PKPD Model Application in Homogeneous/Heterogeneous Conditions

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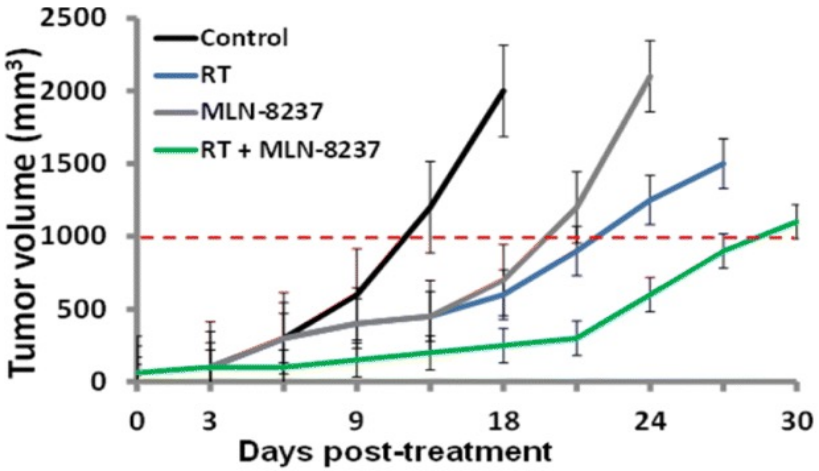
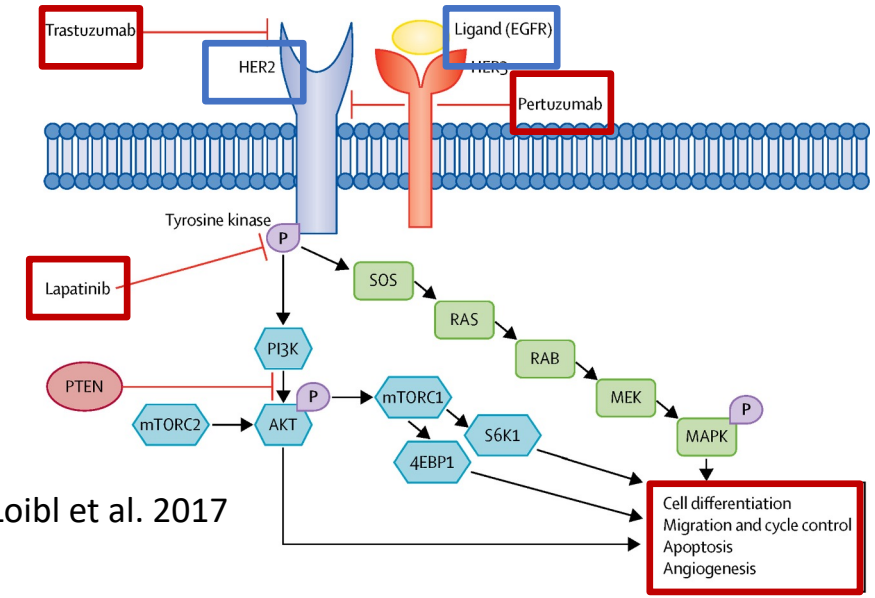
Motivation



Ningbo Liu et al.



Loibl et al. 2017

Tumor delays induced by treatment

Mathematical modeling

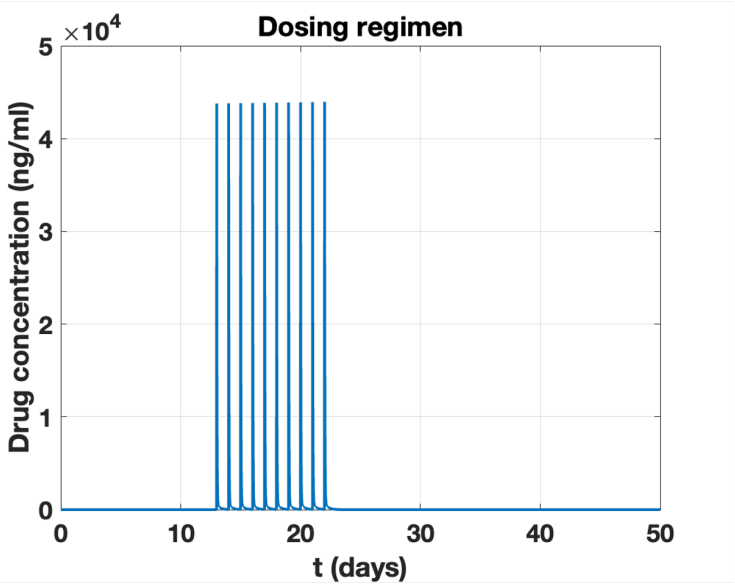
PK model: Measure drug concentration C from dosing regimens

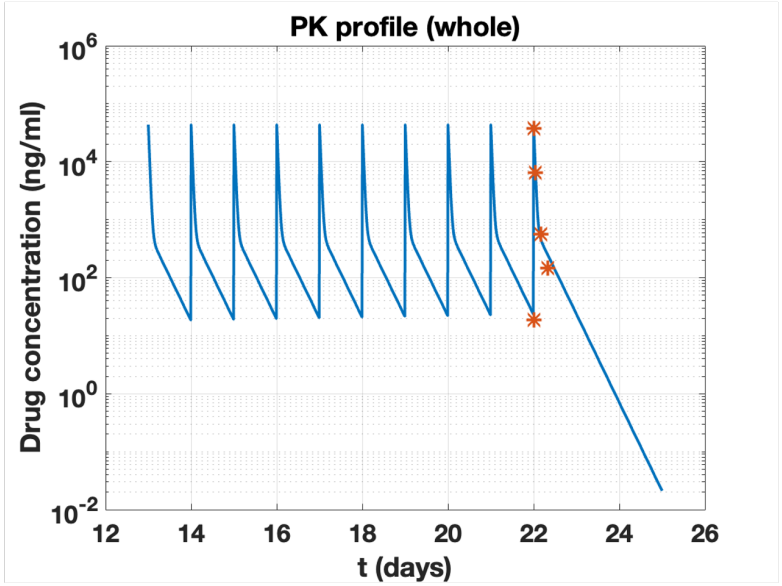
PK model (two compartments)

