Modelling temozolomide chronoefficacy: from cellular pharmacokinetics-pharmacodynamics to heterogeneous cancer cell population

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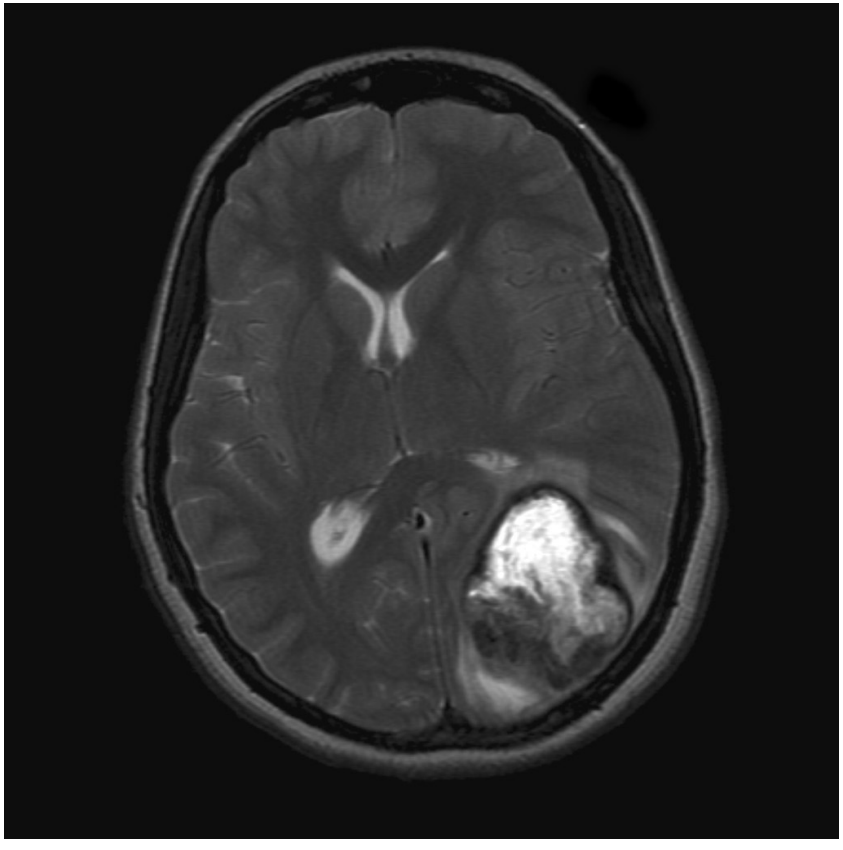
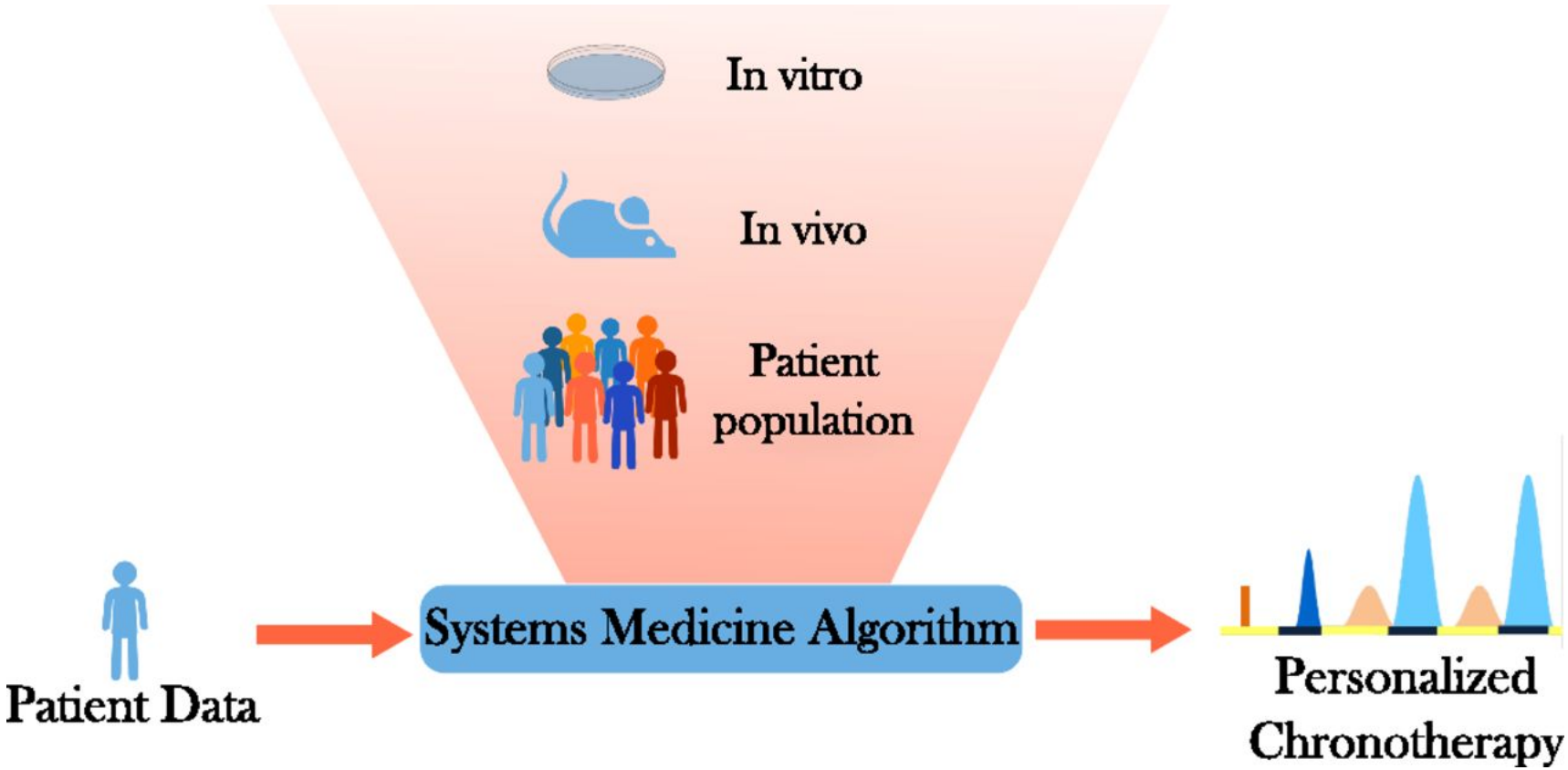
Glioblastoma multiforme (GBM)

