frac{\ln(2)}{DT^{tumor}} \times Drug_{b,dt}^{cell,cyto}}_{\text{To dilution as cells grow and divide}} \underbrace{- K_{off}^{Drug,E3} \times Drug_{b,dt}^{cell,cyto}}_{\text{To unbinding from E3-ligase}}$$

$$+\alpha \times \underbrace{\frac{K_{on}^{Drug,E3} \times SF}{V^{cell}} \times Drug\_DrugTarget_{b}^{cell,cyto} \times \left(E3_{f}^{cell,cyto} - Drug\_E3_{b}^{cell,cyto} - Drug_{b,dt}^{cell,cyto} - Meta1\_E3_{b}^{cell,cyto} \right)}_{\text{From binding to E3-ligase}}$$

$$+\alpha \times \underbrace{\frac{K_{on}^{Drug,Target} \times SF}{V^{cell}} \times Drug\_E3_{b}^{cell,cyto} \times \left(\begin{matrix} DrugTarget_{f}^{cell,cyto} - Drug\_DrugTarget_{b}^{cell,cyto} - Drug_{b,dt}^{cell,cyto} \\ -Meta2\_DrugTarget_{b}^{cell,cyto} \end{matrix} \right)}_{\text{From binding to drug target}}$$

$$\underbrace{- K_{off}^{Drug,Target} \times Drug_{b,dt}^{cell,cyto}}_{\text{To unbinding from drug target}}$$

Number of target molecules in cytosol on a single cell

$$\frac{d(DrugTarget_f^{cell,cyto})}{dt} = \underbrace{-\frac{\ln(2)}{DT^{tumor}} \times DrugTarget_f^{cell,cyto}}_{\text{To dilution as cells grow and divide}} + \underbrace{K_{off}^{Drug,Target} \times Drug\_DrugTarget_b^{cell,cyto}}_{\text{From unbinding from drug}}$$

$$\underbrace{-\frac{K_{on}^{Drug,Target} \times SF}{V^{cell}} \times Drug_f^{cell,cyto} \times \left(\begin{array}{c} DrugTarget_f^{cell,cyto} - Drug\_DrugTarget_b^{cell,cyto} - Drug_{b,dt}^{cell,cyto} \\ -Meta2\_DrugTarget_b^{cell,cyto} \end{array} \right)}_{\text{To binding to } Drug\_DrugTarget_b^{cell,cyto} \text{ with drug}}$$

$$\underbrace{-\alpha \times \frac{K_{on}^{Drug,Target} \times SF}{V^{cell}} \times Drug\_E3_b^{cell,cyto} \times \left(\begin{array}{c} DrugTarget_f^{cell,cyto} - Drug\_DrugTarget_b^{cell,cyto} - Drug_{b,dt}^{cell,cyto} \\ -Meta2\_DrugTarget_b^{cell,cyto} \end{array} \right)}_{\text{To binding to } Drug_{b,dt}^{cell,cyto} \text{ with } Drug\_E3_b^{cell,cyto}}$$

$$\underbrace{+K_{off}^{Drug,Target} \times Drug_{b,dt}^{cell,cyto}}_{\text{From unbinding from } Drug_{b,dt}^{cell,cyto}} \underbrace{- K_{met}^{Drug} \times DrugTarget_f^{cell,cyto}}_{\text{To metabolism}} \underbrace{+ K_{off}^{Meta,Target} \times Meta2\_DrugTarget_b^{cell,cyto}}_{\text{From unbinding from } Meta2\_DrugTarget_b^{cell,cyto}}$$

$$\underbrace{-\frac{K_{on}^{Meta,Target} \times SF}{V^{cell}} \times Meta2_f^{cell,cyto} \times \left(\begin{array}{c} DrugTarget_f^{cell,cyto} - Drug\_DrugTarget_b^{cell,cyto} - Drug_{b,dt}^{cell,cyto} \\ -Meta2\_DrugTarget_b^{cell,cyto} \end{array} \right)}_{\text{To binding to } Meta2\_DrugTarget_b^{cell,cyto} \text{ with } Meta2_f^{cell,cyto}} + k_{prod}$$

Number of E3-ligase molecules in cytosol on a single cell

$$\frac{d(E3_f^{cell,cyto})}{dt} = 0$$

Als Konstante!

$$-\frac{K_{on}^{Drug,E3} \times SF}{V^{cell}} \times Drug_f^{cell,cyto} \times E3_f^{cell,cyto}$$

$$+K_{off}^{Drug,E3} \times Drug\_E3_b^{cell,cyto} - \frac{K_{on}^{Drug,E3} \times SF}{V^{cell}} \times Drug\_DrugTarget_b^{cell,cyto} \times E3_f^{cell,cyto}$$

$$+K_{off}^{Drug,E3} \times Drug_{b,dt}^{cell,cyto} - \frac{\ln(2)}{DT^{tumor}} \times E3_f^{cell,cyto} + k_{prod} \times \left(E3_f^{cell,cyto}(0) - E3_f^{cell,cyto}\right)$$