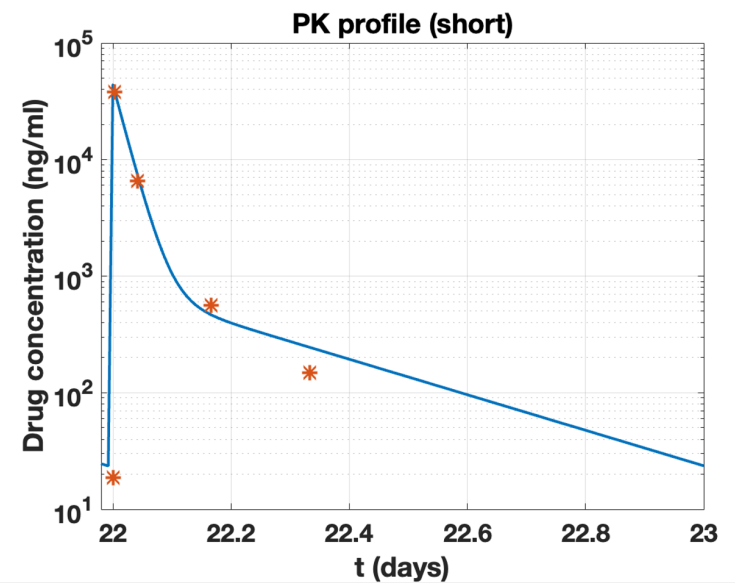
$$\frac{dq_2}{dt} = k_{21}q_1(t) - k_{12}q_2(t), \qquad \boldsymbol{C(t) = \frac{q_1(t)}{V}}$$

Dosing option

$$\frac{dq_1}{dt} = In(t) - k_{01}q_1(t) - k_{21}q_1(t) + k_{12}q_2(t)$$



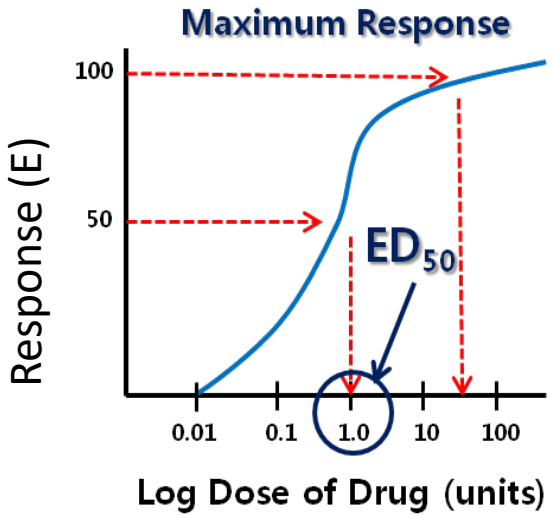




Reproduction of Simeoni et al. study

PD modeling: Dose-response curve

Dose-response curve



Modeling/
Calibrating

Sigmoid Emax model

$$E = \frac{E_{max} C^n}{ED_{50}^n + C^n}$$

- E: Drug effect
- ED_{50} : Half maximum concentration (EC_{50}, IC_{50})
- C: Drug concentration
- n: Hill coefficient
- E_{max} : Maximum Response

Outline

01

TRANSIT COMPARTMENT MODELS (TCMS)

-ERLANG DISTRIBUTION

02

TCMS

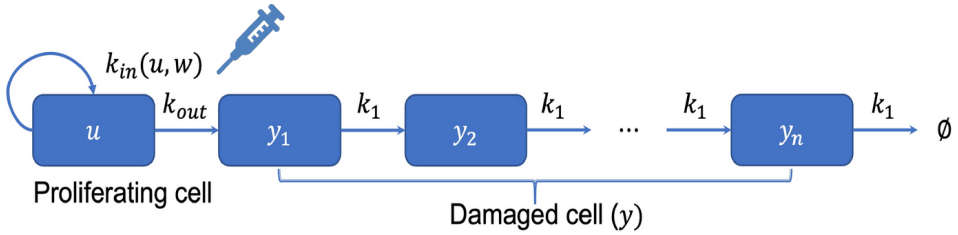
-COXIAN DISTRIBUTION

-MITTAG-LEFFLER DIST.

03

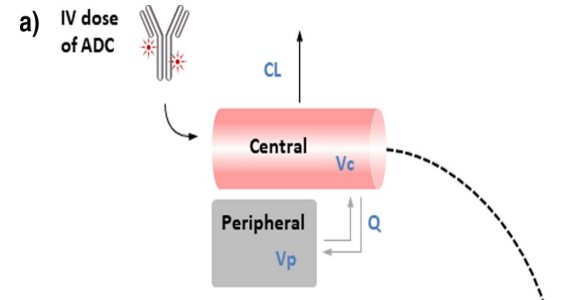
RESULTS

Transit compartment model (TCM)



Transit compartment model describes the way in which drugs inhibit the growth of tumors.