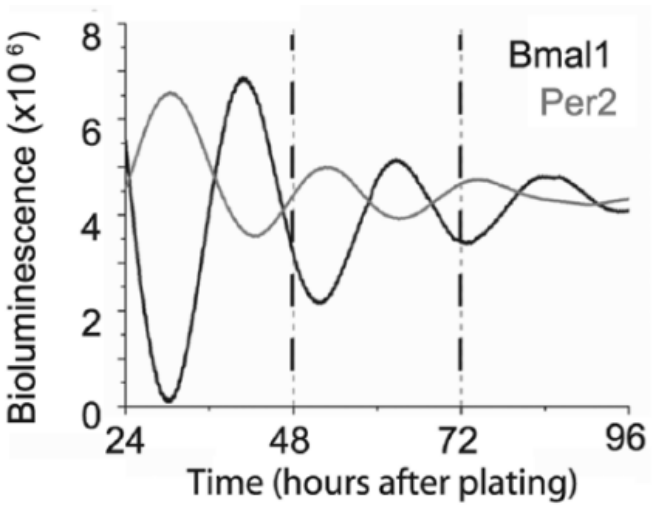


- Most frequent and agressive brain tumor
- Yet rare: 2 or 3 cases per 100000 people in Europe and USA
- Standard treatment: surgery, radiotherapy and chemotherapy
- Median survival duration $\sim$18 months
- Cornerstone of treatment: temozolomide (TMZ)

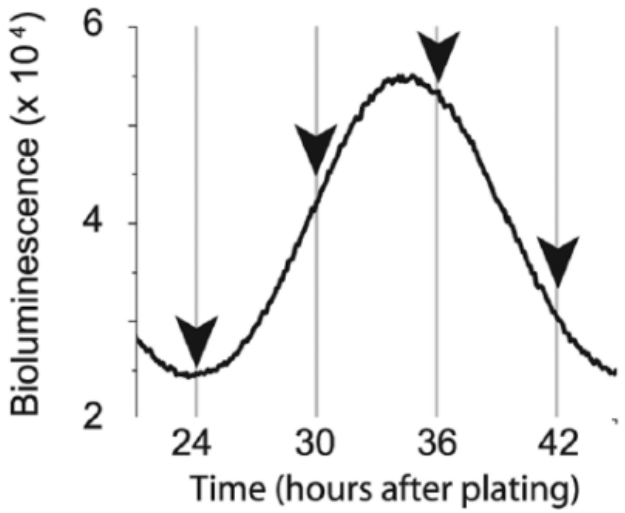
Personnalized therapy



Rhythms in genes expression in male mes-GBM astrocytes[1]



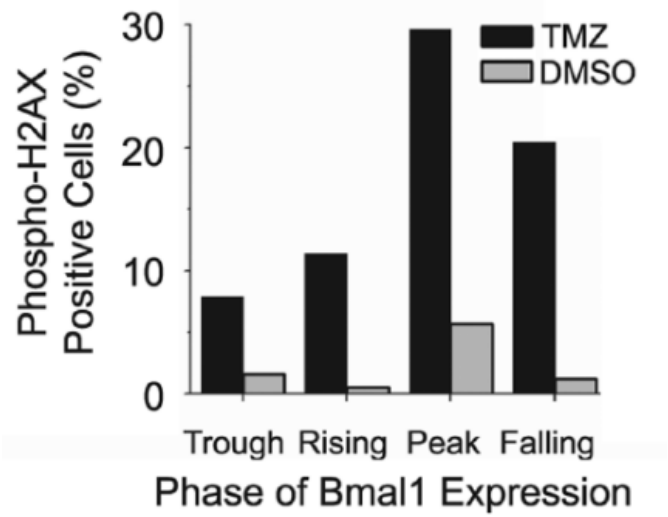
Rhythms of two clock genes: Per2 and Bmal1

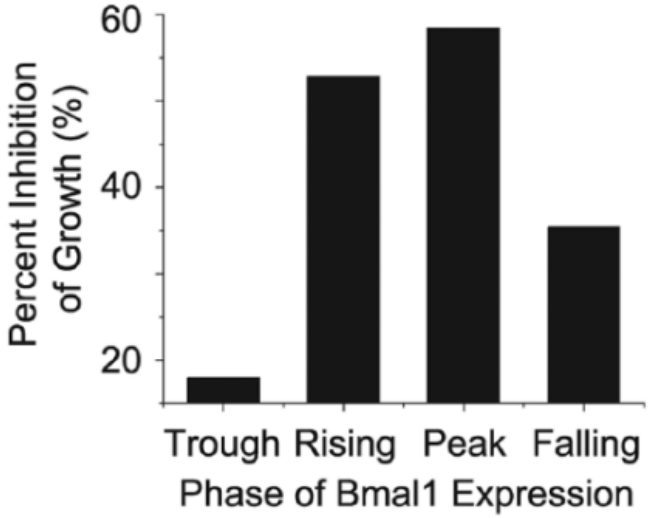


Rhythm in Bmal1 RNA activity. Arrows: ttimes of administration of the drug

[1] Slat *et al.*, *Journal of Biological Rhythms*, 2017

Result of treatments at different CT



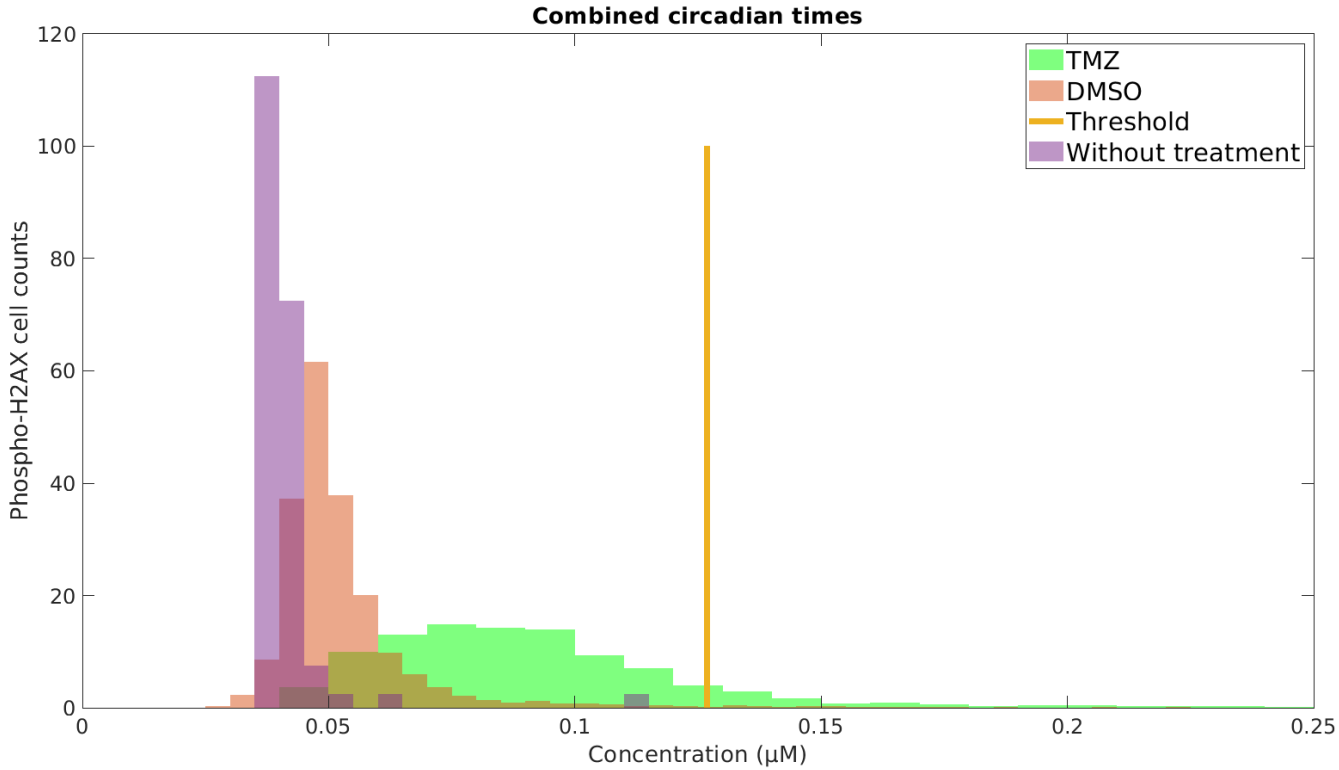


Proportion of cells with brightness higher than a fixed threshold

Ratio of the number of living cells after treatment over control

- TMZ: main drug against GBM, with initial concentration 1 mM
- DMSO: vehicle, liquid in which TMZ is diluted

