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Optimal dosing of cancer chemotherapy using model predictive control and moving horizon state/parameter estimation

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ABSTRACT

Model predictive control (MPC), originally developed in the community of industrial process control, is a potentially effective approach to optimal scheduling of cancer therapy. The basis of MPC is usually a state-space model (a system of ordinary differential equations), whereby existing studies usually assume that the entire states can be directly measured. This paper aims to demonstrate that when the system states are not fully measurable, in conjunction with model parameter discrepancy, MPC is still a useful method for cancer treatment. This aim is achieved through the application of moving horizon estimation (MHE), an optimisation-based method to jointly estimate the system states and parameters. The effectiveness of the MPC-MHE scheme is illustrated through scheduling the dose of tamoxifen for simulated tumour-bearing patients, and the impact of estimation horizon and magnitude of parameter discrepancy is also investigated.

1. Introduction

Cancer has caused the second largest number of deaths (after heart disease) around the developed World. World Health Organization estimated that 7.9 million people died of cancer in 2007. In England, approximately 410,500 people were diagnosed with cancer in 2008 alone [1]. The increasing threat of cancer to human life has promoted rapid advances of treatment technologies, including surgery, radiotherapy, chemotherapy, immunotherapy and their combinations. These therapies need to be properly scheduled to ensure effective treatment, i.e. the provision of the right therapy of the right dose at the right time. The current clinical practice for scheduling is to follow some established standards with respect to the choice of therapy/dose/time, usually adjusted according to the phase of tumour, patient's bodyweight, white blood cell level, among other factors. The limitation of this largely empirical approach has increasingly been recognised in the scientific and clinical communities, a situation that motivates the study of mathematical model-based solutions to optimal therapy scheduling.

In the past decades, various mathematical models for tumour growth kinetics, human immune system, pharmacokinetics and patient's response to therapies (pharmacodynamics) have been successfully validated against clinical observations, providing the foundation of model-based optimisation of cancer treatment. Model-based optimisation or optimal control has been demonstrated to be attractive in various studies [2–8]. Among existing investigations, significant

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emphasis has been to formulate biologically relevant objective functions to improve treatment efficacy [9], sometimes leading to multi-objective optimisation problems [10]. Preliminary clinical application of the model-based optimisation approach was also reported [11]. However, current research is largely limited to open-loop optimisation whereby the therapy schedule is devised solely according to the patient's condition at the beginning of treatment. Clearly, this "feed-forward" approach does not attempt to compensate for the unavoidable mismatch between a generic model and a specific patient, the mismatch being the result of model imperfection, parameter uncertainty, inter-patient variability, and time-varying state of patient. Furthermore, the feed-forward method does not revise the schedule according to the patient's clinical response during the treatment.

More recently, a few studies examined the issue with open-loop therapy scheduling by utilising feed-back control methodology, predominantly model predictive control (MPC) that originated from the community of industrial process control [12,13]. Given a state-space model, MPC is formulated as the repeated solution of an open-loop optimal control problem within a finite time horizon into the future. Yet unlike optimal control, MPC only applies the optimised manipulated variable (the dosing schedule in the context of cancer treatment) until the next state measurement becomes available. Then, the optimal control problem will be solved again whereby the model prediction is calculated by using the newly measured system states. Following the concept of feed-back control, Florian Jr. et al. [14] applied MPC to schedule chemotherapy for a simulated cycle-specific tumour growth model. Kiran and Lakshminarayanan [15] used global sensitivity analysis to identify sensitive parameters, and studied the effectiveness of closed-loop control in the presence of parametric uncertainty. Adaptive parameter estimation along with MPC was suggested in [16]. In contrast, Chareyron and Alamir [9] argued that adaptive compensation of the bias between the model and patient might be more favourable than direct update of the parameters. In addition, when developing a reliable mechanistic model becomes difficult, a purely data-based empirical model may instead be used for MPC [17].

The afore-reviewed MPC studies did not explicitly consider the situation where system states are not directly measurable and have to be estimated from measurements. However, measurement of complete states is usually impractical. Whilst tumour cell population and drug concentration may be clinically monitored, measuring the populations of natural killer and $CD8^+$ T cells (required in [9]) or cycle-specific cells (required in [14]) may be unrealistic under the present clinical practice.

