

Modelling of Tumour Growth with Respect to the use of Anti-Cancer Agents

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Introduction and Objectives

- Cancer ranks as a major factor in global mortality [1].
- Tumour Volume Models (TVMs) contribute to **treatment decisions** and **predict** patient outcomes.
- Utilised data from the **PDXNet Portal** online database (<https://portal.pdxnetwork.org/>)

Objectives:

- Characterise the **kinetics** describing cancerous tumour growth upon **intraperitoneal** administration of **Docetaxel**, by developing novel mathematical models.
- Compare and contrast the **performance** of TVMs from the literature ([2] and [3]), identifying which **coupling mechanisms** are more adept in encapsulating the observed dynamics.

Tumour Volume Models

- The TVMs utilised are defined by ODEs and assume the geometry of a **spherically symmetric tumour**, characterised by 2 compartments: **proliferative** and **necrotic** regions, as illustrated in Fig. 1:

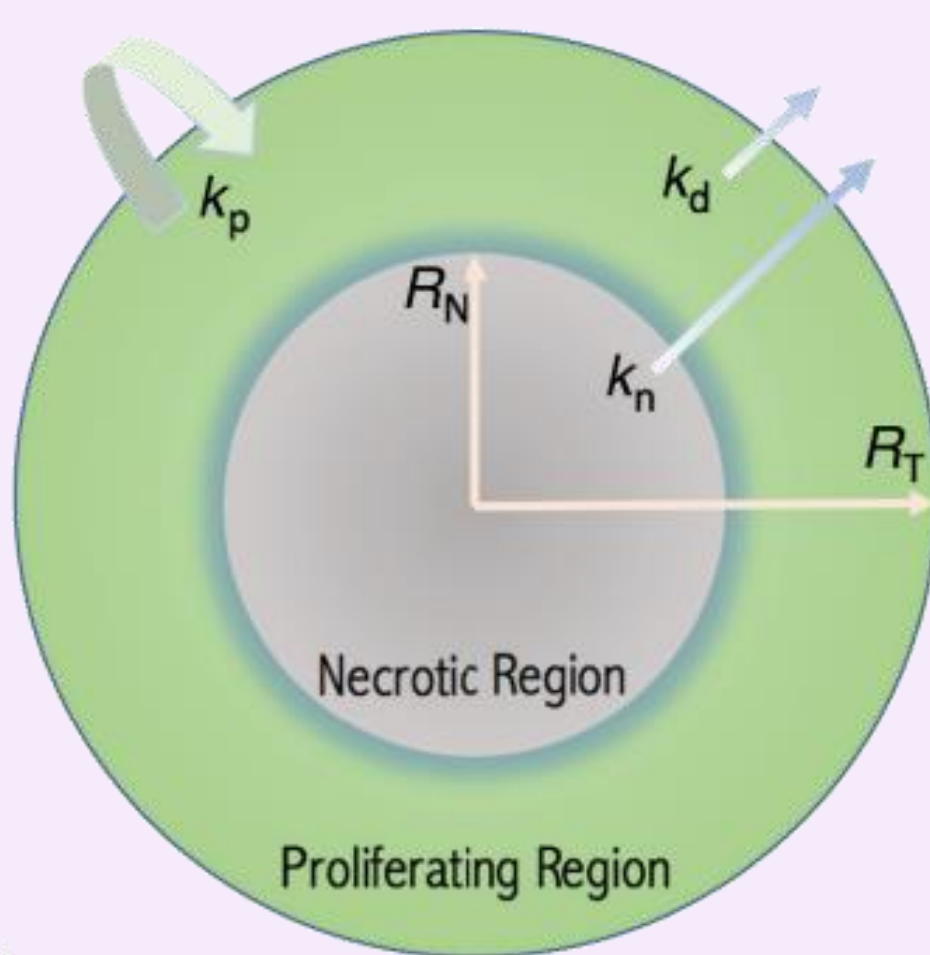


Figure 1: Geometry of a spherically shaped tumour [2]