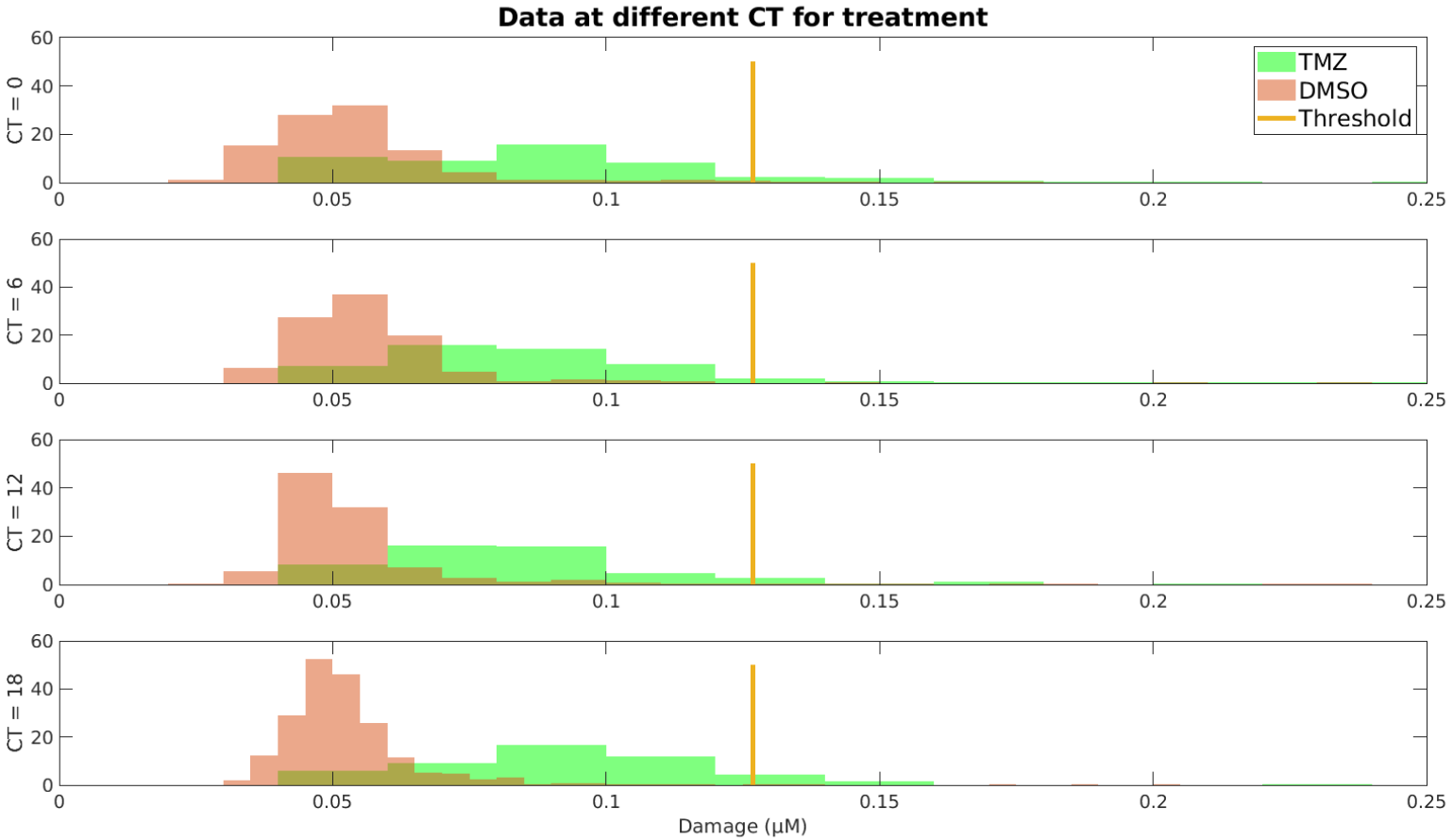
Combined circadian times



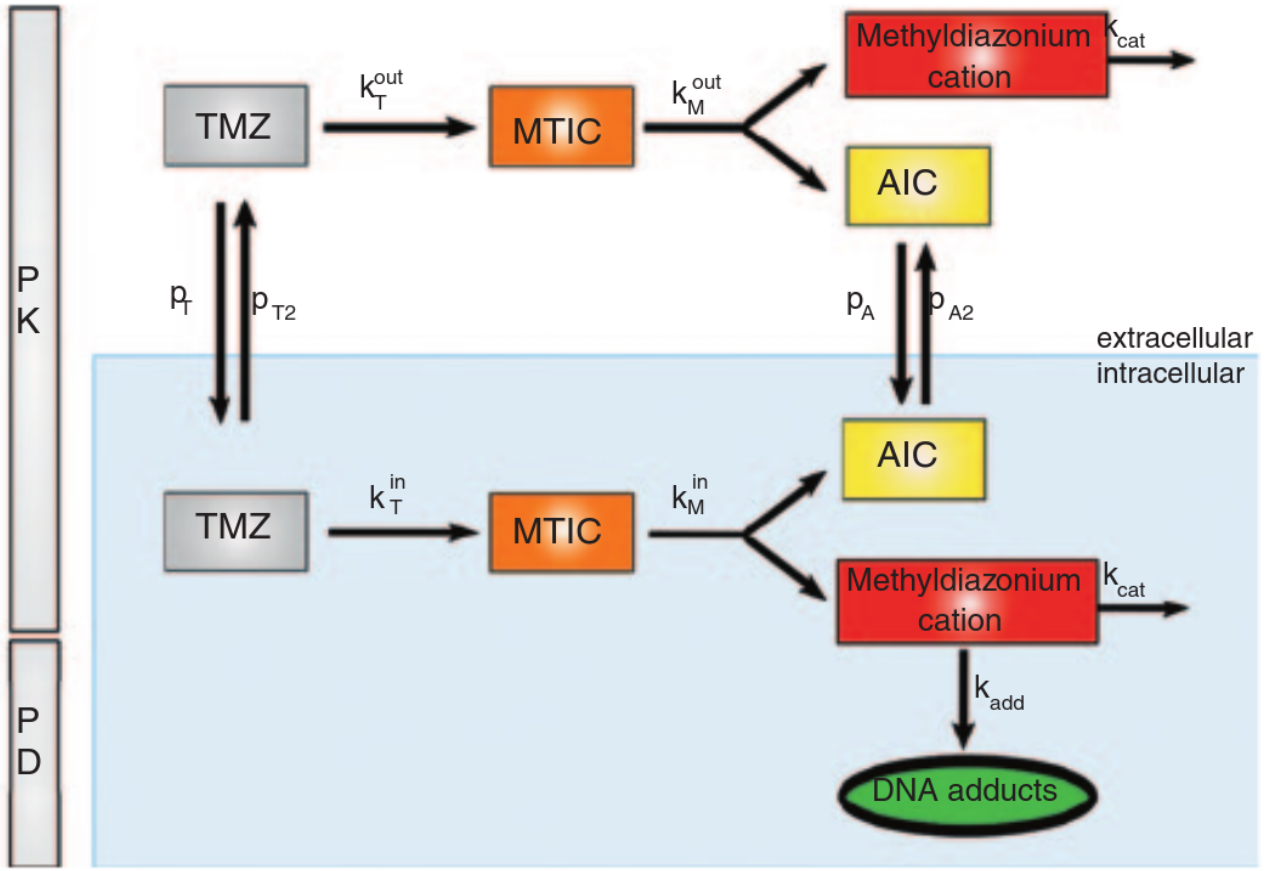
Scaling:

1. data $\leftarrow$ data $\times \frac{3.5 \times 10^{-4} \mu M}{\text{mode of raw data (brightness)}}$
2. pdf normalization: total area of bars $= 1$

A closer look: treatment at different circadian times



Published model of TMZ cellular PK[2]



PK parameters estimated on experimental data.

[2] Ballesta *et al.*, *CPT: pharmacometrics and systems pharmacology*, 2014

Single cell level: a PK -PD model

$$V_{out}\frac{\mathrm{d}[TMZ_{out}]}{\mathrm{d}t} = -p_{T_{out}}[TMZ_{out}] + p_{T_{in}}[TMZ_{in} - k_{T_{out}}V_{out}[TMZ_{out}]$$

$$V_{in}\frac{\mathrm{d}[TMZ_{in}]}{\mathrm{d}t} = p_{T_{out}}[TMZ_{out}] - p_{T_{in}}[TMZ_{in}] - k_{T_{in}}V_{in}[TMZ_{in}]$$

$$\frac{\mathrm{d}[MTIC]}{\mathrm{d}t} = k_{T_{in}}[TMZ_{in}] - k_{M_{in}}[MTIC]$$

$$\frac{\mathrm{d}[C]}{\mathrm{d}t} = k_{M_{in}}[MTIC] - k_{add}[C] - k_{cat}[C]$$

$$\frac{\mathrm{d}D}{\mathrm{d}t} = k_{DMSO} + k_{add}[C] - k_{HR}D$$

Single cell level with rhythm on repair: model $\mathcal{R}$

$$V_{out}\frac{\mathrm{d}[TMZ_{out}]}{\mathrm{d}t} = -p_{T_{out}}[TMZ_{out}] + p_{T_{in}}[TMZ_{in} - k_{T_{out}}V_{out}[TMZ_{out}]$$

$$V_{in}\frac{\mathrm{d}[TMZ_{in}]}{\mathrm{d}t} = p_{T_{out}}[TMZ_{out}] - p_{T_{in}}[TMZ_{in}] - k_{T_{in}}V_{in}[TMZ_{in}]$$

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$$\frac{\mathrm{d}[C]}{\mathrm{d}t} = k_{M_{in}}[MTIC] - k_{add}[C] - k_{cat}[C]$$

$$\frac{\mathrm{d}D}{\mathrm{d}t} = (k_{DMSO} + k_{add}[C]) - k_{HR}D\left(1 + A\cos\left(\frac{2\pi}{T_{Bmal1}}(t-\varphi)\right)\right)$$

[2] Ballesta *et al.*, *CPT: pharmacometrics and systems pharmacology*, 2014

Single cell level with rhythm on damage formation: model $\mathcal{D}$

$$V_{out}\frac{\mathrm{d}[TMZ_{out}]}{\mathrm{d}t} = -pT_{out}[TMZ_{out}] + pT_{in}[TMZ_{in} - kT_{out}V_{out}[TMZ_{out}]$$

$$V_{in}\frac{\mathrm{d}[TMZ_{in}]}{\mathrm{d}t} = pT_{out}[TMZ_{out}] - pT_{in}[TMZ_{in}] - kT_{in}V_{in}[TMZ_{in}]$$

$$\frac{\mathrm{d}[MTIC]}{\mathrm{d}t} = kT_{in}[TMZ_{in}] - kM_{in}[MTIC]$$

$$\frac{\mathrm{d}[C]}{\mathrm{d}t} = k_{M_{in}}[MTIC] - k_{add}[C]\left(1 + A\cos\left(\frac{2\pi}{T_{Bmal1}}(t-\varphi)\right)\right) - k_{cat}[C]$$

$$\frac{\mathrm{d}D}{\mathrm{d}t} = (k_{DMSO} + k_{add}[C])\left(1 + A\cos\left(\frac{2\pi}{T_{Bmal1}}(t-\varphi)\right)\right) - k_{HR}D$$

Population level: a structured PDE

- Structuration of the population in DNA damage d
- Two phenomena at work: transport and death

$$\begin{cases} \frac{\partial}{\partial t}u(t,d) + \frac{\partial}{\partial d}\left(F(t,d)u(t,d)\right) + \mu(d)u(t,d) = 0 \\ u(t,0) = 0, \quad u(0,x) = u_0(x) \end{cases}$$

