Uncertainty quantification and control of kinetic models of tumour growth under clinical uncertainties

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PhD Spring Workshop 2022 – March 16

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Outline

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- From the Boltzmann equation with uncertainties to the multiagent systems
- Kinetic models for tumour growth
- Calibration of the model from clinical data
- Numerical results

The Boltzmann equation

Boltzmann equation & multiagent systems

The Boltzmann equation[1] (1872) describes the behaviour of a rarefied gas, i.e., a physical system composed of many interacting particles.

$$\frac{\partial}{\partial t} f(t,x,v) + v \cdot \nabla_x f(t,x,v) = \frac{1}{\epsilon} Q(f,f)(t,x,v).$$

[1] C. Cercignani, 1988; G. Dimarco, R. Caflisch, L. Pareschi, 2010.

[2] L. Pareschi, G. Toscani, 2013; B. Düring, P.A. Markowich, J.-F. Pietschmann, M.-T. Wolfram, 2009; J.A. Carrillo, M. Fornasier, J. Rosado, G. Toscani, 2010; P. Degond, S. Motsch, 2008.

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Interacting multiagent systems[2] (from $\sim$ 2000): systems composed of a huge number of interacting and autonomous agents who, as a result of their mutual interactions, exhibit emerging collective behaviour.

Different research fields ranging from biological context (tumour growth model, epidemiology, genomic) to socio-economic dynamics (wealth distribution, traffic flow, opinion dynamics, pedestrian model).

[1] C. Cercignani, 1988; G. Dimarco, R. Caflisch, L. Pareschi, 2010.

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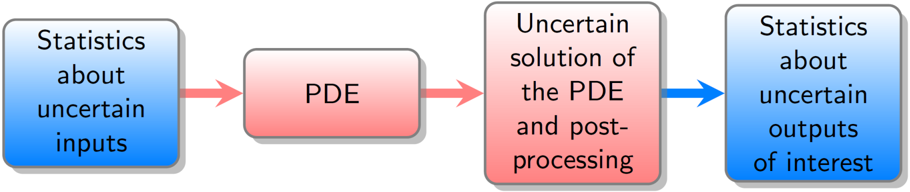
Uncertainty Quantification



UQ: parameters as random variables $z \in \mathbb{R}^d$ collecting all the sources of uncertainties

$$\frac{\partial}{\partial t} f(t, x, v, z) + v \cdot \nabla_x f(t, x, v, z) = \frac{1}{\epsilon} Q(f, f)(t, x, v, z), \qquad z \sim p(z)$$

From a numerical point of view we have to face the increase of dimensionality: curse of dimensionality.

Other approaches for tumour growth

Some literature:

- first order ODE-based models: Gompertz[3], von Bertalanffy[4], logistic growth

- PDE-based models[5], deterministic description of a tumour spheroid: free boundary problem[6], diffuse interface approach[7]

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[3] L. Norton, 1988; J. West, P.K. Newton, 2019.
[4] G.B. West, J.H. Brown, B.J. Enquist, 2001.
[5] V. Cristini, J. Lowengrub, 2010.
[6] H.M. Bryne, M.A. Chaplain, 1995.
[7] P. Colli, A. Signori, J. Sprekels, 2021; C.M. Elliott, H. Garcke, 1996; G. Schimperna, 2007; A. Agosti, P. Ciarletta, H. Garcke, M. Hinze, 2020.

The model

The model - free growth

Space-homogeneous Boltzmann equation, with free growth collisional operator

$$\partial_t f(t, x, z) = Q_G(f)(t, x, z).$$

[8] L. Preziosi, G. Toscani, and M. Zanella, 2021.

The model - free growth

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$$\partial_t f(t,x,\boldsymbol{z}) = Q_G(f)(t,x,\boldsymbol{z}).$$

Microscopic interaction[8]: for a given volume $x \in \mathbb{R}_+$ of cancer cells, we characterise an elementary variation $x \to x'$, with $\delta(\boldsymbol{z}) \in [-1,1]$, $\mu(\boldsymbol{z}) \in (0,1)$, $\lambda(\boldsymbol{z}) \in [0,1)$ as

$$x' = x + \Phi_\delta^\epsilon(x/x_L, \boldsymbol{z})x + x\eta_\epsilon, \qquad \Phi_\delta^\epsilon(y,\boldsymbol{z}) = \mu \frac{1 - e^{\epsilon(y^\delta - 1)/\delta}}{(1+\lambda)e^{\epsilon(y^\delta-1)/\delta} + 1 - \lambda}, \qquad y = \frac{x}{x_L},$$

