Alternative approaches to cancer treatment: towards stochastic tumour control

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BUILD-IT2023 Workshop

BUILding a DIgital Twin: requirements, methods, and applications

IASI BioMatLab
National Research Council of Italy
Institute of Systems Analysis and Computer Science
Biomathematics Laboratory

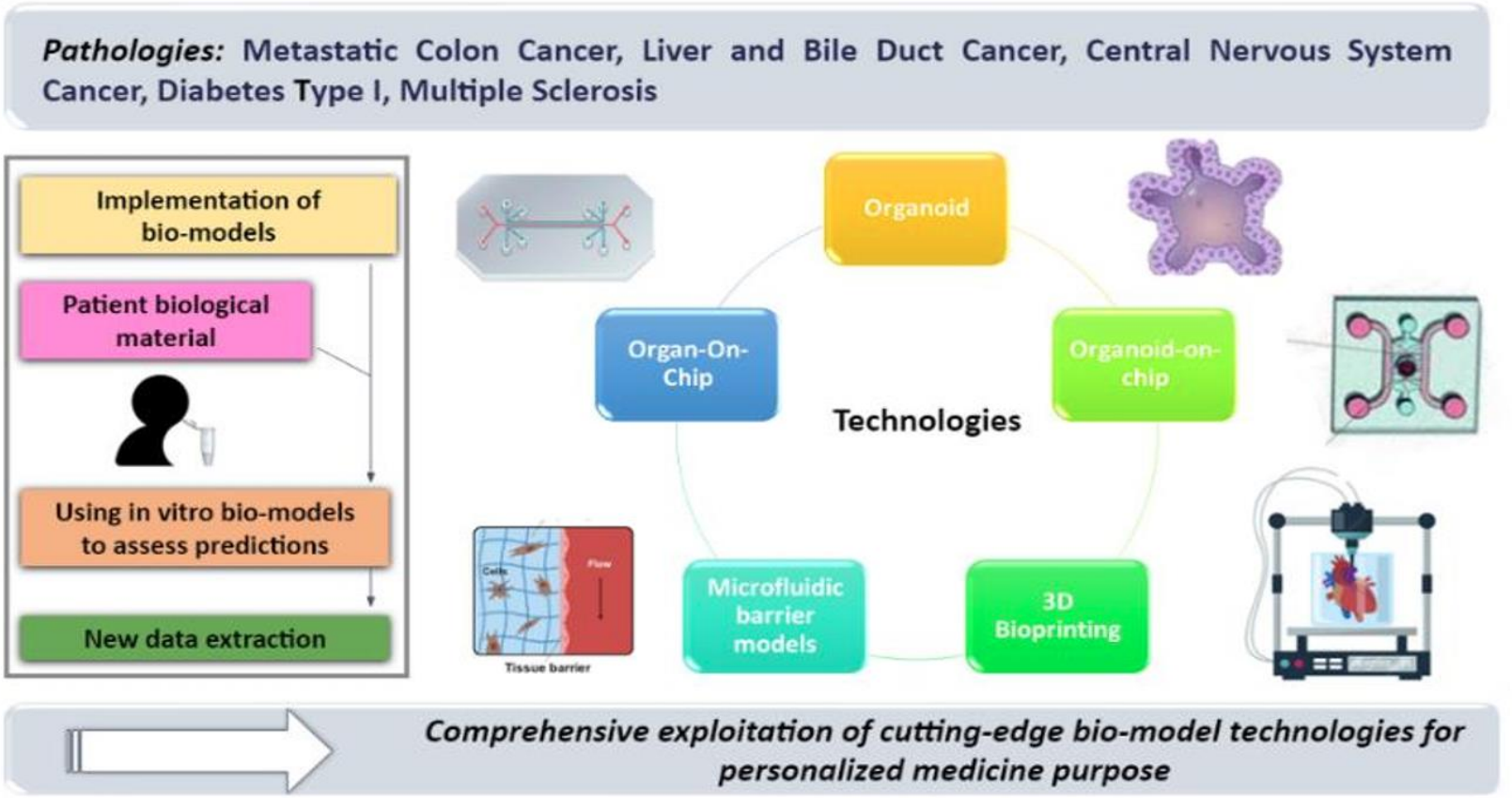
UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA

Consiglio Nazionale delle Ricerche
Istituto di Analisi dei Sistemi ed Informatica "Antonio Ruberti"

D³-4-Health

"Digital Driven Diagnostics, prognostics and therapeutics for sustainable Health care"
Funded by the Italian National Recovery and Resilience Plan (**NRRP**) complementary fund

Goal: Delivery of **accessible and affordable diagnostic, monitoring and therapeutic pathways** for 5 reference diseases



Spoke 3 - Wearable technologies, sensors and biomarkers for care through Digital Twin approaches

Leader: UNIRM1
Co-leader: CNR, UNIMOL
Affiliates: UniSA, POLITO, POLIBA, Neuromed, AOUS, UNICZ, CROB, ISS, ASL 3 Nuoro, UNIMI

REFERENCE DISEASE

P1	P2	P3	P4	P5
Metastatic colon cancer	Liver and bile duct cancer	Central Nervous System cancer	Diabetes type I	Multiple sclerosis

1 CLINICAL USE CASES AND NEW MODELS OF CARE SUPPORTED BY AI/E-HEALTH BASED SOLUTIONS (Uni Milano)

2 MULTILAYER PLATFORM FOR GENERATION OF PATIENTS' DIGITAL TWIN (Uni Salerno)

3 WEARABLE TECHNOLOGIES, SENSORS AND BIOMARKERS FOR CARE THROUGH DIGITAL TWIN APPROACHES (Sapienza)

4 BIOLOGICAL AND BIOENGINEERED IN VITRO MODELS FOR CARE THROUGH DIGITAL TWIN APPROACHES (Politecnico di Torino)

Outline of this talk

- The challenge of **tumour growth control** is here addressed exploiting a **minimally parametrized and low-dimensional model** that takes proliferating and necrotic tumour cells dynamics into account, as well as the level of an anti-tumour drug.