PK

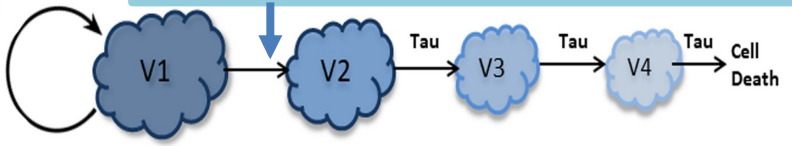


PD

(b) **TCM**

$$\frac{kg_{ex}\times\left(1-\frac{TV}{V_{max}}\right)\times V1}{\left(1+\left(\frac{kg_{Ex}}{kg}\times TV\right)^{\varphi}\right)^{\frac{1}{\varphi}}}$$

Drug-response model: $\boldsymbol{E=\frac{E_{max}C^n}{ED_{50}^n+C^n}}$



Tau: Mean residence time
Vi: Transit compartment

- $\frac{dv_1}{dt}=\frac{kg_{ex}\left(1-\frac{TV}{V_{max}}\right)}{\left(1+\left(\frac{g_{ex}}{kg}TV\right)^{\phi}\right)^{\frac{1}{\phi}}}-k_1\cdot E(t)\cdot v_1$
- $\frac{dv_2}{dt}=k_1E(t)\cdot v_1-\frac{1}{Tau}\cdot y_1(t)$
- $\frac{dv_n(t)}{dt}=\frac{1}{Tau}\left(v_{n-1}(t)-v_n(t)\right),n=2,3,\cdots$

TCM is widely used in PKPD study

- Tumor inhibition (delay) induced by drug administration is determined by

(i) Tumor growth (PK model ⟶ Drug effect ⟶ TCM (first equation))
(ii) Number of transit compartments in TCM ($v_n(t)$)

- How do we determine (ii) ?

- In addition, using (i) and (ii), can we capture various tumor delays?

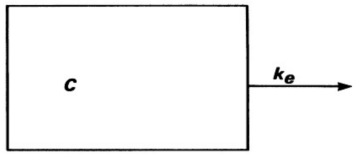
Fractal PK

- Fick's law says ``the change of amount of drug per unit area per unit time is proportional to the change of concentration" i.e.,

$$\frac{dM}{dt} = -k_V(C_1 - C_2)$$

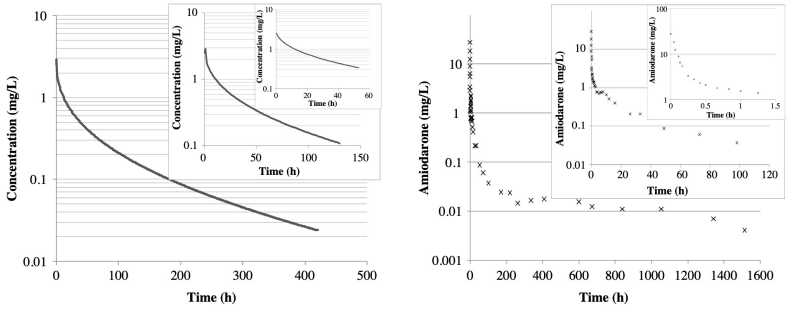
- Divide volume and consider the situation yields

$$\frac{dC}{dt} = -k_e C$$



- **Some drugs do not follow Fick's law.**
- For diffusion-limited reaction, fractal kinetics is used

$$\frac{dC}{dt} = -k_e C^n \text{ or } \frac{dC}{dt} = -k_e(t)C$$



OK. could we apply this concept to tumor models?

Capturing tumor delay caused by drug

Age-structured model: McKendrick (1926) and Von Foerster (1959) model

$$\frac{du}{dt} = k_{in}(u, w) - k_{out}(C, u)$$

$$\frac{\partial \phi}{\partial t} + \frac{\partial \phi}{\partial a} \cdot \frac{da}{dt} = -\mu(a, C)\phi(a, t)$$

- u **: proliferating cells,** $u(0) = u_0$
- $\phi(a, t)$: **damaged tumor cells (age)**
- $C = C(t)$: **drug concentration**
- $w = w(t) = u + y$ **: Total tumor cells**
- $y(t) = \int_0^\infty \phi(a, t)da$: **Total damaged tumors cells**
- $\phi(0, t) = k_{out}(C, u)$: **Boundary condition**
- $\phi(a, 0) = 0$: **Initial condition**

Modeling for capturing the delays

$$\frac{du}{dt} = k_{in}(u, w) - k_{out}(C, u)$$

$$\frac{\partial \phi}{\partial t} + \frac{\partial \phi}{\partial a} \cdot \frac{da}{dt} = -\mu(a, C)\phi(a, t)$$

Integration

By the method of characteristics,

$$\phi(a, t) = k_{out}\big(C(t-a), u(t-a)\big) e^{-\int_0^a \mu(\alpha) d\alpha}, \; t \geq a$$

Hazard rate

Survival function

$$\frac{dy}{dt} = k_{out}(C, u) - \int_0^\infty \mu(a)\phi(a, t)\, da$$

- $w = w(t) = u + y, \; y(t) = \int_0^\infty \phi(a, t) da$
- $\phi(0, t) = k_{out}(C, u)$

$$\frac{du}{dt} = k_{in}(u, w) - k_{out}(C, u)$$

Probability density

$$\frac{dy}{dt} = k_{out}(C, u) - (k_{out} * f)(t)$$

E(t)

Particles stay for time $t - a$ and are removed at age a.