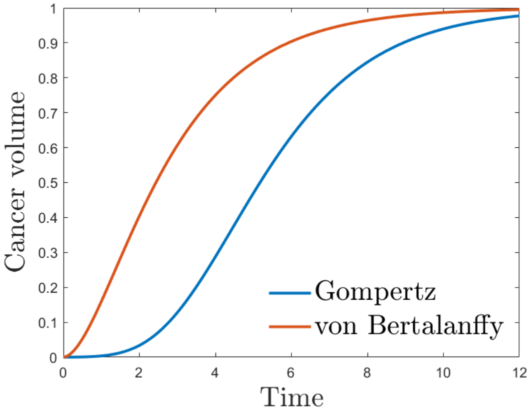
being x_L the carrying capacity.

[8] L. Preziosi, G. Toscani, and M. Zanella, 2021.

ODE-based model

In the regime $\epsilon \ll 1$, the microscopic variation is coherent with well-known tumour growth ODE-based models: Gompertz[9] ($\delta \to 0^+$) and von Bertalanffy[10] ($\delta < 0$) models:

$$\lim_{\epsilon \to 0^+} \frac{\Phi_\delta^\epsilon(x/x_L, \boldsymbol{z})}{\epsilon} = \frac{\mu}{2\delta}\left(1 - \left(\frac{x}{x_L}\right)^\delta\right)$$



[9] L. Norton, 1988; J. West, P.K. Newton, 2019.
[10] G.B. West, J.H. Brown, B.J. Enquist, 2001.

Fokker-Planck asymptotics

In the regime $\epsilon \ll 1$, the microscopic variation in quasi invariant: grazing limit[11], we derive a Fokker-Planck-type equation:

$$\partial_t f(t,x,\boldsymbol{z}) = \partial_x \left[-\Phi_\delta(x/x_L,\boldsymbol{z}) x f(t,x,\boldsymbol{z}) + \frac{\sigma^2}{2} \partial_x (x^2 f(t,x,\boldsymbol{z})) \right]$$

[11] C. Villani, 1998-2002. G. Toscani, 2006

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whose steady states in the case $\delta(\boldsymbol{z}) < 0$ are fat-tailed Amoroso-type distributions

$$f^\infty(x,\boldsymbol{z}) = \frac{|\delta|}{\Gamma(k/|\delta|)} \frac{\theta^k}{x^{k+1}} exp\left\{ -\left(\frac{\theta}{x}\right)^{|\delta|} \right\}, \quad k(\boldsymbol{z}) = \frac{1}{\gamma\delta}+1, \ \theta(\boldsymbol{z}) = x_L(\boldsymbol{z}) \left(\frac{1}{\gamma\delta^2}\right)^{1/|\delta|}$$

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The model - control growth

We insert into the kinetic equation a new collisional operator $Q_C(f)(t,x,\boldsymbol{z})$

$$\partial_t f(t,x,\boldsymbol{z}) = Q_G(f)(t,x,\boldsymbol{z}) + Q_C(f)(t,x,\boldsymbol{z})$$

[12] A.M., G. Colelli, L. Farina, A. Bacila, P. Bini, E. Marchioni, S. Figini, A. Pichiecchio, M. Zanella, 2022.

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associated to the microscopic deterministic and controlled volume variation[12] $x \to x''$, with target volume $x_d > 0$

$$x'' = x + \epsilon S(x) u \qquad u = \operatorname*{arg\,min}_{u\in\mathcal{U}} \{(x''-x_d)^2 + \epsilon\kappa|u|^p\} \qquad p = 1,2.$$

$S(x) > 0$ is a selective function, κ is the penalization and u is the control.

[12] A.M., G. Colelli, L. Farina, A. Bacila, P. Bini, E. Marchioni, S. Figini, A. Pichiecchio, M. Zanella, 2022.