- Based on a **Chemical Reaction Network** (CRN) modelling approach, a double **stochastic/deterministic description** of the system is given. The deterministic **ODE** model can be exploited for control purposes particularly when the **number of tumour cells** is **high**.

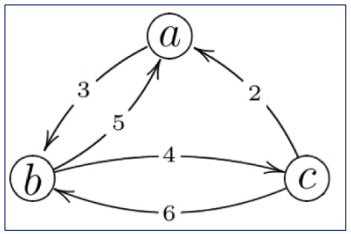
- **Two alternative control approaches** are investigated in the deterministic context: (i) a constant drug infusion, (ii) a state-feedback control scheme, with partial or complete knowledge of the state. Asymptotical guarantees of **tumour eradication** are given.

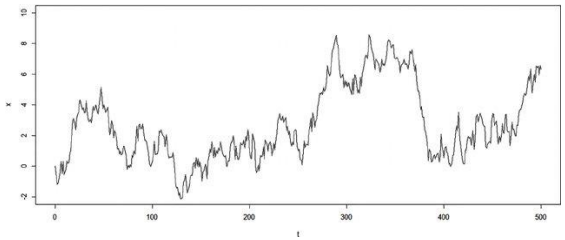
- When the **number of tumour cells** becomes relatively **low**, the **stochastic formulation** provides a more accurate description of the dynamic behaviour of the system and allows to compute a statistics of the **eradication time**.

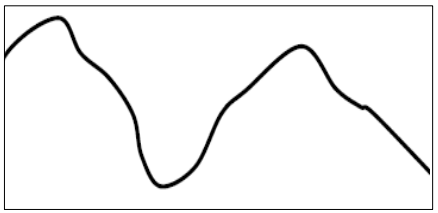
Multi-scale modeling

SYSTEM SIZE

microscopic	mesoscopic	macroscopic
(few units)		(many units)
high randomness		**low randomness**
CTMC	**SDE**	**ODE**
stochastic	**stochastic**	**deterministic**
discrete state	**continuous state**	**continuous state**
high complexity	**low complexity**	**low complexity**



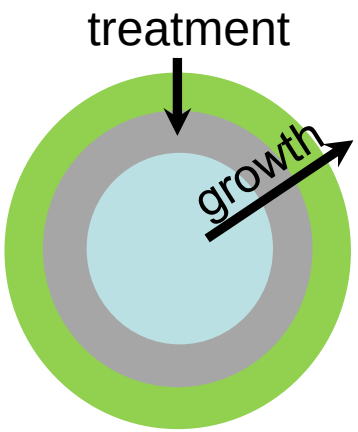




Deterministic Vs Stochastic Modelling of Tumour Growth and Treatment

- The proposed deterministic-stochastic modelling framework generalizes the deterministic CRN-based approach introduced by Drexler et al. (2019).

- We describe by means of the following CRN some physiological aspects of the tumour growth, as well as the growth inhibition due to tumour-drug interaction.



Tumour mass

proliferating cells

necrotic cell core

Species

X_1 – proliferating tumour cells
X_2 – dead tumour cells
X_3 – drug molecules

CRN	Processes
$R_1: X_1 \rightarrow 2X_1,$	(cell proliferation)
$R_2: X_1 \rightarrow X_2,$	(cell necrosis)
$R_3: X_2 \rightarrow \emptyset,$	(washout of dead cells)
$R_4: X_3 \rightarrow \emptyset,$	(drug clearance)
$R_5: X_1 + X_3 \rightarrow X_2,$	(drug action)
$R_6: \emptyset \rightarrow X_3.$	(drug administration)

Deterministic formulation

- The deterministic formulation of the model is obtained by means of two steps:

1) following the usual mechanism-based description of a CRN (based on flux balances), we first derive a basic model representation in terms of chemical species concentrations

CRN **Basic deterministic representation**

$$
\begin{aligned}
&R_1{:}\, X_1 \xrightarrow{k_1} 2X_1,\\
&R_2{:}\, X_1 \xrightarrow{k_2} X_2,\\
&R_3{:}\, X_2 \xrightarrow{k_3} \emptyset,\\
&R_4{:}\, X_3 \xrightarrow{k_4} \emptyset,\\
&R_5{:}\, X_1 + X_3 \xrightarrow{k_5} X_2,\\
&R_6{:}\, \emptyset \xrightarrow{k_6} X_3.
\end{aligned}
\quad \Leftrightarrow \quad
\frac{d[\mathbf{X}]}{dt} = S\mathbf{v}([\mathbf{X}]),
$$

$$
[\boldsymbol{X}] = \begin{pmatrix} [X_1] \\ [X_2] \\ [X_3] \end{pmatrix}
\qquad
S = \begin{bmatrix} 1 & -1 & 0 & 0 & -1 & 0 \\ 0 & 1 & -1 & 0 & 1 & 0 \\ 0 & 0 & 0 & -1 & -1 & 1 \end{bmatrix}
$$

$$
\mathbf{v}([\mathbf{X}]) = \begin{pmatrix} \nu_1([\boldsymbol{X}]) \\ \nu_2([\boldsymbol{X}]) \\ \nu_3([\boldsymbol{X}]) \\ \nu_4([\boldsymbol{X}]) \\ \nu_5([\boldsymbol{X}]) \\ \nu_6([\boldsymbol{X}]) \end{pmatrix}
\qquad
\begin{aligned}
&\nu_1 = k_1[X_1],\\
&\nu_2 = k_2[X_1],\\
&\nu_3 = k_3[X_2],\\
&\nu_4 = k_4[X_3]/(K_4 + [X_3]),\\
&\nu_5 = k_5[X_1][X_3]/(K_5 + [X_3]),\\
&\nu_6 = k_6.
\end{aligned}
$$

2) we express the obtained ODE model in terms of countable variables, i.e., cells and drug molecules copy numbers

Deterministic model

$$
\begin{aligned}
\frac{dn_1}{dt} &= (k_1 - k_2)n_1 - k_5 n_1 \frac{n_3}{M_5 + n_3},\\
\frac{dn_2}{dt} &= k_2 n_1 - k_3 n_2 + k_5 n_1 \frac{n_3}{M_5 + n_3},\\
\frac{dn_3}{dt} &= -\rho \frac{n_3}{M_4 + n_3} - k_5 n_1 \frac{n_3}{M_5 + n_3} + r,
\end{aligned}
$$

n_i: number of cells/molecules of the species X_i ($n_i = V[X_i]$, i=1,2,3, V: volume of the reaction system)

$\rho = V k_4$, $r = V k_6$, $M_j = V K_j$, $j = 4, 5$

- The countable deterministic model shows a little abuse of notation, since it provides a continuous description (in terms of ODEs) of cell/molecule copy numbers, which are intrinsically discrete state variables. However, such a formulation allows a direct comparison with the stochastic formulation.