TCM derivation

Using Erlang distribution,

$$\boldsymbol{f_n(a) = \frac{(k_1 a)^{n-1}}{(n-1)!} \cdot k_1 e^{-k_1 a}}$$

Erlang distribution represents time distribution when n events happen

$$\frac{du}{dt} = k_{in}(u,w) - k_{out}(C,u)$$

$$\frac{dy}{dt} = k_{out}(C,u) - E_n(t)$$

TCM model using linear trick

$$y = y_1 + \cdots + y_n \text{ and } \quad y_n = E_n(t) = (k_{out} * f_n)(t)$$

$$\frac{du}{dt} = k_{in}(u,w) - k_{out}(C,u)$$

$$\frac{dy_1}{dt} = k_{out}(C,u) - k_1 \cdot y_1(t)$$

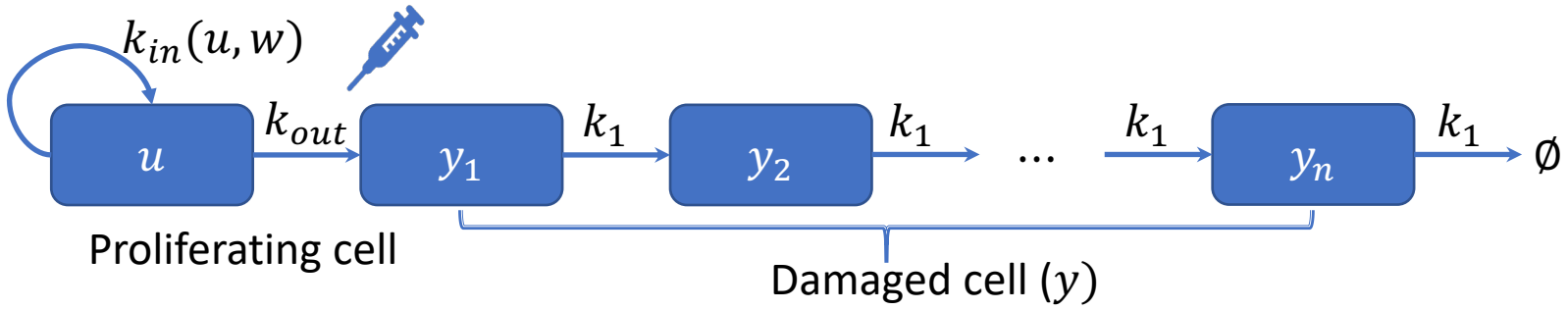
$$\frac{dy_2(t)}{dt} = k_1\big(y_1(t) - y_2(t)\big)$$

$$\vdots$$

$$\frac{dy_n(t)}{dt} = k_1\big(y_{n-1}(t) - y_n(t)\big)$$

Ok. TCM is derived using a specific probability density.

In application: TMC integrating PKPD



PK model

$$\frac{dq_2}{dt} = k_{21}q_1(t) - k_{12}q_2(t), \quad \boldsymbol{C(t) = \frac{q_1(t)}{V}}$$

$$\frac{dq_1}{dt} = -k_{01}q_1(t) - k_{21}q_1(t) + k_{12}q_2(t) + v(t)$$

- $k_{in}(u,w) = \dfrac{\lambda_0 u}{\left(1+\left(\frac{\lambda_0}{\lambda_1}w\right)^{\phi}\right)^{\frac{1}{\phi}}}$
- $w = u + y$ (total tumor)
- $k_{out}(C,u) = k_1 \cdot C(t) \cdot u$

TCM from Simeoni et al.

$$\frac{du}{dt} = k_{in} - k_{out}$$

$$\frac{dy_1}{dt} = k_1 \cdot C \cdot u - k_1 \cdot y_1(t)$$

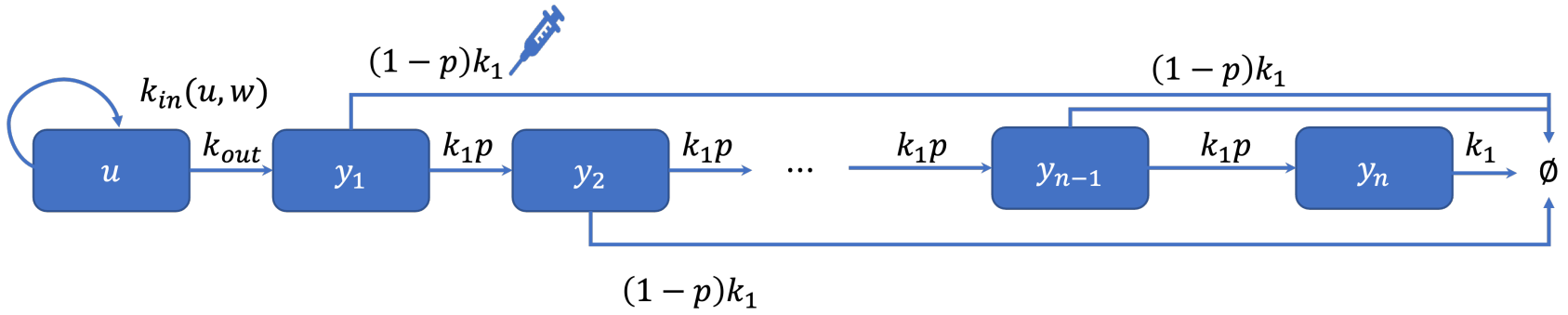
$$\frac{dy_2(t)}{dt} = k_1\left(y_1(t) - y_2(t)\right)$$

$$\vdots$$

$$\frac{dy_n(t)}{dt} = k_1\left(y_{n-1}(t) - y_n(t)\right)$$

Ages are discretely considered as n steps

Coxian TCM



Coxian density is derived from Phase distribution

$$\frac{df_1}{dt} = -k_1 f_1,\ \frac{df_i}{dt} = p_{i-1}k_{i-1}f_{i-1} - k_i f_i,\ i = 2,3,\cdots n, 0 \le p_i \le 1$$

Key assumption: $(1 - p_1)k_1 = \cdots = (1 - p_n)k_n$,

Letting on $y_i = \frac{k_{out} * f_i}{(1-p_1)k_1}$.