Fokker-Planck asymptotics (again)

Controlled Fokker-Planck-type equation in the case $p = 2$

$$\partial_t f(t,x,\boldsymbol{z}) = \partial_x \left[-\Phi_\delta(x/x_L, \boldsymbol{z}) x f(t,x,\boldsymbol{z}) + \frac{\sigma^2}{2} \partial_x (x^2 f(t,x,\boldsymbol{z})) \right] + \frac{1}{\kappa} \partial_x \left[S^2(x)(x - x_d) f(t,x,\boldsymbol{z}) \right]$$

Fokker-Planck asymptotics (again)

Controlled Fokker-Planck-type equation in the case $p = 2$

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whose steady states in the case $\delta(\boldsymbol{z}) < 0$ are

$$f^\infty(x,\boldsymbol{z}) = C(\boldsymbol{z}) \left(\frac{1}{x}\right)^{\frac{1}{\gamma|\delta|}+2} exp \left\{ -\frac{2}{\sigma^2\delta^2}\left(\frac{x}{x_L}\right)^\delta \right\} \times exp \left\{ -\frac{2}{\sigma^2\kappa} \int \frac{S^2(x)(x-x_d)}{x^2} dx \right\}$$

Uncertainty damping

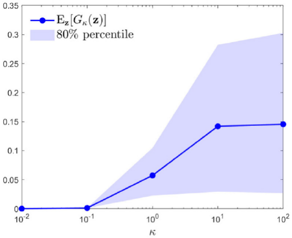
Uncertainty damping ($p=2$): for all $z \in \mathbb{R}^d$ and a penalization $\kappa \to 0^+$:

$$|m^\infty(z) - x_d| \le \frac{\kappa\mu}{1-\lambda-\kappa\mu} x_d \quad \text{if} \quad S(x) = 1$$

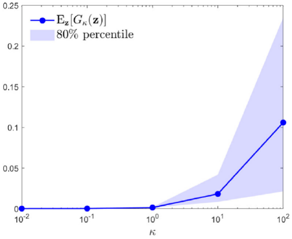
$$|m^\infty(z) - x_d| \le \frac{\kappa\mu}{1-\lambda} \quad \text{if} \quad S(x) = \sqrt{x}$$

Numerical result (spoiler): at fixed time $T > 0$ the function $G_\kappa(z)$ quantifies the ”distance” from the target volume x_d

$$G_\kappa(z) = \int_{\mathbb{R}_+} (x - x_d)^2 f(T, x, z) dx$$



(a) $p = 1,\ S(x) = 1$



(c) $p = 2,\ S(x) = 1$

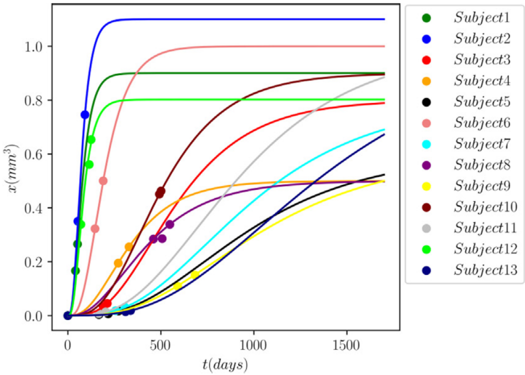
Model calibration

Parameters estimation[13]

For each subject we solve the minimization problem, adopting the von Bertalanffy growth model with $\Theta = (a, q, x_L)$:

$$\min_{\Theta} \left[\sum_{h \in H_i} |x_i(t^h) - \hat{x}_i(t^h)| + \beta \|\Theta\|_{L^1} \right],$$

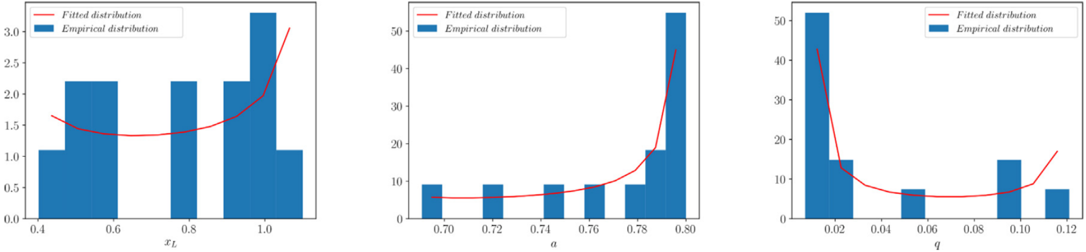
with t^h time point at which the tumour sizes are evaluated, $x_i(t^s)$ theoretical value, $\hat{x}_i(t^s)$ measured volume, and H_i subject-based number of observations of the tumour volume.



[13] Clinical data (brain tumour, primary glioblastoma) collected from 2011 to 2021 at IRCCS Mondino.