Model 1: Nasim et al. TVM [2]	Model 2: Yates et al. TVM [3]
$\frac{dV}{dt} = K_V(V) \cdot V - L_{Drug}(w, GF) \cdot V$ $V(0) = V_0$	$\frac{dV}{dt} = m \cdot V \cdot (GF - GF_\infty); V(0) = V_0$ $GF_\infty = \frac{\mu_Q}{m}$
$\frac{dGF}{dt} = \frac{m \cdot (GF - GF_\infty)}{m \cdot (GF - GF_\infty) + \frac{1}{3}(1 - GF)^2 - \frac{1}{3}(1 - GF)^3}$ $GF(0) = GF_0$	$\frac{dGF}{dt} = \frac{m \cdot (GF - GF_\infty) \cdot [(1 - GF) - (1 - GF)^2]}{m \cdot (GF - GF_\infty) + \frac{1}{3}(1 - GF)^2 - \frac{1}{3}(1 - GF)^3}$ $GF(0) = GF_0$
Control: $L_{Drug}(w, GF) = 0$	Control: $m = \beta - \mu_P + \mu_Q$
Drug: $L_{Drug}(w, GF) = K_{kill} \cdot GF \cdot w$	Drug: $m = \beta \left(1 - \frac{I_{max} c_p}{IC50 + c_p} \right) - \mu_P - K_{kill} c_p + \mu_Q$

Table 1: ODEs of 2 TVMs ([2] and [3]) used in the analysis

Here: V : Tumour Volume (mm^3), $K_V(V)$: Net growth rate, $L_{Drug}(w, GF)$: Describes cell loss as a function of the drug concentration $w(t)$, GF : Growth Fraction of the tumour, GF_∞ : Growth Fraction when tumour size plateaus, β : rate of proliferation (day^{-1}), μ_P : rate of cell death in the proliferating compartment (day^{-1}), μ_Q : rate of cell death in the quiescent compartment (day^{-1}), I_{max} : maximum unbound systematic concentration ($\mu M/L$), $IC50$: half-maximal inhibitory concentration ($\mu M/L$), K_{kill} : drug potency ($L/(\mu M day)$) and c_p : plasma concentration ($\mu mol/L$)

Growth Models

- Growth models previously used in preclinical modelling have been analysed to identify the most accurate and representative one.

Model	$K_V(V)$
Surface Growth (SG)	$a \cdot V^{-\frac{1}{3}}$
Diffusion-Limited (DL)	$(k_p - k_d) \cdot GF - k_n \cdot (1 - GF)$

Table 2: Growth models used as part of the analysis [2]

Compartmental Model

- The PK model used for Docetaxel consists of 2 compartments (Fig. 2):