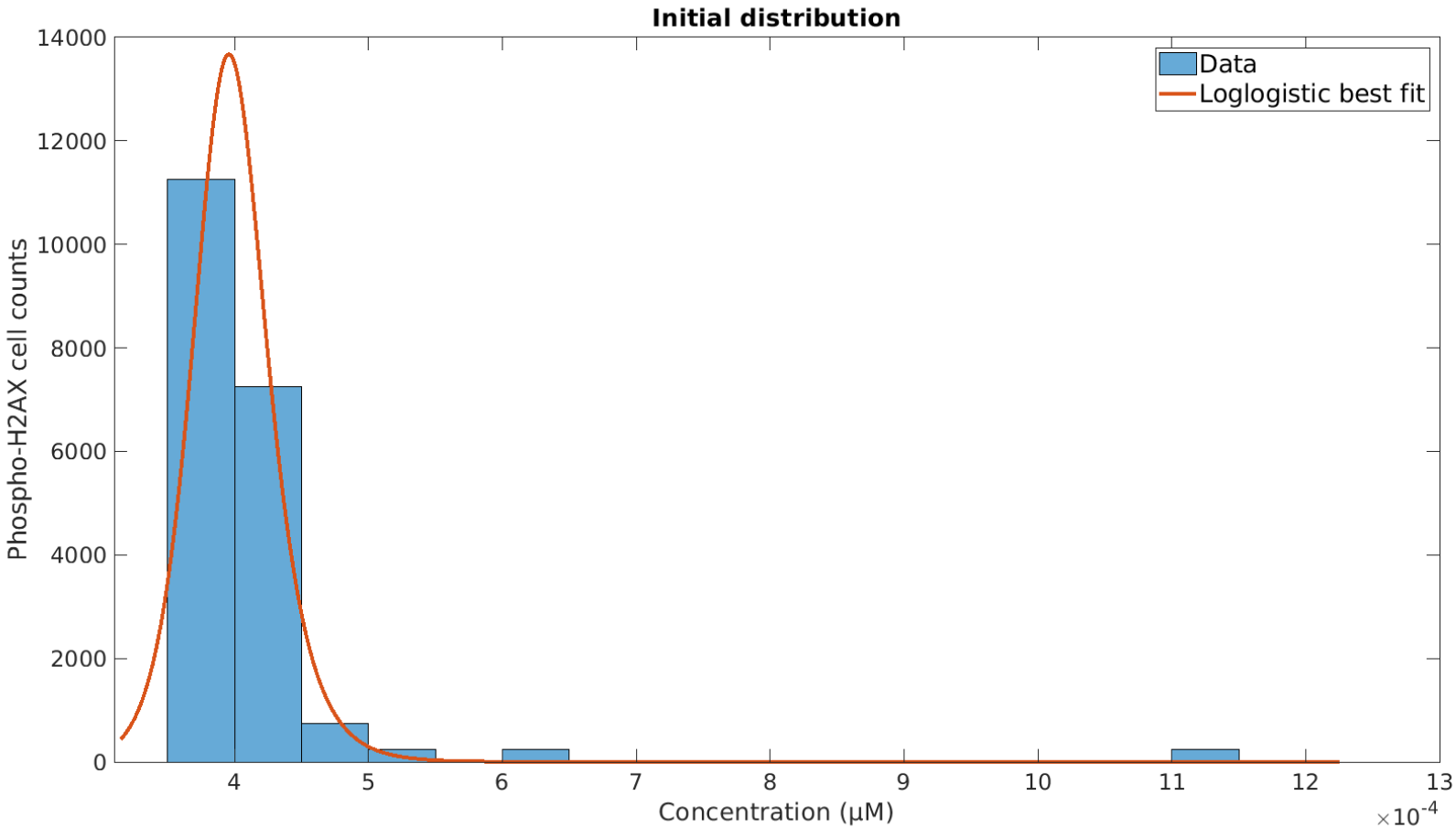
with the velocity field given by the last ODE of the system:

$$\frac{\mathrm{d}D}{\mathrm{d}t} = F(t, D(t))$$

and death term:

$$\mu(d) = C\frac{d^n}{K^n + d^n}$$

Initial distribution



u_0 gien by the probability density function of a loglogistic distribution fitted on the data without treatment

Explicit solution

For generality, let write

$$F(t,d) = \rho_1(t) f(t) - \rho_2(t) k_{HR} d$$

with $f(t) = k_{DMSO} + k_{add}[C]$.

Recall:

- $\rho_1(t) = 1$ and $\rho_2(t) = 1 + A\cos\left(\frac{2\pi}{T}(t-\phi)\right)$ in model $\mathcal{R}$
- $\rho_1(t) = 1 + A\cos\left(\frac{2\pi}{T}(t-\phi)\right)$ and $\rho_2(t) = 1$ in model $\mathcal{D}$

Explicit solution with the method of Characteristics

$$u(t,d) = u_0\left(d\mathrm{e}^{k_{HR}\int_0^t \rho_2(s)\mathrm{d}s} - \int_0^t \rho_1(s) f(s) \mathrm{e}^{k_{HR}\int_0^s \rho_2(\sigma)\mathrm{d}\sigma}\mathrm{d}s\right)$$
$$\times\, \mathrm{e}^{k_{HR}\int_0^t \rho_2(s)\mathrm{d}s} \mathrm{e}^{-\int_0^t \mu\left(d\mathrm{e}^{k_{HR}\int_\tau^t \rho_2(s)\mathrm{d}s} - \int_\tau^t \rho_1(s) f(s) \mathrm{e}^{k_{HR}\int_\tau^s \rho_2(\sigma)\mathrm{d}\sigma}\mathrm{d}s\right)\mathrm{d}\tau}$$