Stochastic formulation

- $n(t) = (n_1(t), n_2(t), n_3(t))$ is a Continuous Time Markov Chain defined by the reaction parameters c_i (c_i dt: probability that a particular combination of R_i-reactants reacts in (t,t+dt) in the volume V).
- Given the propensities a_i the probability that a generic step R_i reacts in (t,t+dt) is $a_i\,\mathrm{d}t = h_i(n(t))\,c_i\,\mathrm{d}t$.

CRN

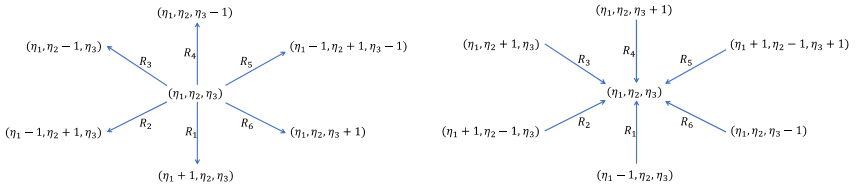
$$
\begin{aligned}
&R_1: X_1 \xrightarrow{c_1} 2X_1,\\
&R_2: X_1 \xrightarrow{c_2} X_2,\\
&R_3: X_2 \xrightarrow{c_3} \emptyset,\\
&R_4: X_3 \xrightarrow{c_4} \emptyset,\\
&R_5: X_1 + X_3 \xrightarrow{c_5} X_2,\\
&R_6: \emptyset \xrightarrow{c_6} X_3.
\end{aligned}
$$

Stochastic representation

Event	Resets	propensities
R_1	$n_1 \mapsto n_1 + 1$	$a_1 = c_1 n_1$
R_2	$\begin{cases} n_1 \mapsto n_1 - 1 \\ n_2 \mapsto n_2 + 1 \end{cases}$	$a_2 = c_2 n_1$
R_3	$n_2 \mapsto n_2 - 1$	$a_3 = c_3 n_2$
R_4	$n_3 \mapsto n_3 - 1$	$a_4 = c_4 \frac{n_3}{H_4 + n_3}$
R_5	$\begin{cases} n_1 \mapsto n_1 - 1 \\ n_2 \mapsto n_2 + 1 \\ n_3 \mapsto n_3 - 1 \end{cases}$	$a_5 = c_5 \frac{n_1 n_3}{H_5 + n_3}$
R_6	$n_3 \mapsto n_3 + 1$	$a_6 = c_6$

$$\partial P(\eta;t)/\partial t = \sum_{i=1}^{6} [a_i(\eta - \delta_i)P(\eta - \delta_i;t) - a_i(\eta)P(\eta;t)]$$

Stochastic model



The propensities a_i have the same expression of the fluxes υ_i.

- First-order moment equations are obtained by applying the van Kampen approximation (2007) for the nonlinear propensities a_4, a_5.

1-st moment system

$$\frac{d\mathrm{E}\{n(t)\}}{dt} \approx S a\left(\mathrm{E}\{n(t)\}\right),$$

$$
\begin{aligned}
\frac{d\mathrm{E}\{n_1\}}{dt} &\approx (c_1 - c_2)\mathrm{E}\{n_1\} - c_5 \mathrm{E}\{n_1\} \frac{\mathrm{E}\{n_3\}}{H_5 + \mathrm{E}\{n_3\}},\\
\frac{d\mathrm{E}\{n_2\}}{dt} &\approx c_2 \mathrm{E}\{n_1\} - c_3 \mathrm{E}\{n_2\} + c_5 \mathrm{E}\{n_1\} \frac{\mathrm{E}\{n_3\}}{H_5 + \mathrm{E}\{n_3\}},\\
\frac{d\mathrm{E}\{n_3\}}{dt} &\approx -c_4 \frac{\mathrm{E}\{n_3\}}{H_4 + \mathrm{E}\{n_3\}} - c_5 \mathrm{E}\{n_1\} \frac{\mathrm{E}\{n_3\}}{H_5 + \mathrm{E}\{n_3\}} + c_6.
\end{aligned}
$$

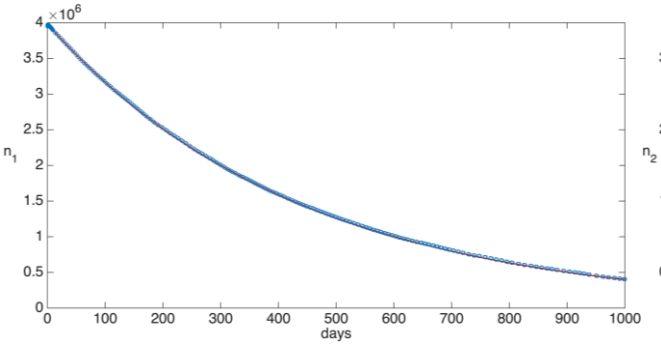
The 1-st order moment system has the same structure of the deterministic model.