This paper aims to demonstrate that MPC is an effective approach for scheduling cancer therapy even if system states are not fully measured and need to be estimated from available measurements. In fact, states and parameters should be jointly estimated to fully account for the model–patient mismatch. This is especially important for model-based therapy scheduling, since individual patients may have very different characteristics in tumour growth and pharmacodynamics, leading to the actual parameters significantly deviating from those of the nominal model. Such level of model–patient mismatch is not commonly seen in industrial control applications. In addition, these parameters may not be estimated off-line by subjecting the patients to various experiments. Joint state/parameter estimation for dynamic systems is an active research topic and a variety of methods have been proposed in the literature. These methods may be categorised into three classes: statistical filters, adaptive observers, and optimisation based algorithms. Probably the most well-known filtering technique is the (extended) Kalman filter and recent extensions like unscented Kalman filter [18,19] and particle filter [20–22]. The major advantage of adaptive filters/observers is the computational efficiency, since they only consider the most recent sampling (measurement) time (the first-order Markovian property). Whilst computation is a crucial factor when using MPC for rapid changing industrial processes, it may not be a major issue for cancer treatment since the sampling interval is in the scale of days. Therefore, the computationally more intensive method, the so-called moving horizon estimation (MHE) [23,22] that formulates the state/parameter estimation into an optimisation problem, is adopted in this study. The effectiveness of the MPC-MHE method is illustrated through the scheduling of chemotherapy for a simulated tumour model taken from [14].

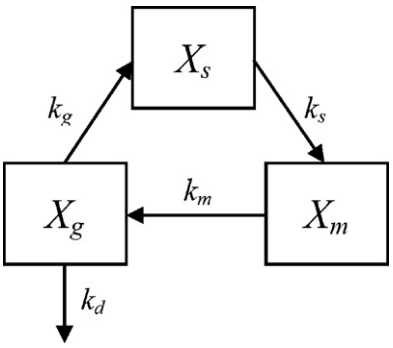

Fig. 1 – Schematic of the tumour growth model in Eqs. (1)–(3).

The rest of this paper is organised as follows. Section 2 provides an overview of the coupled tumour growth, phamarcokinetic and pharmacodynamic model. Section 3.1 presents the methodology of MPC and highlights the need for joint state/parameter estimation, which is to be accomplished by using MHE. The results of applying MPC for optimising cancer chemotherapy are discussed in Section 4. Finally, Section 5 concludes this paper.

2. The mathematical model

The interaction between tumour growth, drug absorption and the effect of drug can be described by coupled models for growth kinetics, pharmacokinetics and pharmacodynamics. In this paper, a spatially-uniform tumour model in [14] is utilised to demonstrate the importance of on-line state/parameter estimation for MPC. This model assumes a homogeneous distribution of cycle-specific cells within a tumour, as illustrated in Fig. 1. Cell-cycle models are relevant to describing the effect of cycle-specific anticancer compounds such as doxorubicin, paclitaxel and tamoxifen

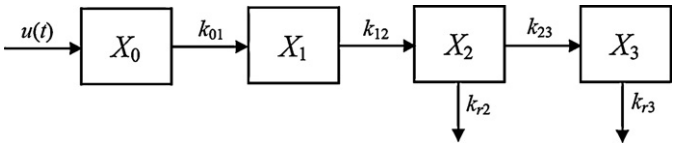

Fig. 2 – Schematic of the pharmacokinetic model in Eqs. (4)–(7).

(TM). In particular, the tumour growth is described by the following ordinary differential equations (ODEs):

$$\frac{dX_g}{dt} = -k_g X_g \ln(\theta/N) + 2k_m X_m \ln(\theta/N) - k_d X_g (X_2/V + cX_3/V) \quad (1)$$

$$\frac{dX_s}{dt} = -k_s X_s + k_g X_g \ln(\theta/N) \quad (2)$$

$$\frac{dX_m}{dt} = -k_m X_m \ln(\theta/N) + k_s X_s \quad (3)$$

where X_g, X_s and X_m are the volume of tumour cells in the growing, DNA synthesis and mitosis phases, respectively; $N = X_g + X_s + X_m$ is the total tumour volume. It was assumed that each cell has a constant volume and 1 mm^3 is equivalent to 10^6 cells. The model parameters include the transfer rates between cell phases (k_g, k_s and k_m), and the plateau population of the tumour (θ) to account for the saturation of tumour growth. The last term in Eq. (1) represents the drug-induced tumour death with a rate constant k_d, whereby X_2/V and X_3/V are the concentration of TM and its active metabolite 4-hydroxytamoxifen (HTM), respectively. The parameter c is to account for the different binding affinity of TM and HTM [24].