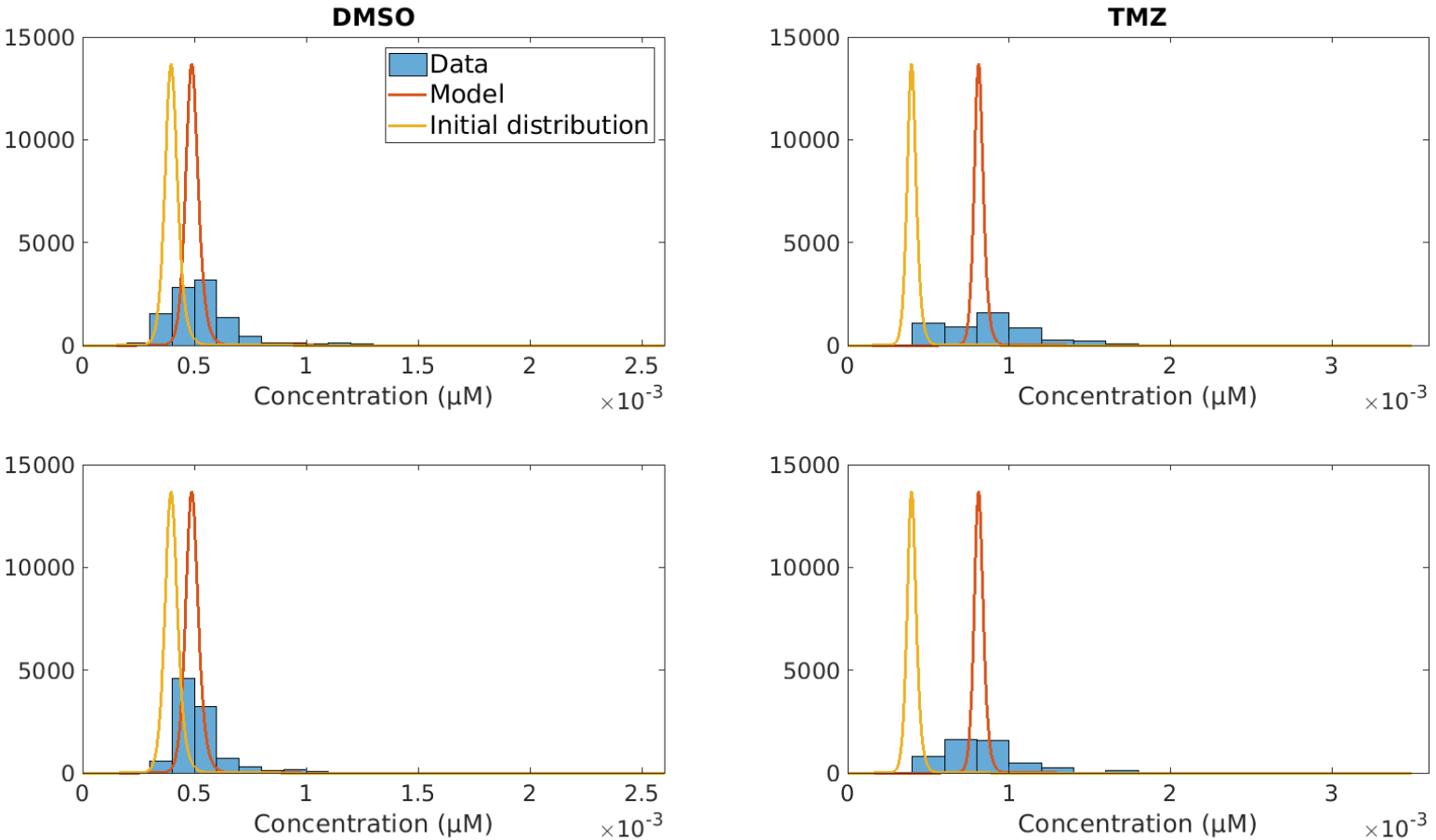
Fitness evaluation and minimization

1. Denote $e_0, \cdots, e_{K+1}$ the edges of the bars plot (= space discretization) with constant step Δe
2. Denote $h_0, \cdots, h_K$ the heights in the bars plot
3. Compute $p_0, \cdots, p_K$ as $p_k = h_k \times \Delta e$ the area between e_k and e_{k+1}
4. $$\tilde{u}_{param}(t, d) := \frac{u_{param}(t, d)}{\int_0^\infty u_{param}(t, d')\mathrm{d}d'}$$
5. Kinetic parameters:
   $param = \{k_{DMSO}, k_{TMZ}, A, \varphi, k_{HR}, C, K, n\}$
6. Compute with CMA-ES[3]

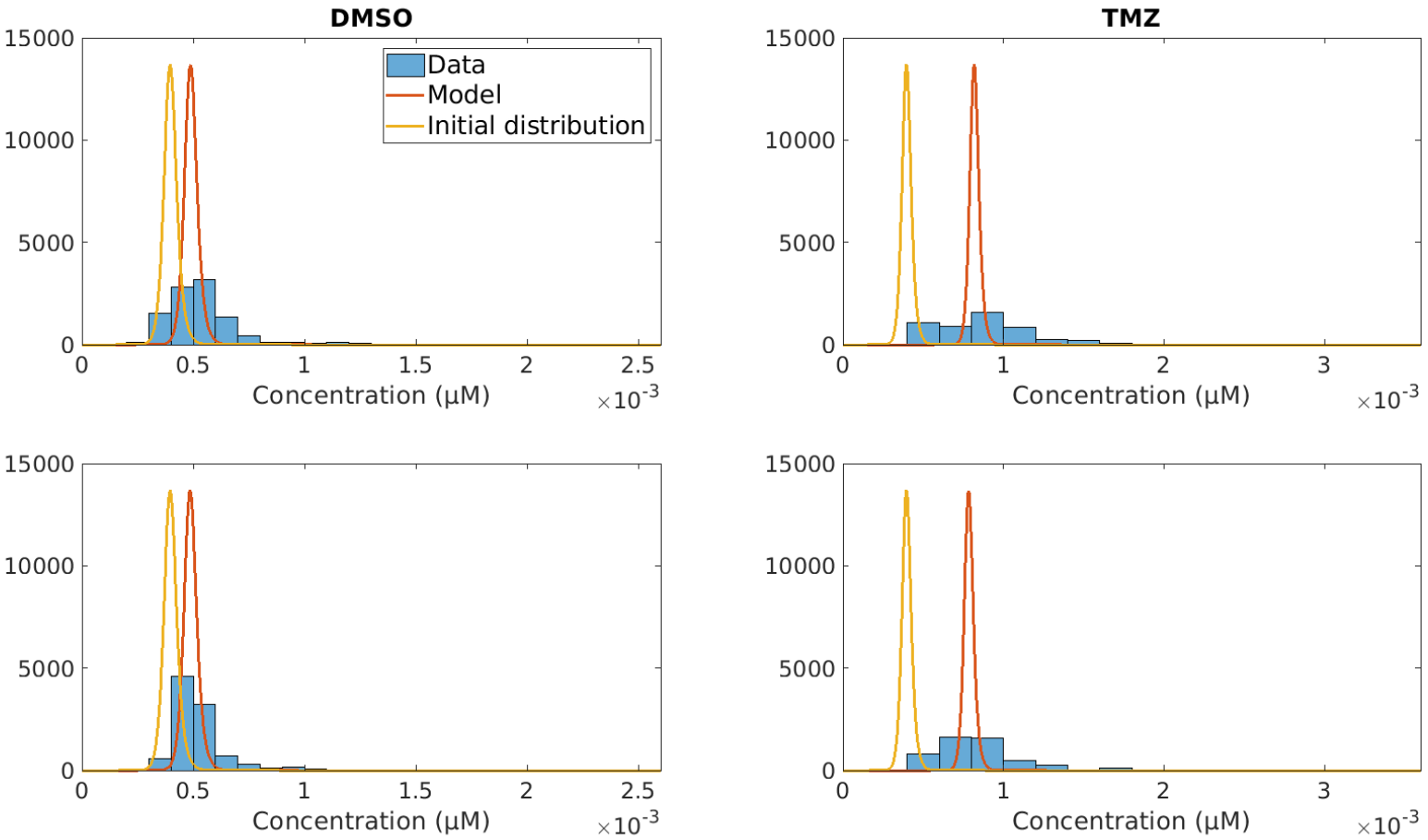
$$\min_{param} \sum_{k=0}^{K} \left(\int_{e_k}^{e_{k+1}} \tilde{u}_{param}(t, d)\mathrm{d}d - p_k \right)^2$$

[3] Hansen, *Towards a new evolutionary computation. Advances in estimation of distribution algorithms*, 2006

Best fit for model $\mathcal{R}$



Best fit for model $\mathcal{D}$



In models $\mathcal{R}$ and $\mathcal{D}$, the main behavior is captured, but there is a lack of spreading.

Addition of a heterogneity parameter

We aim at a spreading of the distribution $\Rightarrow$ inclusion of a variability parameter $v \in (0,1)$, that modulates the speed of the drug-induced DNA damage formation.