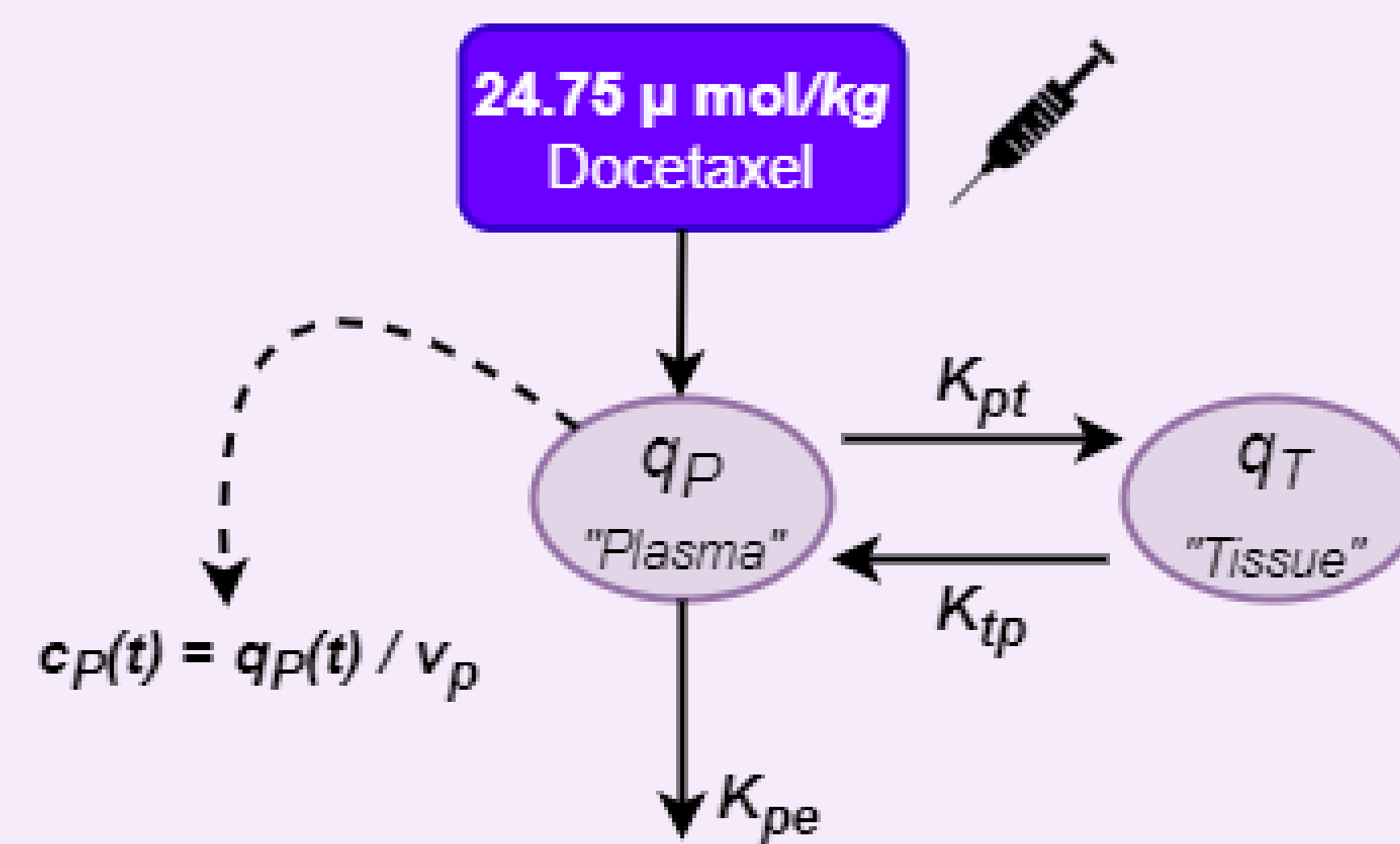


Figure 2: Compartmental model for Docetaxel [4]

K_{pe} : Rate constant of Doc20 flow from the plasma to the external environment (day^{-1}), K_{pt} : Rate constant of Doc20 flow from the plasma to the tissue (day^{-1}), K_{tp} : Rate constant of Doc20 flow from the tissue to the plasma (day^{-1}), q_P : Doc20 quantity in plasma ($\mu mol/kg$), q_T : Doc20 quantity in tissue ($\mu mol/kg$), c_P : Doc20 concentration in plasma ($\mu mol/L$) and v_P : mean plasma volume of distribution per kilogram (L/kg)

Model Equations

Linear model ODEs (Units are amounts in $\mu mol/kg$):

$$\frac{dq_P(t)}{dt} = -(K_{pe} + K_{pt})q_P(t) + K_{tp}q_T(t) + D\delta(t)$$

$$\frac{dq_T(t)}{dt} = K_{pt}q_P(t) - K_{tp}q_T(t)$$

Observation:

$$c_P(t) = \frac{q_P(t)}{v_P}$$

Initial conditions:

$$q_P(0) = Dose = 24.75 \mu mol/kg$$

$$q_T(0) = 0 \mu mol/kg$$

Model Parameterisation

- The model parameters for the PK model were estimated as described in the study [4] and scaled to daily units, as shown in Table 3:

Parameter (units)	Value
$K_{pe} (day^{-1})$	0.382/24
$K_{pt} (day^{-1})$	0.523/24
$K_{tp} (day^{-1})$	0.196/24
$v_P (L/kg)$	1.30

Table 3: Summary of PK model parameters [4]

- Population parameter estimation analysis was conducted in Monolix, employing the **SAEM algorithm** (Stochastic Approximation Expectation-Maximisation) [5] via a Non-Linear Mixed Effects (**NLME**) modelling approach, yielding the following parameter estimates:

TVMs	Estimated Parameters (units)	Pop. Value	S.E.	R.S.E. (%)	AIC	BIC
Model 1 – SG model coupled with Hill function	$V_0 (mm^3)$	103.08	49.55	48.1	6788.89	6800.86
	$K_{kill} (L/\mu M day)$	0.24	0.099	40.9		
	$IC50 (\mu M/L)$	1967.57	1555.83	79.1		
Model 1 – DL model coupled with Power function	$V_0 (mm^3)$	151.72	22.27	14.7	7968.28	7975.76
	$K_{kill} (L/\mu M day)$	0.00015	0.000062	42.6		
	$I_{max} (\mu M/L)$	0.73	-	-		
Model 2 coupled with Michaelis-Menten function	$V_0 (mm^3)$	135.73	-	-	-	-
	$K_{kill} (L/\mu M day)$	4×10^{-11}	-	-		
	$IC50 (\mu M/L)$	48×10^{-9}	-	-		