If $p_i = 0$, then it returns to the Erlang TCM.

$$E_n(t) = k_{out} * f = \sum_{i=1}^{n} (k_{out} * f_i)(t)$$

$$\frac{dy_1}{dt} = k_{out}(C,u) - k_1 y_1, \cdots, \frac{dy_i}{dt} = p_1 k_1 y_{i-1} - k_1 y_i$$

$$\frac{du}{dt} = k_{in}(u,w) - k_{out}(C,u), \frac{dy}{dt} = k_{out}(C,u) - E_n(t)$$

Coxian TCM

Coxian density is derived from Phase distribution

$$\frac{df_1}{dt} = -k_1 f_1,\ \frac{df_i}{dt} = p_{i-1}k_{i-1}f_{i-1} - k_i f_i,\ i = 2,3,\cdots n.\ 0 \le p_i \le 1$$

- **Some cells may be removed without age-stages.**
- **Relax the condition that is number of transit compartments**

Key assumption: $(1 - p_1)k_1 = \cdots = (1 - p_n)k_n$,

Letting on $y_i = \frac{k_{out} * f_i}{(1-p_1)k_1}$.

If $p_i = 0$, then it returns to the Erlang TCM.

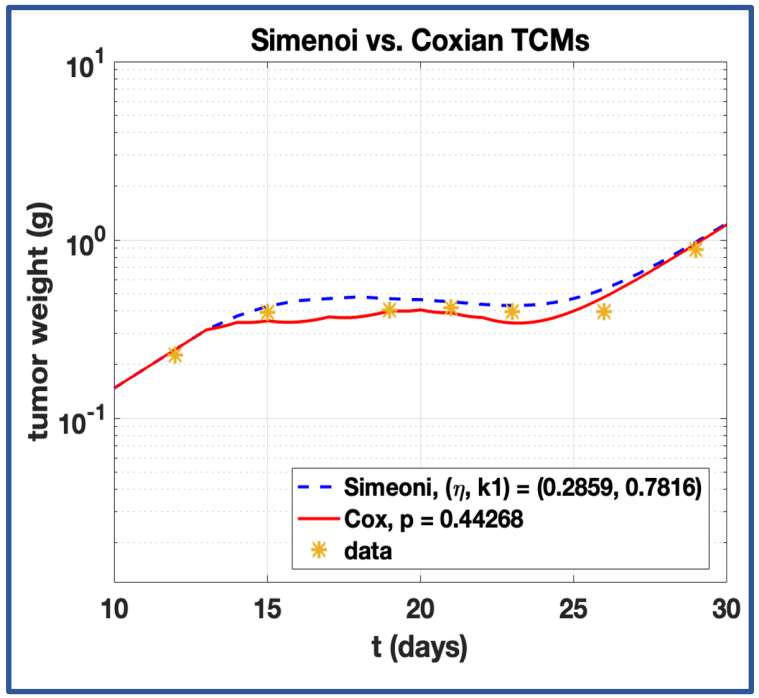
$$E_n(t) = k_{out} * f = \sum_{i=1}^{n} (k_{out} * f_i)(t)$$

$$\frac{dy_1}{dt} = k_{out}(C,u) - k_1 y_1, \cdots, \frac{dy_i}{dt} = p_1 k_1 y_{i-1} - k_1 y_i$$

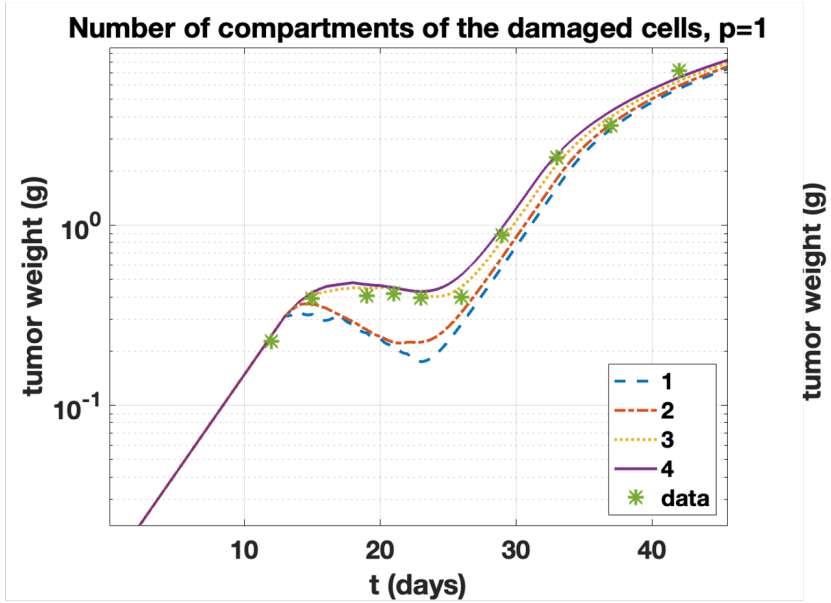
$$\Rightarrow \frac{du}{dt} = k_{in}(u,w) - k_{out}(C,u)$$

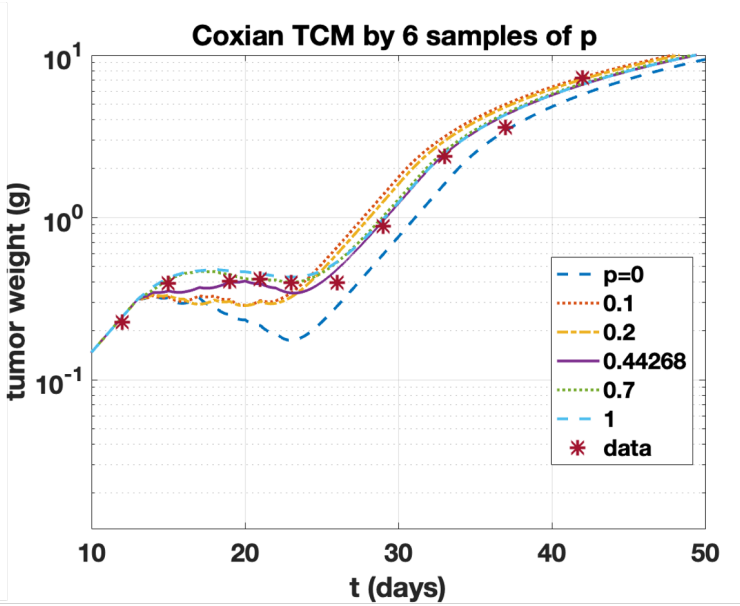
$$\frac{dy}{dt} = k_{out}(C,u) - E_n(t)$$