Number of E3-ligase-bound drug molecules in cytosol on a single cell

$$\frac{d(Drug\_E3_b^{cell,cyto})}{dt} = -\frac{\ln(2)}{DT^{tumor}} \times Drug\_E3_b^{cell,cyto} + K_{off}^{Drug,Target} \times Drug_{b,dt}^{cell,cyto}$$

To dilution as cells grow and divide   From unbinding from drug target

$$-\alpha \times \frac{K_{on}^{Drug,Target} \times SF}{V^{cell}} \times Drug\_E3_b^{cell,cyto} \times \left(\begin{array}{c} DrugTarget_f^{cell,cyto} - Drug\_DrugTarget_b^{cell,cyto} - Drug_{b,dt}^{cell,cyto} \\ -Meta2\_DrugTarget_b^{cell,cyto} \end{array} \right)$$

To binding to drug target

$$+\frac{K_{on}^{Drug,E3} \times SF}{V^{cell}} \times Drug_f^{cell,cyto} \times \left(E3_f^{cell,cyto} - Drug\_E3_b^{cell,cyto} - Drug_{b,dt}^{cell,cyto} - Meta1\_E3_b^{cell,cyto} \right)$$

From binding to E3-ligase

$$-K_{off}^{Drug,E3} \times Drug\_E3_b^{cell,cyto}$$

To unbinding from E3-ligase

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

$$\frac{d(Drug\_DrugTarget_b^{cell,cyto})}{dt} = -\frac{\ln(2)}{DT^{tumor}} \times Drug\_DrugTarget_b^{cell,cyto} + K_{off}^{Drug,E3} \times Drug_{b,dt}^{cell,cyto}$$

To dilution as cells grow and divide   From unbinding from E3-ligase

$$-\alpha \times \frac{K_{on}^{Drug,E3} \times SF}{V^{cell}} \times \left(E3_f^{cell,cyto} - Drug\_E3_b^{cell,cyto} - Drug_{b,dt}^{cell,cyto} - Meta1\_E3_b^{cell,cyto}\right) \times Drug\_DrugTarget_b^{cell,cyto}$$

To binding to E3-ligase

$$+\frac{K_{on}^{Drug,Target} \times SF}{V^{cell}} \times Drug_f^{cell,cyto} \times \left(\begin{array}{c} DrugTarget_f^{cell,cyto} - Drug\_DrugTarget_b^{cell,cyto} - Drug_{b,dt}^{cell,cyto} \\ -Meta2\_DrugTarget_b^{cell,cyto} \end{array}\right)$$

From binding to drug target

$$-K_{off}^{Drug,Target} \times Drug\_DrugTarget_b^{cell,cyto}$$

To unbinding from drug target

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

$$\frac{d(Meta2\_DrugTarget_b^{cell,cyto})}{dt} = -K_{off}^{Meta,Target} \times \underbrace{Meta2\_DrugTarget_b^{cell,cyto}}_{\text{To unbinding from drug target}} - \underbrace{\frac{\ln(2)}{DT^{tumor}} \times Meta2\_DrugTarget_b^{cell,cyto}}_{\text{To dilution as cells grow and divide}}$$

$$+ \underbrace{\frac{K_{on}^{Meta,Target} \times SF}{V^{cell}} \times Meta2_f^{cell,cyto} \times \left(\begin{array}{c} DrugTarget_f^{cell,cyto} - Drug\_DrugTarget_b^{cell,cyto} - Drug_{b,dt}^{cell,cyto} \\ -Meta2\_DrugTarget_b^{cell,cyto} \end{array} \right)}_{\text{From binding to drug target}}$$

Number of E3-ligase-bound Metabolite1 molecules in cytosol on a single cell

$$\frac{d(Meta1\_E3_b^{cell,cyto})}{dt} = \underbrace{-K_{off}^{Meta,E3} \times Meta1\_E3_b^{cell,cyto}}_{\text{To unbinding from E3-ligase}} \underbrace{- \frac{\ln(2)}{DT^{tumor}} \times Meta1\_E3_b^{cell,cyto}}_{\text{To dilution as cells grow and divide}}$$

$$+ \underbrace{\frac{K_{on}^{Meta,E3} \times SF}{V^{cell}} \times Meta1_f^{cell,cyto} \times \left(E3_f^{cell,cyto} - Drug\_E3_b^{cell,cyto} - Drug_{b,dt}^{cell,cyto} - Meta1\_E3_b^{cell,cyto} \right)}_{\text{From binding to E3-ligase}}$$

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

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

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

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

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

$$t_l^{DC} = \ln\left(\frac{Drug_{b,dt}^{cell,cyto} \times SF}{V^{cell}}\right) - \ln(DC_{50})$$

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

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

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

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