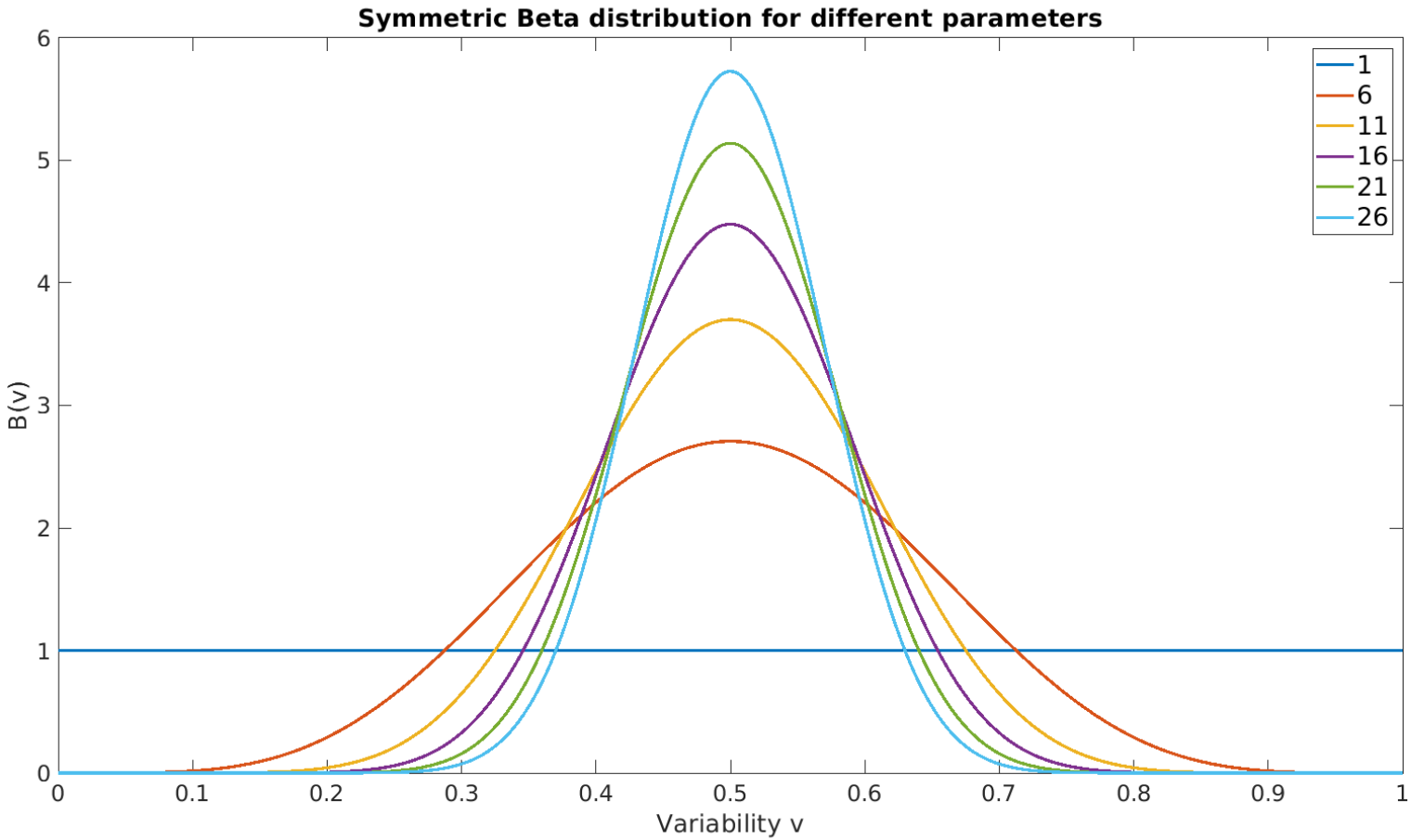
$$\begin{cases} \frac{\partial}{\partial t} u^v(t,x) + \frac{\partial}{\partial d}\left(F^v(t,d)u^v(t,d)\right) + \mu(d)u^v(t,d) = 0 \\ u^v(t,0) = 0, \qquad u_0^v(d) = u_0(d) \quad \forall v \in (0,1) \end{cases}$$

$$F^v(t,d) = v(k_{basal} + k_{add}[C])\left(1 + A\cos\left(\frac{2\pi}{T_{Bmal1}}(t-\varphi)\right)\right) - k_{HR}d$$

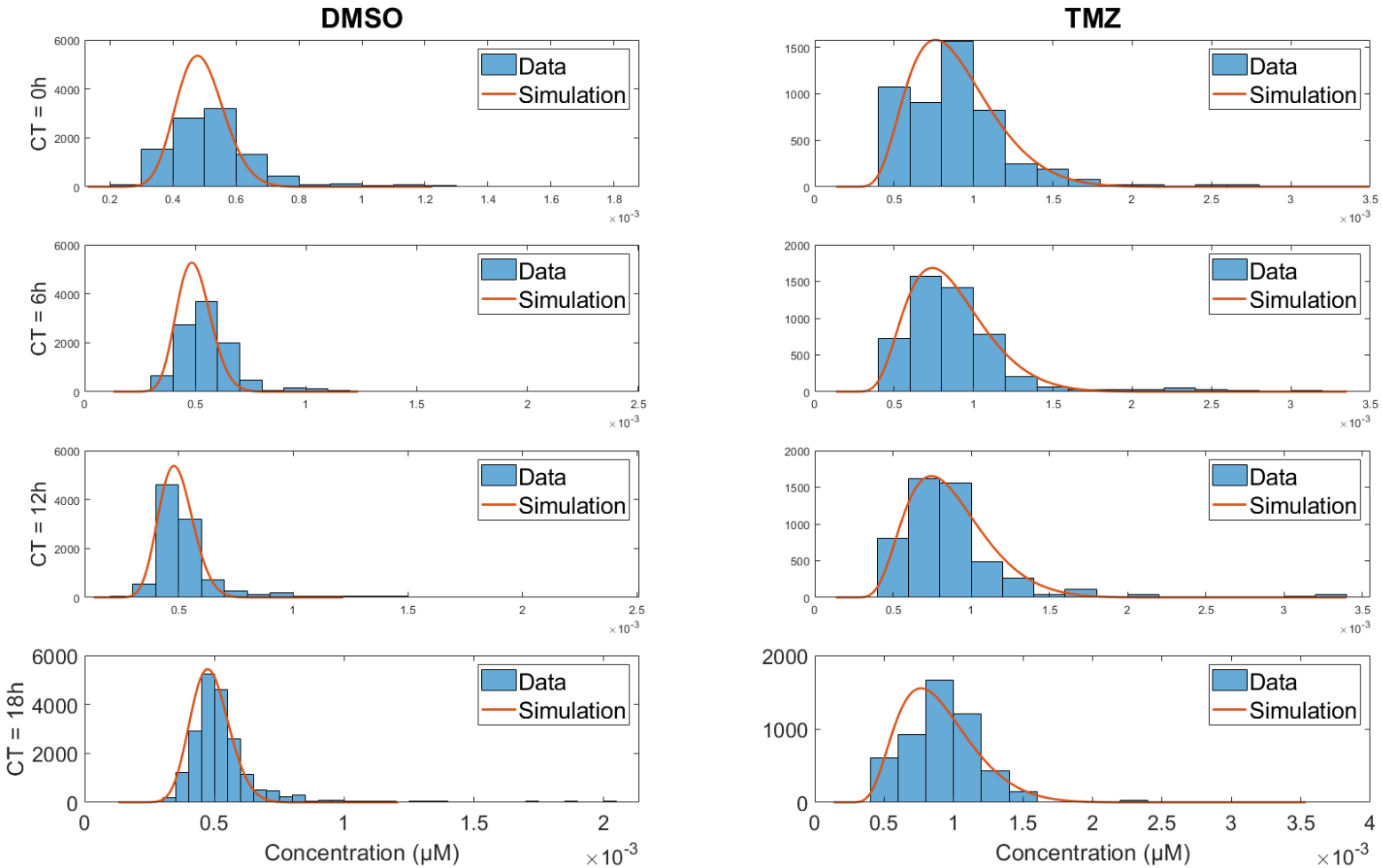
Example: heterogeneity and rhythm on damage formation $\rightarrow$ model $\mathcal{D} - \mathcal{D}$