The pharmacokinetics is expressed by a four-compartment oral dosing model:

$$\frac{dX_0}{dt} = -k_{01} X_0 + u(t) \quad (4)$$

$$\frac{dX_1}{dt} = -k_{12} X_1 + k_{01} X_0 \quad (5)$$

$$\frac{dX_2}{dt} = -k_{r2} X_2 - k_{23} X_2 + k_{12} X_1 \quad (6)$$

$$\frac{dX_3}{dt} = -k_{r3} X_3 + k_{23} X_2 \quad (7)$$

where X_0 and X_1 are the TM mass (μg) in the two initial compartments; X_2 and X_3 are the TM and HTM mass in the central compartment. The dose of TM, $u(t)$, is the manipulated variable to be determined by MPC. This pharmacokinetic model is illustrated in Fig. 2.

The adverse impact of chemotherapy can be quantified by the circulating lymphocyte (CL) level, which is a common measure of patient health [25]. A more detailed model would describe the involvement of lymphocyte in antibody production, which further affects tumour killing rate. In the present study, such immunological effects are not considered, assuming that the dominant source for tumour killing is the drug.

Table 1 – A summary of system states and the initial value.

State	Description	Initial value
X_g (mm^3)	Volume of tumour cells at the growing phase	900
X_s (mm^3)	Volume of tumour cells at the DNA synthesis phase	50
X_m (mm^3)	Volume of tumour cells at the mitosis phase	50
X_0 (μg)	TM mass at the 0th compartment	0
X_1 (μg)	TM mass at the 1st compartment	0
X_2 (μg)	TM mass at the 2nd compartment	0
X_3 (μg)	HTM mass at the 3rd compartment	0
C	Number of circulating lymphocytes	10^7

The equation for the number of CLs is modified from [25] and given below:

$$\frac{dC}{dt} = \alpha - \beta C - k_c C(X_2/V + bX_3/V) \quad (8)$$

where α is the constant generation rate of CLs, and β corresponds to the natural lifespan of a CL. The presence of drug kills CLs at a rate of k_c, and the different killing effect of TM and HTM is represented by an additional parameter b, similar to the use of binding affinity factor c in eq. (1).

The system states are summarised in Table 1 that also includes the necessary initial conditions for solving the ODEs. In clinical practice, not all the states are directly measurable. It may be reasonable to assume that the available measurements include the total tumour volume (N), the plasma concentration of TM and HTM in the central compartment (X_2/V and X_3/V), and the number of CLs (C). In practice, these measurements are unavoidably subject to certain noise level.

Table 2 lists the model parameters with corresponding nominal values. Those related to cell growth (k_g, k_s, k_m, θ) were determined in [14] through least squares fitting to animal (mouse) data [26]. The pharmacokinetics parameters were

Table 2 – Model parameters and the nominal ("true") values.

Parameter	Nominal value	Parameter	Nominal value
k_g (h^{-1})	0.0013	θ (mm^3)	10^4
k_s (h^{-1})	0.0390	k_d (mL μg^{-1} h^{-1})	0.0062
k_m (h^{-1})	0.0169	c	25
k_{01} (h^{-1})	0.048	α (h^{-1})	1.21×10^5
k_{12} (h^{-1})	0.993	β (h^{-1})	1.20×10^{-2}
k_{23} (h^{-1})	35.932	k_c (mL μg^{-1} h^{-1})	0.010
k_{r2} (h^{-1})	1.145	b	25
k_{r3} (h^{-1})	39.525	V (mL)	8.592

estimated from a separate set of mouse data [27]. The parameters related to CL dynamics are derived from [25]. Since the data are primarily from experiments on mice, the model may be viewed to describe a "mouse patient". The readers are referred to [14] for more details about the model development and source of data for parameter estimation.

3. Model predictive control with joint state and parameter estimation

This section provides an overview of MPC with focus on its application to general non-linear state-space models, followed by the discussion of joint state and parameter estimation when the system states are not entirely measured.