Table 4: Summary of the estimated parameters along with statistical metrics

Model Evaluation

- Model evaluation was performed using goodness-of-fit plots:

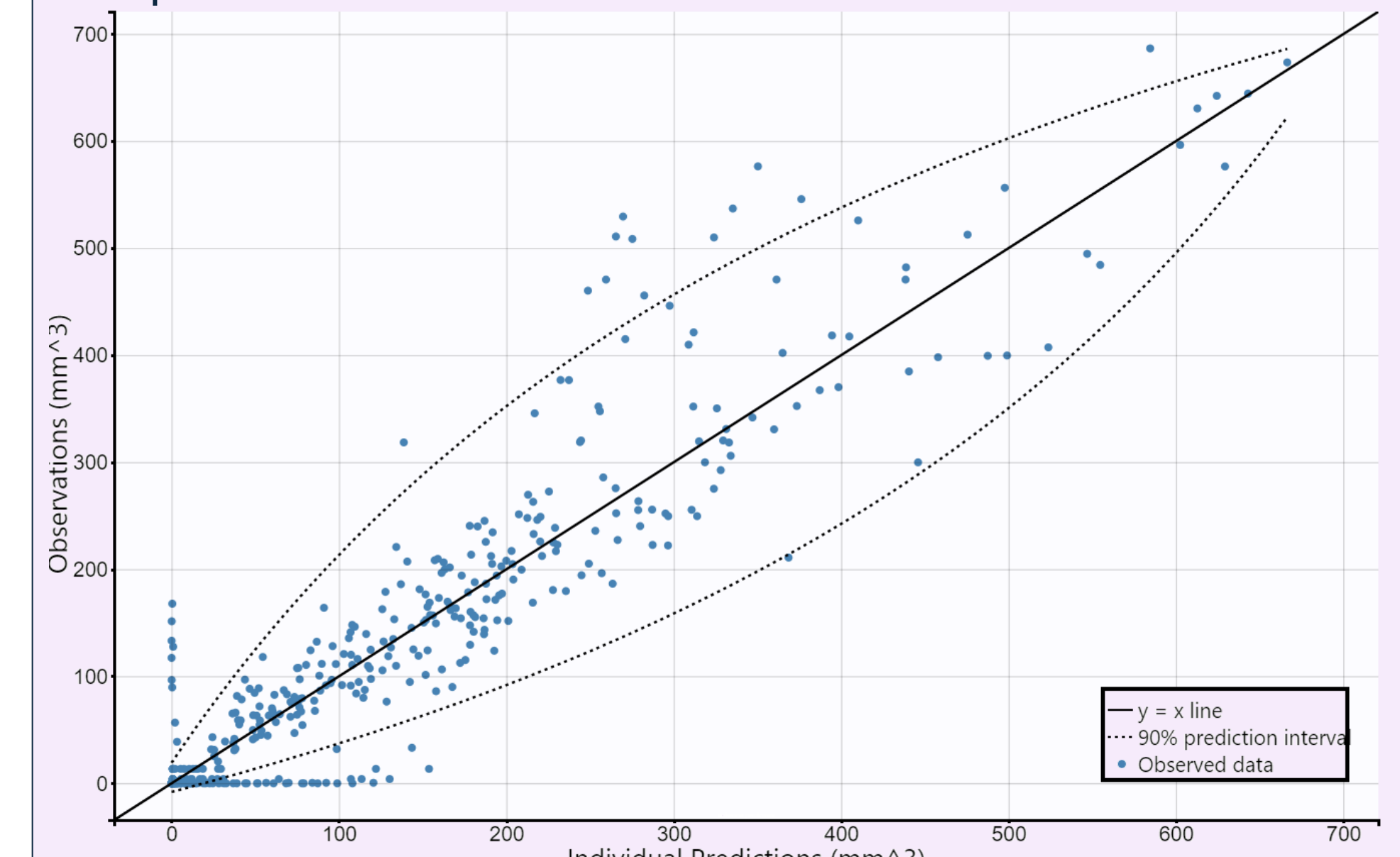
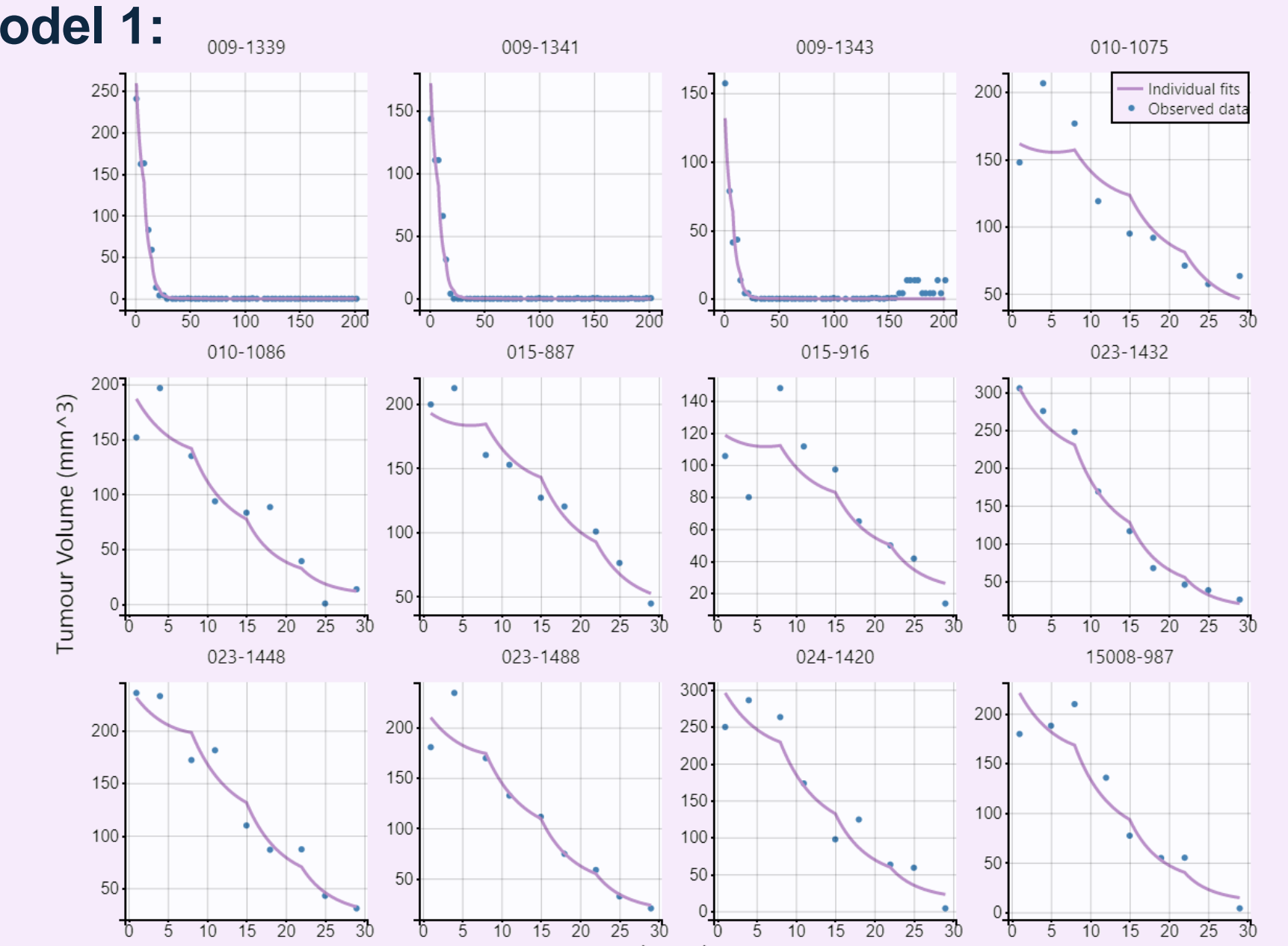