Hypothesis on the heterogeneity

$B(v) = cste \times (x(1-x))^b$ with $b \geqslant 1$ a newly estimated parameter



Best fit of phospho H2AX data for model $\mathcal{D} - \mathcal{D}$



Parameters of the best fits

Heterogeneity	$\emptyset$	$\emptyset$	Damage
Rhythm	Damage	Repair	Damage
RMSE	2.78	2.79	1.14
Parameter (unit)			
k_{DMSO} (μM.h^{-1})			$6.60 \cdot 10^{-5}$
k_{TMZ} (h^{-1})			0.036
A			0.05
φ (h)			$3h46$
k_{HR} (h^{-1})			0.035
C (h^{-1})			7.08
K (μM)	$1.02 \cdot 10^{-7}$	$3.33 \cdot 10^{-7}$	$2.45 \cdot 10^{-4}$
n	8.82	26.07	0.79
b			17.9

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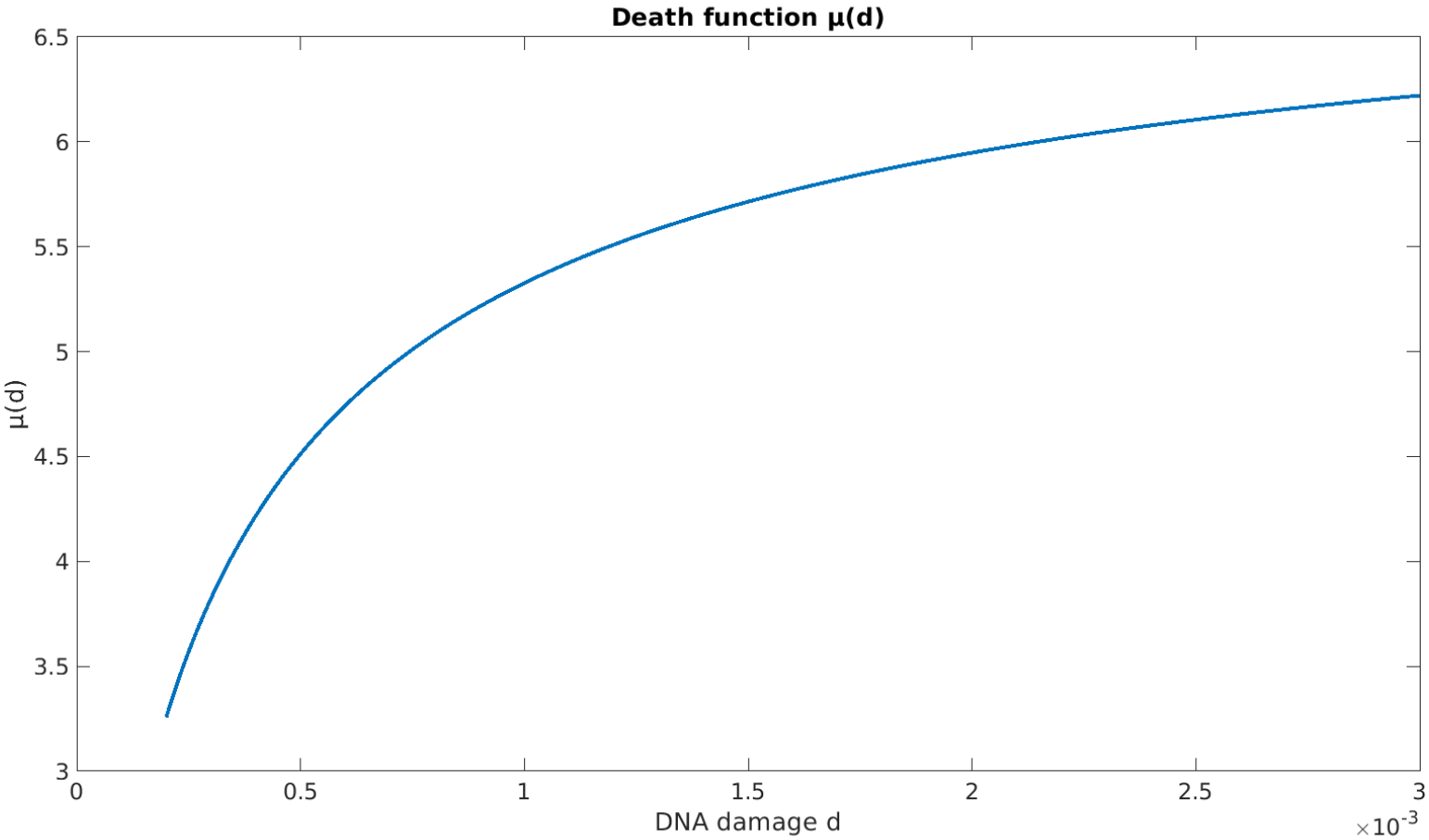
At least one model able to fit the data, that necessarily includes tumor heterogeneity.

Discussion: death term



$$\mu(d) = C\frac{d^n}{K^n + d^n}, \qquad 0 < n < 1$$

Not S-shaped, no threshold effect

Discussion

Straightforward changes in the model: death term $\longrightarrow \mu(d) = Cd^n$

Inclusion of other datasets and changes in the model:

- Population of dying cells: temporal data in concentration of Caspase 3
- Death term $\longrightarrow$ transfer term. Ex of model:

$$\frac{\mathrm{d}C3}{\mathrm{d}t} = \int_0^\infty \mu(d)u(t,d)\mathrm{d}d - C3$$

Data integration:

- Include inhibition of growth data
- Calibrate the models $\mathcal{D} - \mathcal{R}$, $\mathcal{R} - \mathcal{D}$ and $\mathcal{R} - \mathcal{R}$
- Compare these models to obtain (hopefully!) biological insights

IBOMAN

IBOMAN 2021 – Interplay between oncology, mathematics and numerics: focus on treatment studies

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SCOPE

Although mathematics and physics have a long history of interaction, interdisciplinary projects where mathematics interacts with biology and medicine have only become a hot topic in the last decades. To foster such interactions, we offer young researchers to meet each other during a conference highlighting the interplay between oncology, mathematics and numerics: the IBOMAN conference is an opportunity to give the floor to young people involved in interdisciplinary projects related to cancer research, whether fundamental or applied.

This 2021 edition will focus on the topic of treatment, with sessions related to identifying new therapeutic targets or predicting the effect of a treatment. In addition to the talks of young researchers, a master class will be scheduled, as well as talks given by senior researchers who sponsor the conference. To complete the program, a step-aside talk will be provided, in order to stimulate more general discussions around science.

SCHEDULE

SPEAKERS

- Lucie Laplane : Clonal evolution: of which clones?
- Hugues de Thé : Dissecting the mode of action of targeted leukemia therapies
- Victor Pérez-Garcia : Scaling laws, evolutionary dynamics and imaging biomarkers in cancer: from the blackboard to the clinics and back