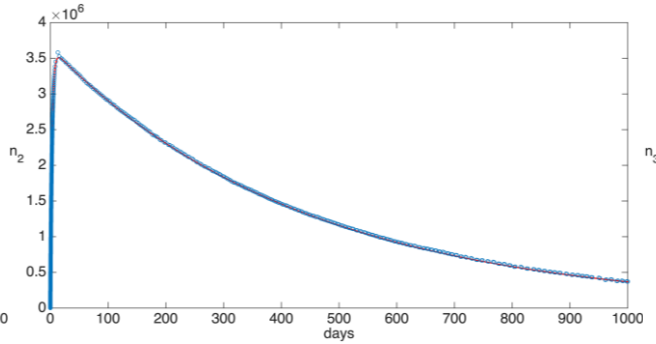
The deterministic model approximates the 1-st order moment provided that the following parameter parameter equivalence holds:

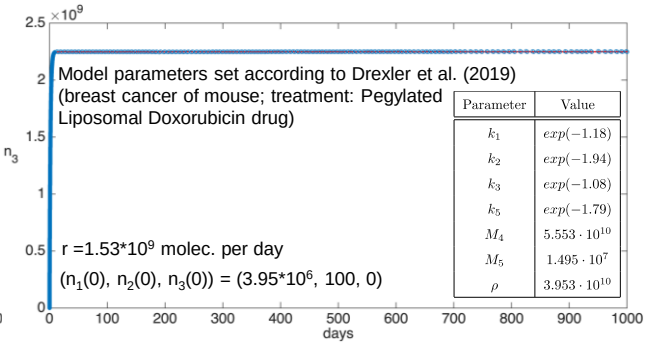
$$
\begin{aligned}
&c_i = k_i, \quad i = 1,2,3,5,\\
&c_4 = \rho,\ c_6 = r,\ H_i = M_i, \quad i = 4,5.
\end{aligned}
$$

Numerical simulations

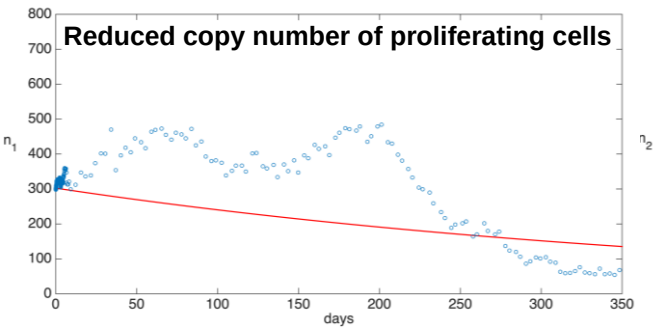
- Random paths (blue dots) obtained by means of the τ-leap simulation algorithm (Gillespie, 2001).
- The deterministic evolution (red line) reproduces the 1st-order moment dynamics.

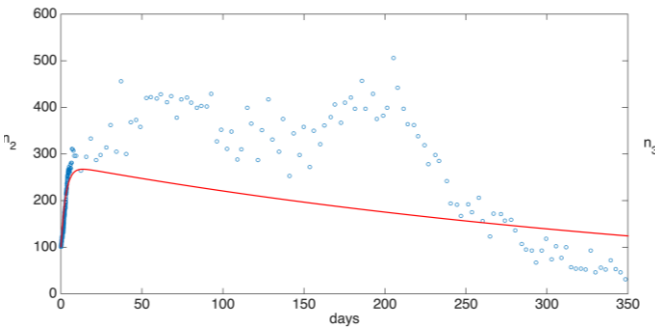


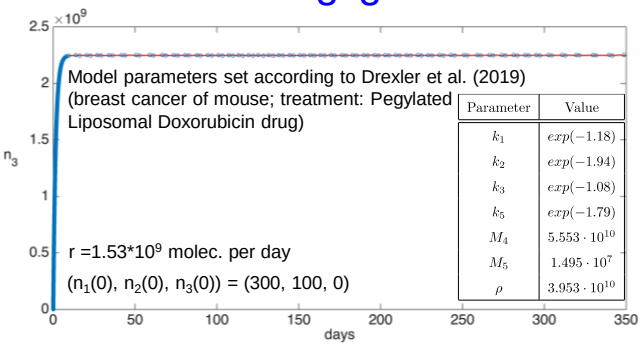




- The high number of proliferating tumour cells makes the stochastic fluctuations negligible.







- The mean trend is still well captured by the ODEs, but fluctuations are now highly detectable.
- Fluctuations let the system reach the absorbing state $n_1=0$ in a finite time, making the stochastic formulation particularly interesting when dealing with strategies for complete tumour eradication.
- At the beginning of the therapy, it is reasonable to assume a high number of tumour cells: the ODE is preferable to lighten the computational burden.
- Dealing with successful therapies, tumour cells reduce to a very low level: the CME is then a preferable representation.

Model dynamics under a constant infusion

- A qualitative analysis is performed with reference to the deterministic model under time-invariant infusion $r(t) = \bar{r}$, obtaining the following brief summary for the existence and the (local) stability properties of the model equilibria.

Parameter region		Infusion rate	Equilibrium	Stability
$k_1 < k_2$		$0 \le \bar{r} < \rho$	E_1	Locally asympt. stable
		$\bar{r} \ge \rho$	$\nexists$	–
$k_1 = k_2$		$\bar{r} = 0$	$^*f(\supset \{E_1\})$	Nothing can be said
		$0 < \bar{r} < \rho$	E_1	Locally asympt. stable
		$\bar{r} \ge \rho$	$\nexists$	–
$k_1 > k_2$	$k_5 \le k_1 - k_2$	$0 \le \bar{r} < \rho$	E_1	Unstable
		$\bar{r} \ge \rho$	$\nexists$	–
	$k_5 > k_1 - k_2$	$0 \le \bar{r} < \beta\rho$	E_1	Unstable
		$\bar{r} = \beta\rho$	$E_1 \equiv E_2$	Nothing can be said
		$\beta\rho < \bar{r} < \rho$	E_1	Locally asympt. stable
			E_2	Unstable
		$\bar{r} \ge \rho$	E_2	Unstable

$^*f = \left\{\left(z, \frac{k_1}{k_5} z, 0\right) : z \ge 0\right\}$

➢ $E_1 = \left(0,\ 0,\ M_4 \dfrac{\bar{r}}{\rho - \bar{r}}\right)$ is the **extinction** equilibrium;

➢ $E_2 = \left(\dfrac{\bar{r} - \beta\rho}{k_1 - k_2},\ \dfrac{k_1}{k_3}\dfrac{\bar{r} - \beta\rho}{k_1 - k_2},\ \dfrac{M_5(k_1 - k_2)}{k_5 - k_1 + k_2}\right)$, with

$$\beta = \frac{M_5(k_1 - k_2)}{M_4(k_5 - k_1 + k_2) + M_5(k_1 - k_2)},$$

is the **persistence** equilibrium;

- Only E_1 is of interest for medical applications.