Figure 3: Goodness-of-fit plot for Model 1 (SG) coupled with Hill

Individual Fit Plots

- Invasive Breast Carcinoma population data from xenografted models, where mice received a $20 mg/kg$ ($24.75 \mu mol/kg$) IP dose of Docetaxel, have been evaluated for Doc20 observation:

Model 1:



Model 2:

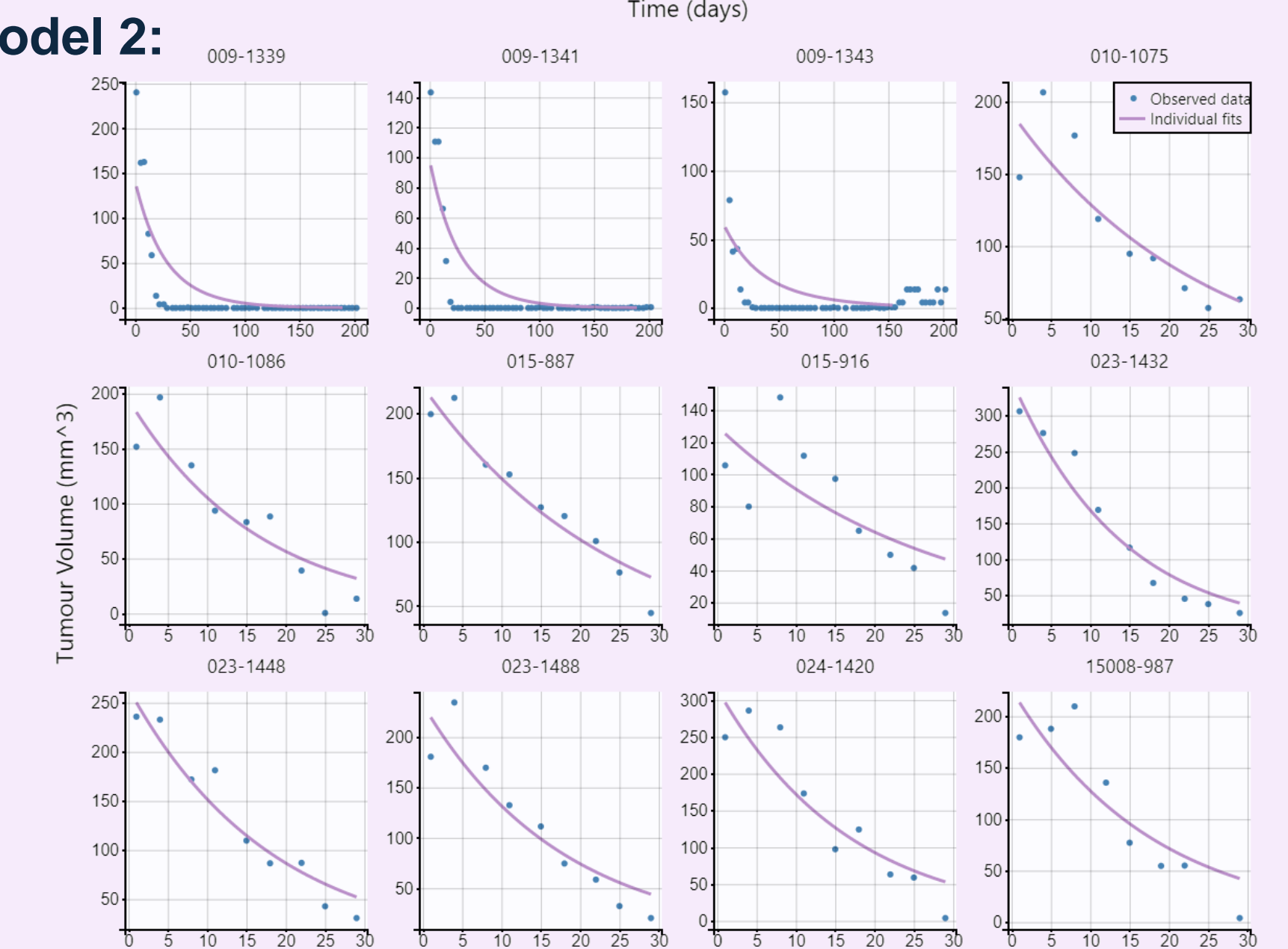


Figure 4: Individual fits of Tumour Volume (mm^3) vs. Time (days) for both Model 1 and Model 2

Conclusions and Future Work

- The **SG model (Model 1)** when coupled with a **Hill Function**, using a **squared power** of the plasma concentration formulation ($n=2$), provided the most accurate results.
- Coupling the **DL model (Model 1)** with a **squared plasma concentration coupling mechanism** formulation, yielded more accurate results than Model 2 with a **Michaelis-Menten** formulation, which exhibited individual variations.
- The ultimate goal is to **generalise** the **model** to describe multiple cancer cell lines and PK models, assisting research in cancer biology and accelerating the **development of new anti-cancer agents**.

References

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