Model Simulation



Data fit quality





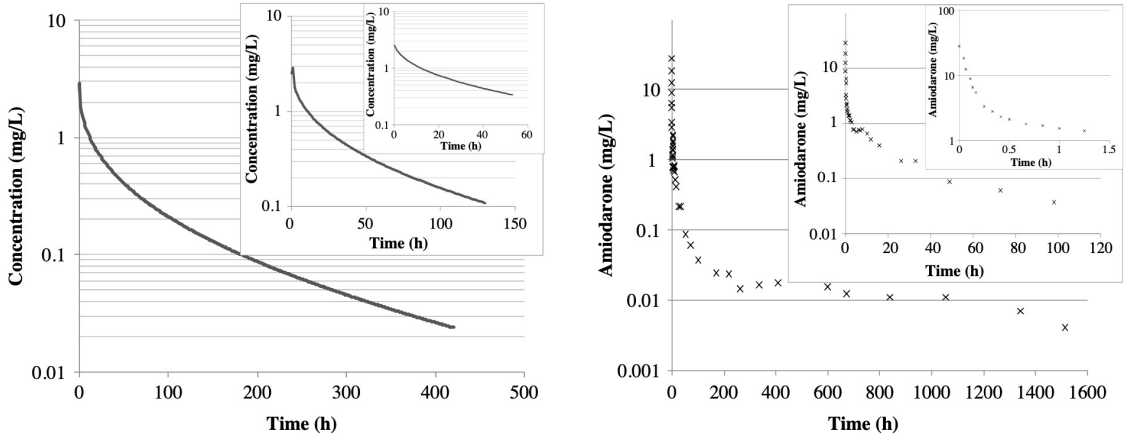
- Left panel :

Change in the number of age compartments

- Right panel :

Fix the number of compartments and change in "*p*".

Is it enough?



Anormal kinetics

- Anormal kinetics

- The age of a cell due to drug effect can be considered random variables with pdf $f(a,t)$
- To describe anormal kinetics, one may apply to sum of exponentials or stochastic models
- Beard et al (1997) showed that a power function can be represented as the sum of scaled basis function, i.e

$$t^{-\alpha} \propto \sum_{i=1}^{m} k_i^{\alpha+1} t exp(-k_i\, t), \alpha > 0 \text{ using } t^{-\alpha} = \frac{1}{\Gamma(\alpha)} \int_0^{\infty} u^{\alpha-1} \exp(-ut)\, du, \alpha > 0$$

If is there a distribution that sum of power functions?

Fractional-order derivative equation (FDE) model derivation

Let $E_\alpha(t) = \sum_{n=0}^{\infty} \frac{t^n}{\Gamma(1+\alpha \cdot n)}$, $\alpha \in (0,1]$.

Let a suvival function $S(t) = E_\alpha\left(-\left(\frac{t}{\tau}\right)^\alpha\right), \tau > 0.$

But density function is not likely to have a closed form.

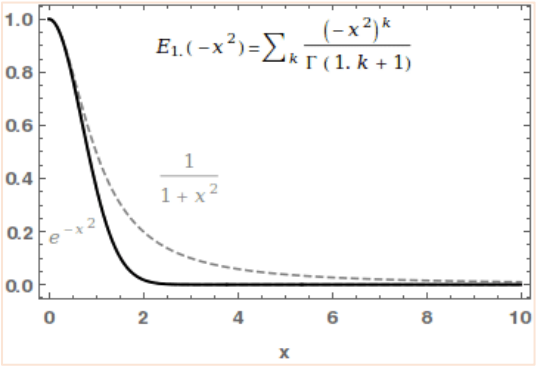


Figure. Survival function according to α. Survival function generates distribution.

wikipedia

Instead, we apply the Laplace transform,

$$\mathcal{L}_t(S(t)) = \frac{1}{s(1+(\tau s)^{-\alpha})}.$$

Since $f = -\frac{dS}{dt}$, $\mathcal{L}_t(f) = 1 - s\mathcal{L}_t(S) = \frac{(\tau s)^{-\alpha}}{1+(\tau s)^{-\alpha}}$.

Define a kernel $K(t)$ by

$$\mathcal{L}_t(K(t)) = \frac{\mathcal{L}_t(f(t))}{\mathcal{L}_t(S(t))} = \tau^{-\alpha} s^{1-\alpha}$$