- Looking for an effective anticancer treatment is reasonable only in the parameter subspace

$$k_1 > k_2, \qquad k_5 > k_1 - k_2,$$

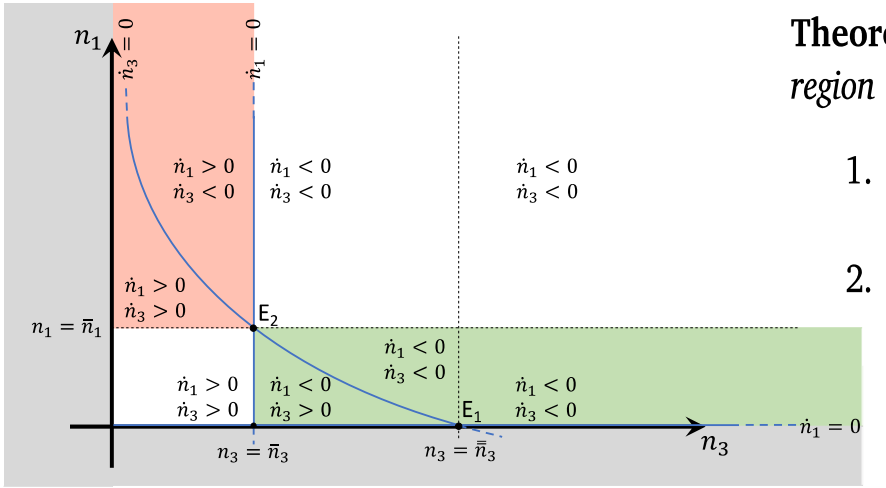
with a constant infusion rate rate $\bar{r}$ in the admissibility range

$$\bar{r} \in (\beta\rho, \rho).$$

Model dynamics under a constant infusion

- A global analysis has been performed for $k_5 > k_1 - k_2 > 0$ and for the administration rate $\bar{r} \in (\beta\rho, \rho)$.

- Two regions with clear dynamical behaviour are found in the positive orthant of the plane (n_3,n_1):



Theorem 1. *The dynamical behaviour of system (3) in the parameter region (7) is such that*

1. *if* $n_3(0) \geq \bar{n}_3$, $0 \leq n_1(0) \leq \bar{n}_1$, *and* $(n_3(0), n_1(0)) \neq (\bar{n}_3, \bar{n}_1)$ *(green area not including* E_2*) then* $(n_3(t), n_1(t)) \to (\bar{\bar{n}}_3, 0)$ *for* $t \to \infty$;
2. *if* $0 \leq n_3(0) \leq \bar{n}_3$, $n_1(0) \geq \bar{n}_1$, *and* $(n_3(0), n_1(0)) \neq (\bar{n}_3, \bar{n}_1)$ *(red area not including* E_2*) then* $(n_3(t), n_1(t)) \to (0, \infty)$ *for* $t \to \infty$.

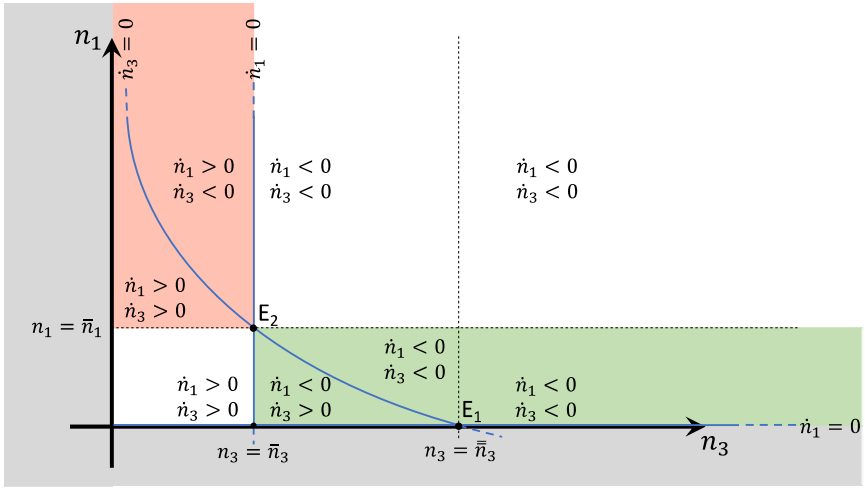
$$\bar{n}_3 = \frac{(k_1 - k_2)M_5}{k_5 - k_1 + k_2} \qquad \bar{n}_1 = \frac{\bar{r} - \beta\rho}{k_1 - k_2} \qquad \bar{\bar{n}}_3 = \bar{r}M_4/(\rho - \bar{r})$$

- Every real scenario starts from the point ($n_3(0)$,$n_1(0)$)=(0,n_{10}), with n_{10}>0: the dynamical behaviour of the state variables strongly depends on their initial values, and in particular on the tumour size n_{10} when the therapy starts.

Model dynamics under a constant infusion

- If the constant administration rate $\bar{r} \in (\beta\rho, \rho)$ is chosen without a proper evaluation of the initial tumour size the therapy can fail.

- If $n_{10} < \bar{n}_1$, the evolution depends on which region (red-vs-green) is reached before the other one.



- Conversely, if $n_{10} \geq \bar{n}_1$ the tumour will indefinitely grow.