Parameters distribution

We construct the associated histograms and we determine the theoretical distributions that better reproduce each of them by maximising the proper likelihood function: a, q, x_L are **Beta**-distributed



Numerical results

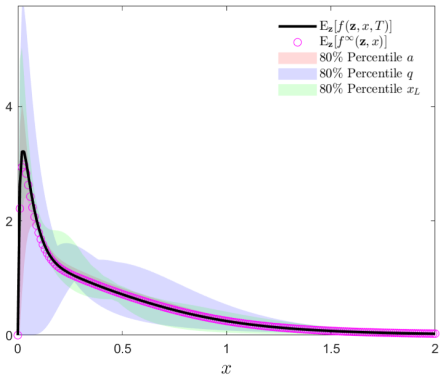
Numerical approach

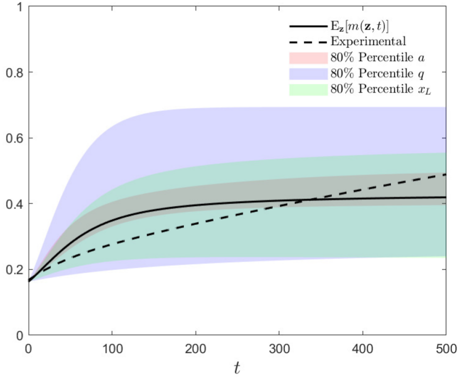
- Direct Simulation Monte Carlo (DSMC) with collocation for the Boltzmann equation

- Stochastic-Galerkin for the Fokker-Planck equation

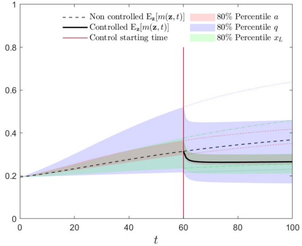
These methods are spectrally accurate in the random parameters space and stable.

Large time distribution (left) & evolution of the mean volume (right), uncontrolled scenario

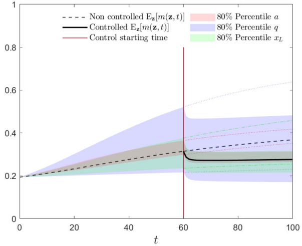




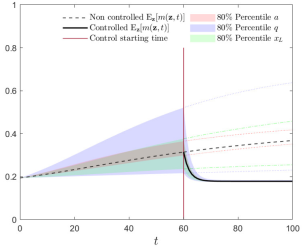
Evolution of the mean volume in the controlled scenario



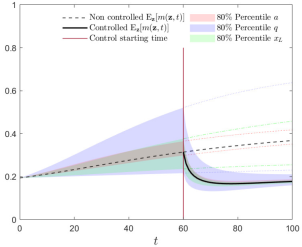
(a) $p = 1,\ \kappa = 1,\ S(x) = 1$



(b) $p = 1,\ \kappa = 1,\ S(x) = \sqrt{x}$

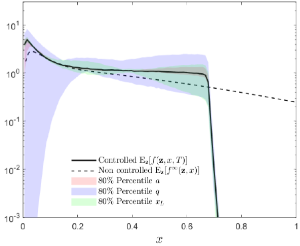


(e) $p = 2,\ \kappa = 1,\ S(x) = 1$



(f) $p = 2,\ \kappa = 1,\ S(x) = \sqrt{x}$

Large time distribution in the controlled scenario



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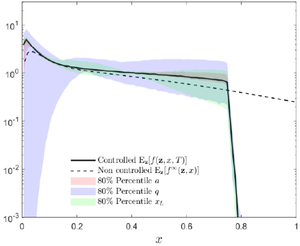

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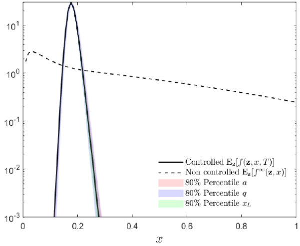
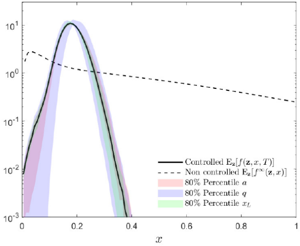


(c) $p = 2,\ \kappa = 1,\ S(x) = 1$



(d) $p = 2,\ \kappa = 1,\ S(x) = \sqrt{x}$

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Thanks for the attention!