$\frac{du}{dt} = k_{in}(u,w) - k_{out}(C,u)$	$\frac{du}{dt} = k_{in}(u,w) - k_{out}(C,u)$
$\frac{\partial \phi}{\partial t} + \frac{\partial \phi}{\partial a} \cdot \frac{da}{dt} = -\mu(a,C)\phi(a,t)$	$\frac{dy}{dt} = k_{out}(C,u) - (k_{out} * f)(t)$

$$\phi(a,t) = k_{out}\big(C(t-a), u(t-a)\big)e^{-\int_0^a \mu(\alpha)d\alpha} \longrightarrow y(t) = (k_{out} * S)(t)$$

$$\boldsymbol{E(t) = (k_{out} * f)(t)}$$

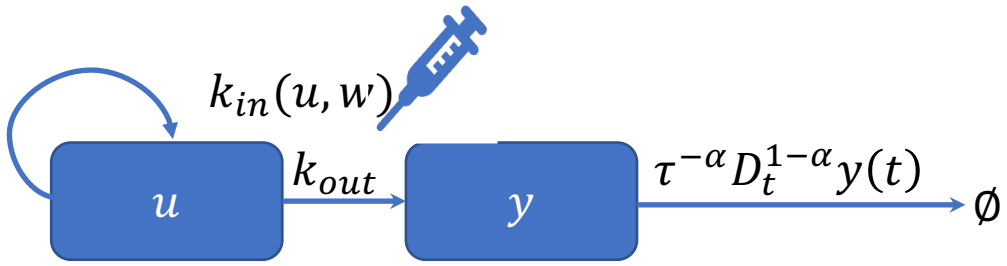
$$\mathcal{L}_t\big(y(t)\big) = \mathcal{L}_t(k_{out})\mathcal{L}_t(S(t)) \text{ and } \mathcal{L}_t\big(E(t)\big) = \mathcal{L}_t(k_{out})\mathcal{L}_t(f(t))$$

$$\mathcal{L}\Big(D_t^{1-\alpha}y(t)\Big) = s^{1-\alpha}\mathcal{L}(y(t) - s^{-\alpha}y(t)\Big|_{t=0} = s^{1-\alpha}\mathcal{L}\big(y(t)\big).$$

$$\mathcal{L}_t\big(K(t)\big) = \frac{\mathcal{L}_t\big(f(t)\big)}{\mathcal{L}_t(S(t))}$$

$$\boldsymbol{\mathcal{L}_t\big(E(t)\big)} = \mathcal{L}_t\big(K(t)\big)\mathcal{L}_t\big(y(t)\big) = \tau^{-\alpha}s^{1-\alpha} \cdot \left(\frac{\mathcal{L}_t\Big(D_t^{1-\alpha}y(t)\Big)}{s^{1-\alpha}}\right) = \boldsymbol{\tau^{-\alpha}\,\mathcal{L}_t\left(D_t^{1-\alpha}y(t)\right)}$$