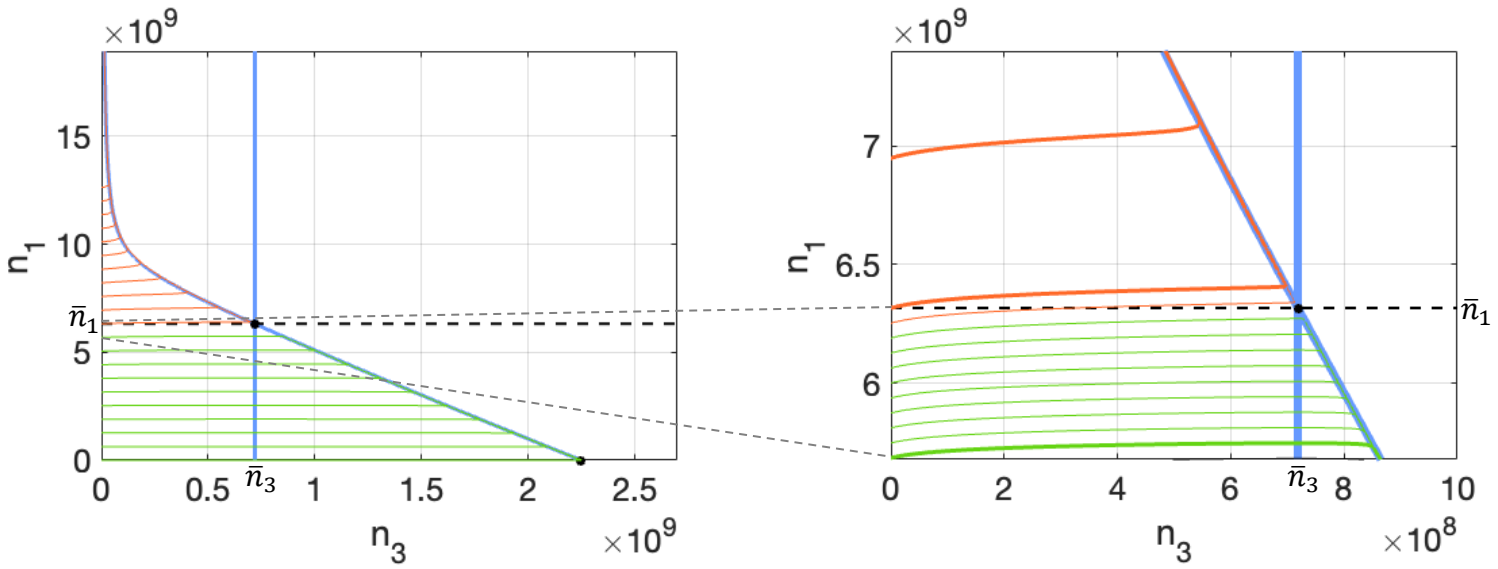
- As $\bar{n}_1$ depends on $\bar{r}$, it is possible to increase $\bar{n}_1$ by increasing $\bar{r}$ (keeping n_{10} far from the critical region of unlimited growth), until the condition $\bar{r} < \rho$ holds.

- Such a tuning of the constant therapy can be accomplished until $n_{10} < n_{10}^{max}$ with $n_{10}^{max} = \dfrac{(1-\beta)\rho}{k_1 - k_2}$.

- If $n_{10} \geq n_{10}^{max}$ there is no admissible constant therapy (i.e., $\bar{r} \in (\beta\rho, \rho)$) such that the condition $n_{10} < \bar{n}_1$ holds.

Model dynamics under a constant infusion

- The figure shows an example of the state trajectories obtained for a constant therapy (with $\bar{r} \in (\beta\rho, \rho)$, $k_5 > k_1 - k_2 > 0$) changing the initial tumour size $n_{10} \in (0, 2\bar{n}_1]$.



Parameter	Value
k_1	$exp(-1.18)$
k_2	$exp(-1.94)$
k_3	$exp(-1.08)$
k_5	$exp(-1.79)$
M_4	$5.553 \cdot 10^{10}$
M_5	$1.495 \cdot 10^{7}$
ρ	$3.953 \cdot 10^{10}$
β	0.0128
n_{10}^{max}	$2.386 \cdot 10^{11}$
$\bar{r} = 1.53 \cdot 10^{9}$	

$\bar{n}_3 = 7.1864 \cdot 10^{8}$, $\bar{n}_1 = 6.3168 \cdot 10^{9}$

- The transition from stability to instability is obtained when n_{10} is very close to the threshold $\bar{n}_1$: instability starts from about the 98% of $\bar{n}_1$.

- Although $\bar{r} \ll \rho$, the initial condition $n_{10} < \bar{n}_1$ produces "nearly always" a stable trajectory.

Model dynamics under feedback control laws

- A constant therapy administration has the advantage that it is only dependent on the system parameters, without requiring any real-time information about the system dynamics.

- However, such a therapy has important **limitations**:

  - big tumours with initial size larger than (or equal to) n_{10}^{max} cannot be eradicated by an admissible administration ($\bar{r} < \rho$);

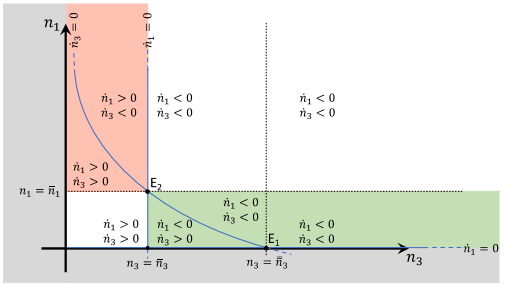
  - there is actually no guarantee that tumours with $n_{10} < n_{10}^{max}$ can be eradicated.

- These limitations come from the necessity of making a **permanent choice** at the beginning of the therapy, exploiting at most an evaluation of the initial tumour size.

- A feedback control is always able to overcome such limitations, allowing to eradicate the tumour even when only partial information about the system dynamics are available.

Model dynamics under feedback control laws

- The main problem of the trajectories related to the constant therapy starting from or entering the red region is that the condition $n_3 > \bar{n}_3$ (characterized by $\dot{n}_1 < 0$) cannot be reached as the increasing tumour mass sooner or later will change the sign of $\dot{n}_3$ (before reaching the condition $n_3 > \bar{n}_3$).



- Conversely, when the administration rate is changed over time based on the state estimation, we can always guarantee an increase of the drug level, independently of the tumour size.

- Based on the conservative estimations $\hat{n}_1(t) \geq n_1(t)$, $\hat{n}_3(t) \geq n_3(t)$, we can build conservative lower bounds for the formulation of a time-varying administration rate *r(t)* guaranteeing drug accumulation.

- For instance, if a complete estimate (tumour and drug level) is available, we define the lower bound as

$$r_{LB}(t) := \rho \frac{\hat{n}_3(t)}{M_4 + \hat{n}_3(t)} + k_5 \hat{n}_1(t) \frac{\hat{n}_3(t)}{M_5 + \hat{n}_3(t)}$$

- Otherwise, if no information on the drug accumulation is available, we can define a higher lower bound for *r(t)* as

$$r_{LB}(t) := \rho + k_5 \hat{n}_1(t)$$

- In both cases, it is $r(t) > r_{LB}(t) \implies \dot{n}_3(t) > 0$, so ensuring drug accumulation for any tumour size: sooner or later the condition $n_3 > \bar{n}_3$, and then $\dot{n}_1 < 0$ (tumour shrinking), will be reached.

Model dynamics under feedback control laws

- In particular, the condition $n_3 > \bar{n}_3$ ($\dot{n}_1 < 0$) can be reached in a finite time assuming the law

$$r(t) = r_{LB}(t) + \frac{\bar{n}_3}{\bar{t}_1}$$

that allows the desired condition for any chosen time $\bar{t}_1$.

- Note that the value of ρ is no more a limitation for the size of the time-varying administration rate. In fact, since the feedback control can be applied for finite time intervals, $r(t)$ can temporarily exceed the value of ρ without risking an unlimited accumulation of drug.

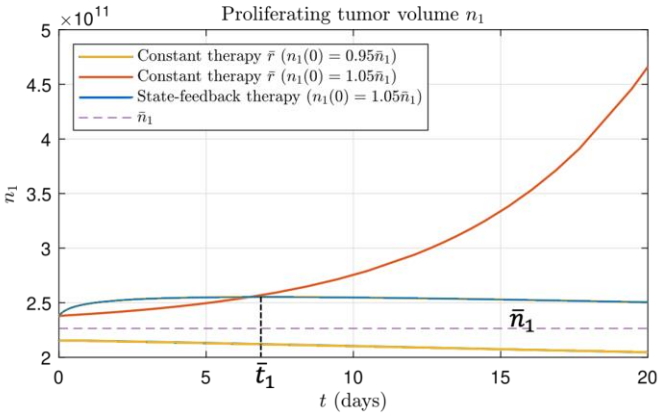
- As it is not recommended a consistent drug accumulation over the threshold $\bar{n}_3$, after the time $\bar{t}_1$ the control action should switch to a lower (possibly constant) administration rate as soon as favourable conditions regarding tumour eradication are reached.

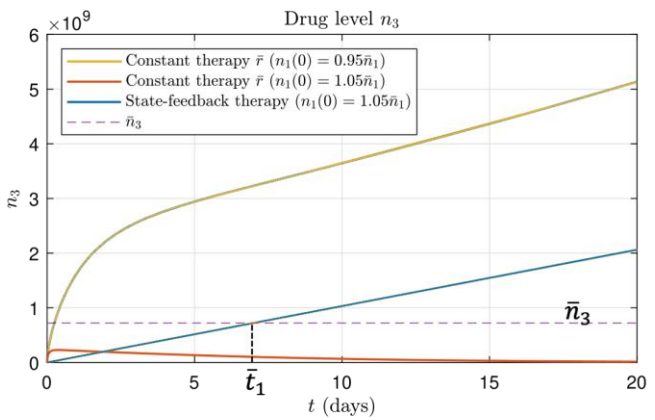
- For instance, we can choose a tolerable constant administration rate $\bar{r}$ (i.e., a specific value in the admissibility range $(\beta\rho, \rho)$), compute the related threshold on the tumour size $\bar{n}_1 = \frac{\bar{r}-\beta\rho}{k_1-k_2}$, and then switch to the constant administration rate $r(t) = \bar{r}$ for $t \geq \bar{t}_2$, where $\bar{t}_2$ is the time at which the tumour shrinking has reached the condition $n_1(\bar{t}_2) = \bar{n}_1$.

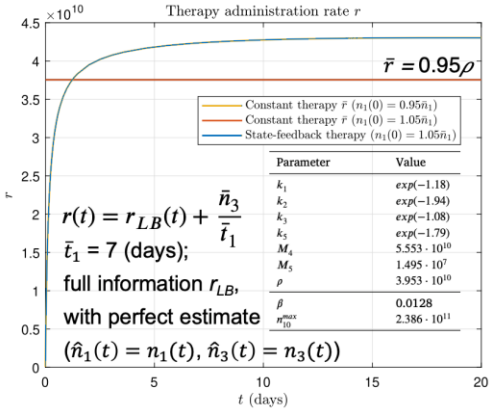
- The conditions $n_1(t) \leq \bar{n}_1$ and $n_3(t) > \bar{n}_3$, obtained for $t \geq \bar{t}_2$, ensure that the trajectory has reached the green zone and then it is approaching E_1.