Simulation of fractional TCM



For the model simulation, we should assume

$\boldsymbol{y(t), D_t^{1-\alpha}y(t)}$ **differentiable continuously.**

for satisfying semigroup property

$$\boldsymbol{y'(t) = D_t^1 y(t) = D_t^{\alpha}(D_t^{1-\alpha}y)}$$

$$E(t) = (k_{out} * f)(t) = \tau^{-\alpha}D_t^{1-\alpha}y(t)$$

$$\frac{du}{dt} = k_{in}(u,w) - k_{out}(C,u)$$

$$\frac{dy}{dt} = k_{out}(C,u) - \tau^{-\alpha}D_t^{1-\alpha}y(t).$$

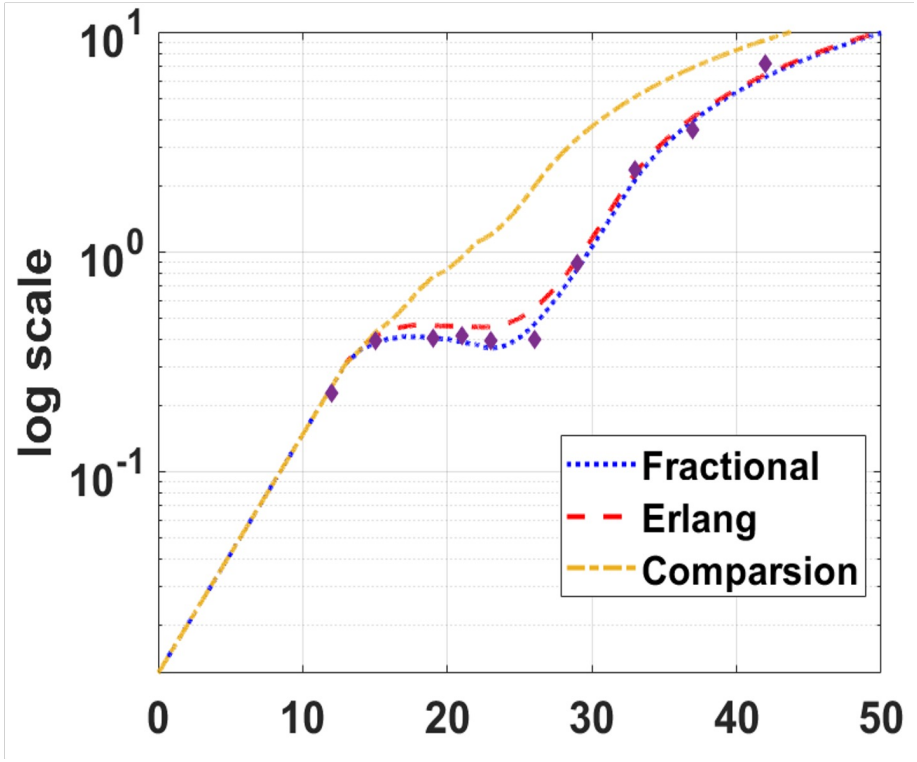
Finally, we have

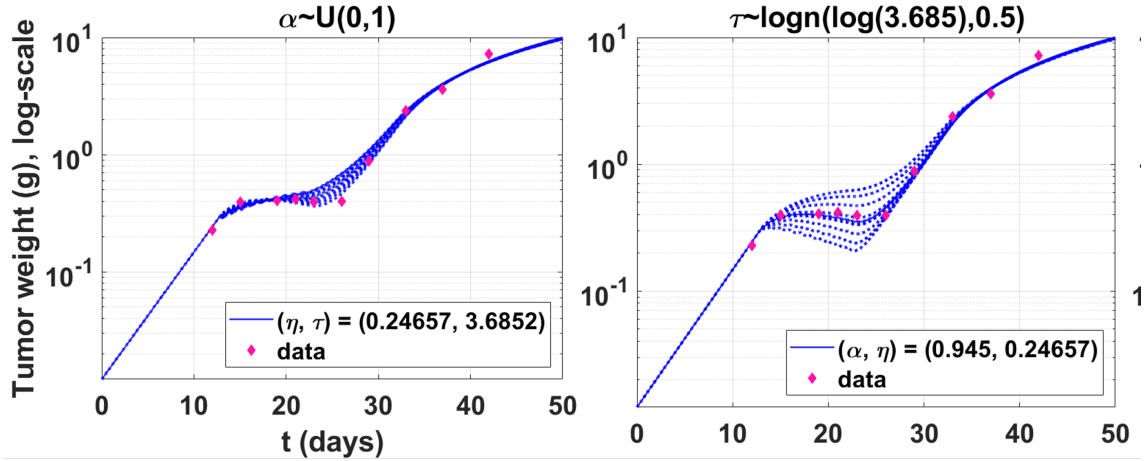
$$\frac{du}{dt} = k_{in} - k_{out}$$

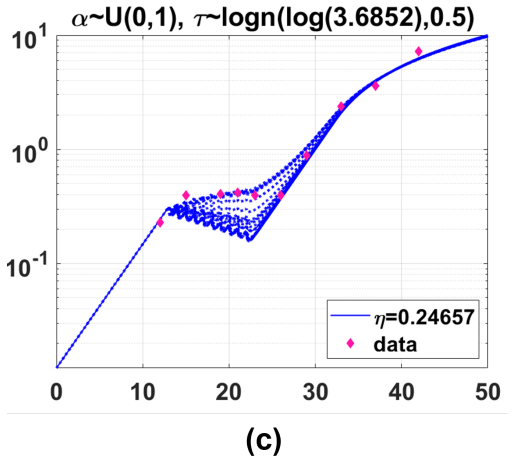
$$D_t^{\alpha}z = \eta \cdot C \cdot u - \tau^{-\alpha}z$$

$$D_t^{1-\alpha}\, y = z$$

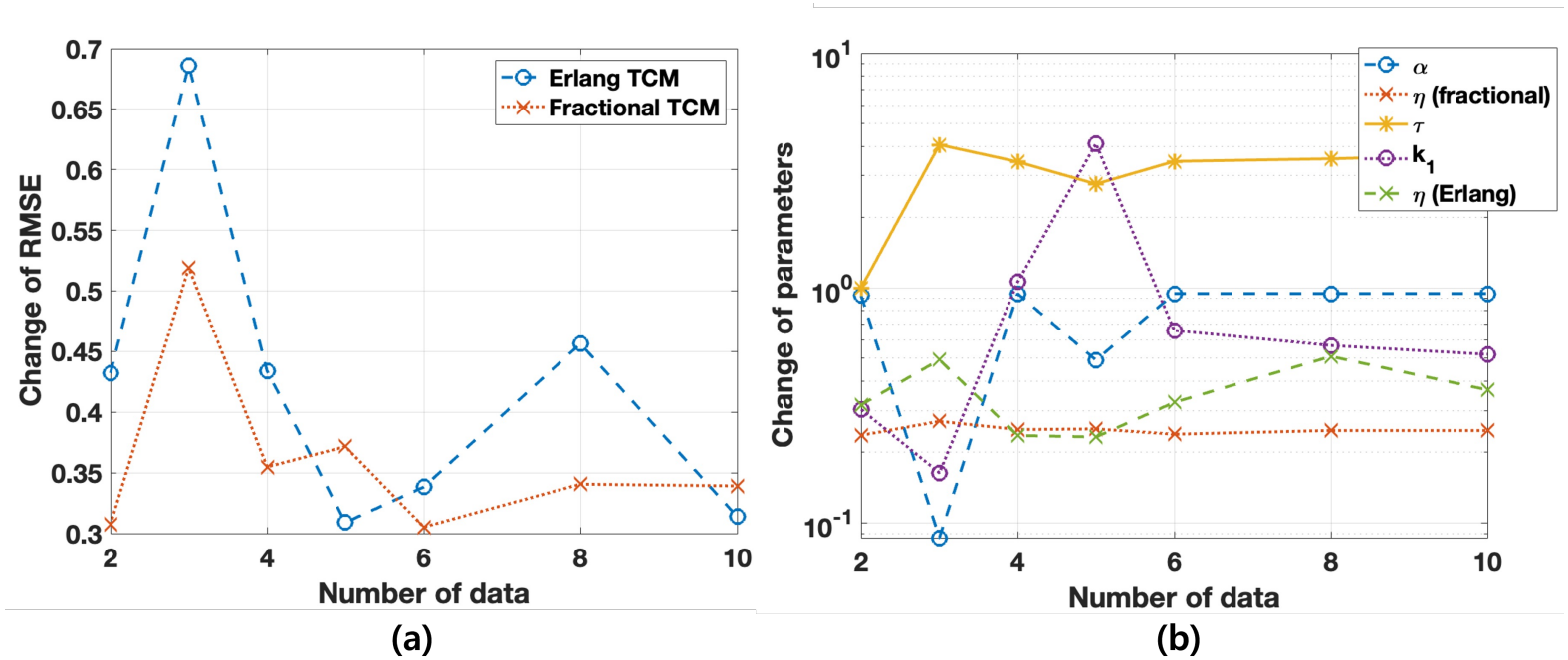
Fractional TCM captures data set







Fractional TCM requires fewer the number of dataset to estimate parameters



Fractional TCM requires less data to capture full data

Thank you for your kind attention

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