Numerical simulations

Constant vs. feedback therapy with full information

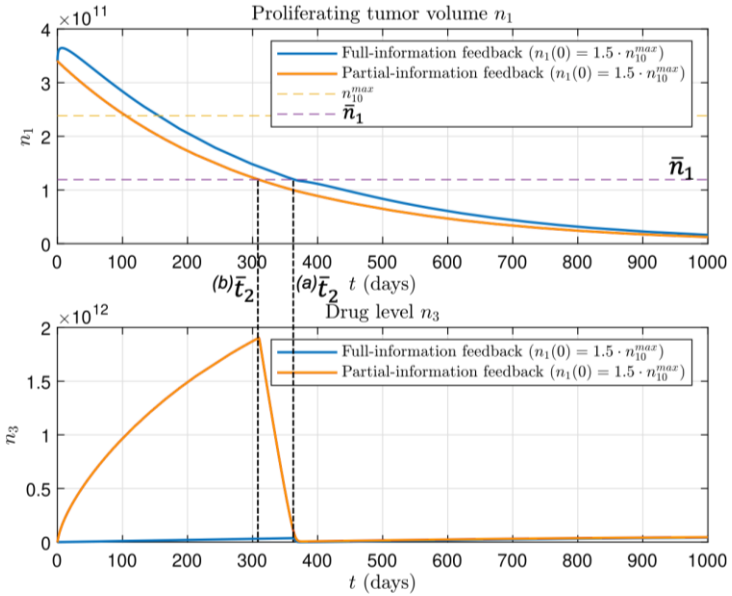


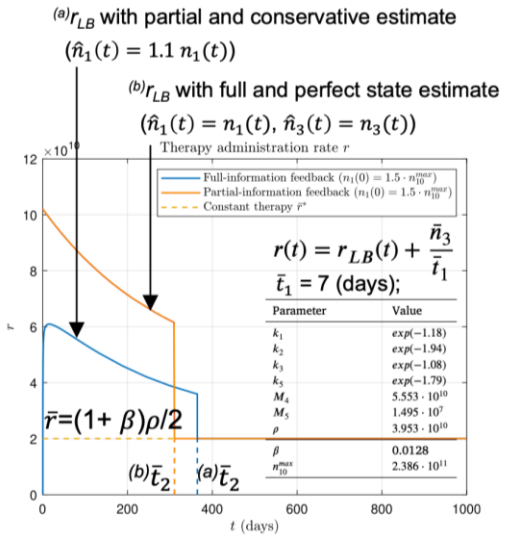




- $n_1(0)$=*1.05*$\bar{n}_1$*: the constant therapy is not able to stop tumour growth while state feedback slowly reduces the tumour growth, after a time interval of $\bar{t}_1 = 7$ days.

Full vs. partial information feedback therapy

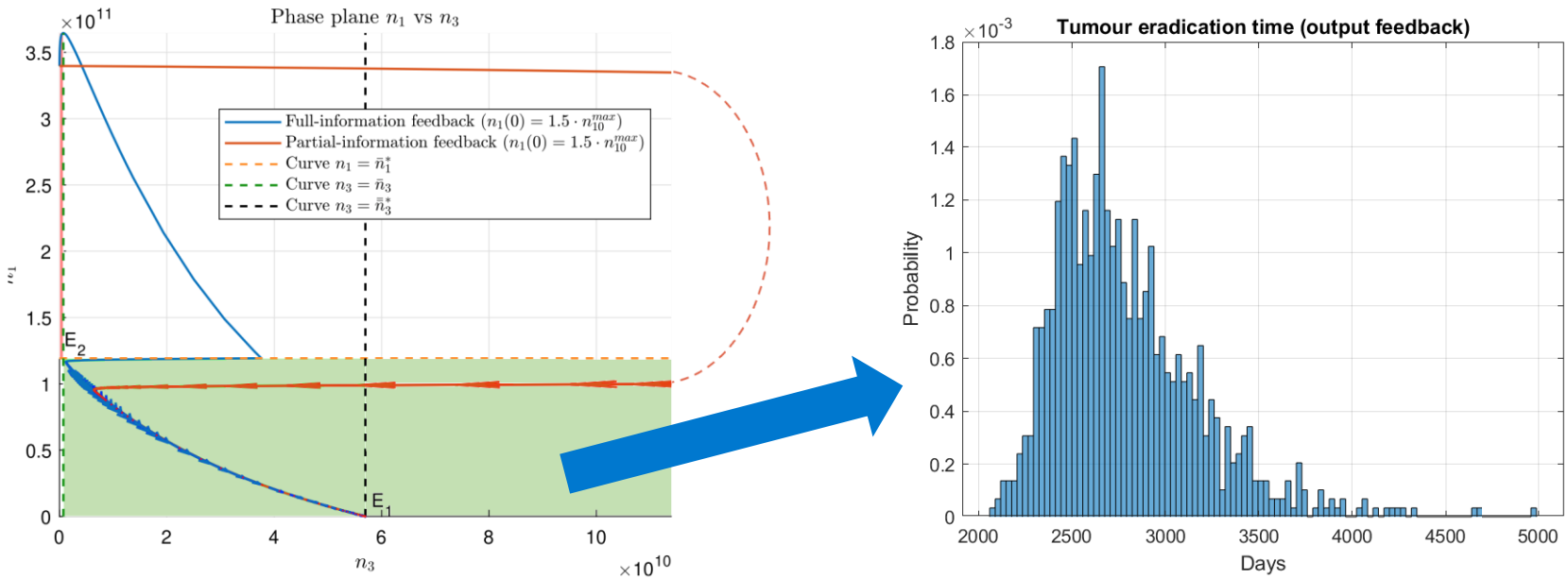




- Due to the tumour size overestimation and the more conservative lower bound, the partial information feedback produces a higher accumulation of drug in the transient than the full state feedback and forces a faster tumour decrease.
- The partial/imperfect information feedback switches to constant therapy before the full/perfect state case ($\bar{t}_2$ = 326 Vs $\bar{t}_2$ = 380 days)

Numerical simulations

Switch to the stochastic formulation



- The time evolution of the ODE system can reach E_1 waiting an **infinite** time interval.

- To evaluate finite (mean) eradication times (for the given parameter setting, i.e., a specific tumour and a particular drug, with a given administration rate) it is necessary to switch to the stochastic formulation.

- The reported histogram depicts the eradication time statistics for breast cancer in mice treated by Pegylated Liposomal Doxorubicin drug obtained over 1000 random paths.

Conclusions

- We address the problem of tumour growth control exploiting a minimally parameterized and low-dimensional model of tumour growth under treatment.
- The system has been described by means of the CRN formalism, providing a double mathematical description, deterministic-vs-stochastic, of the system.
- The deterministic model is a valid tool to describe the system when the number of tumour cell is high, and it allows to plan deterministic control laws to stop tumour growth and to reduce the mass size.
- Two alternative deterministic control approaches are investigated, a constant infusion and a feedback control scheme, exploiting both partial and complete knowledge of the state.
- The constant therapy has several limitations, as the treatment failure caused by too large tumours, while the proposed feedback control is very promising since it allows to eradicate arbitrarily large tumours.
- The deterministic modelling framework suffers from an intrinsic limitation since tumours can be eradicated only asymptotically (i.e., over an infinite time horizon); the stochastic formulation provides a more accurate description of the system dynamics, allowing a statistical evaluation of the eradication time.
- Modelling further physiological mechanisms of the tumour growth and treatment, as well as the planning of a stochastic control law, are future developments of the study.

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