3.1. Model predictive control

MPC considers the following generic state-space model, which encompasses a broad spectrum of mathematical models for dynamic systems (including the tumour model presented in Section 2):

$$\mathbf{x}_{t+1} = \mathbf{f}(\mathbf{x}_t, \mathbf{p}, \mathbf{u}_t) + \mathbf{w}_t \tag{9}$$

$$\mathbf{y}_t = \mathbf{h}(\mathbf{x}_t, \mathbf{p}) + \mathbf{v}_t \tag{10}$$

where $\mathbf{x}$ is a state vector, $\mathbf{y}$ is a measurement vector, and t denotes time index. The state function $\mathbf{f}(\cdot)$ describes the system dynamics that depends on the state at time t, the model parameters $\mathbf{p}$, and the manipulated variables $\mathbf{u}_t$ (also termed input variables). The process noise ($\mathbf{w}_t$) is utilised to describe random mismatch between the model and the actual patient. The measurement is a function ($\mathbf{h}(\cdot)$) of states and parameters subject to noise $\mathbf{v}_t$. Note that without loss of generality the noise terms ($\mathbf{w}_t$ and $\mathbf{v}_t$) are assumed additive. If no specific information is available, both noise terms are assumed to be independent and identically distributed (i.i.d.) according to a multivariate normal distribution: $p_w(\mathbf{w}_t) = N(\mathbf{0}, \mathbf{Q})$, $p_v(\mathbf{v}_t) = N(\mathbf{0}, \mathbf{R})$, where p denotes the probability distribution function (*pdf*). The common practice is to restrict $\mathbf{Q}$ and $\mathbf{R}$ to diagonal matrices. The measurement noise covariance $\mathbf{R}$ is usually derived from the precision properties of the measurement device. The covariance matrix for process noise needs to be either tuned or estimated in order to infer the system states. A variety of methods have been reported to address this issue; see e.g. [28–30].

The basic concept of MPC is to repeatedly (at each time step) solve an open-loop optimal control problem subject to system dynamics and the constraints for states and inputs. Considering the case for cancer treatment as given in the previous section, the objective function for optimisation at the present time step t is formulated as

$$\min_{u_t,\ldots,u_{t+n-1}} \left\{ q_1 \sum_{j=1}^{n} (\hat{N}_{t+j} - S)^2 + q_2 \sum_{j=0}^{n-1} u_{t+j}^2 \right\} \tag{11}$$

where $\hat{N}_{t+j}$ is the predicted total volume of the tumour cells at time $t+j$, S is the target tumour volume, q_1 and q_2 are the weights to specify the relative importance of reducing tumour volume (termed "set-point tracking" in the control community) and using less drug. We assign predominant emphasis on reducing tumour volume in the objective function and set $q_1 = 100$ and $q_2 = 1$, since unlike [14], the preference of using less drug will be accounted for by imposing lower limit on the number of CLs. The above formulation implies that the optimisation problem is solved within a horizon of n time steps. The constraints include the state space model (Eqs. (1)–(8)), the fact that all states are non-negative, the upper limit for a single dose, and the lower limit for the number of CLs to maintain the patient's health. For the present study, the upper limit of the dose is set to 800 μg. Following [25], The target is chosen as $S = 25\,\mathrm{mm}^3$ and the lower limit for the number of CLs is set to 4×10^6, i.e. 40% of the initial CL number.

In the community of process control, the manipulated variable is usually parameterised to be piecewise constant or linear with respect to time. However in chemotherapy dosing, drug is delivered instantaneously per time step. For example, TM was given as a bolus each day by oral gavage in animal studies [14]. Therefore, the manipulated variable u is the dose of TM (μg) given to a mouse at the beginning of a time interval (each day in this study). In the terminology of control theory and signal processing, such an input signal u is termed "impulse".

In summary, a standard MPC scheme runs as follows [12]:

1. Obtain estimate of the system states at the current time.
2. Solve the constrained optimisation problem in eq. (11) over the prediction horizon using the system model and the current state estimate for prediction.
3. Implement the optimal input until the next measurement (sampling) time.
4. Continue with step 1.

In Step 3, the measurement time interval is not necessarily the same as that for the input. For example, the drug may be given to a mouse each day but the tumour volume and CL number are only measured every five days. Throughout this paper, the time step t refers to the measurement or sampling time. In this example, the manipulated variable to be optimised is actually a vector containing the drug dose at the beginning of each of the five days.

The original formulation of MPC assumes that the full system states at current time are available through direct measurement for the prediction of future states, which is the basis for the calculation of the objective function. However, this condition is rarely met in practice, and thus the system states need to be estimated by using e.g. moving horizon estimation as presented subsequently.

3.2. Moving horizon estimation

The estimation of system states (and/or parameters) in a dynamic system is usually cast into an optimal filtering problem, whereby the well-known Kalman filter is an optimal solution if the state function is linear and the states are normally distributed [31]. When these assumptions are not valid, approximate methods need to be utilised, such as extended Kalman filters, unscented Kalman filters [18,19] and more

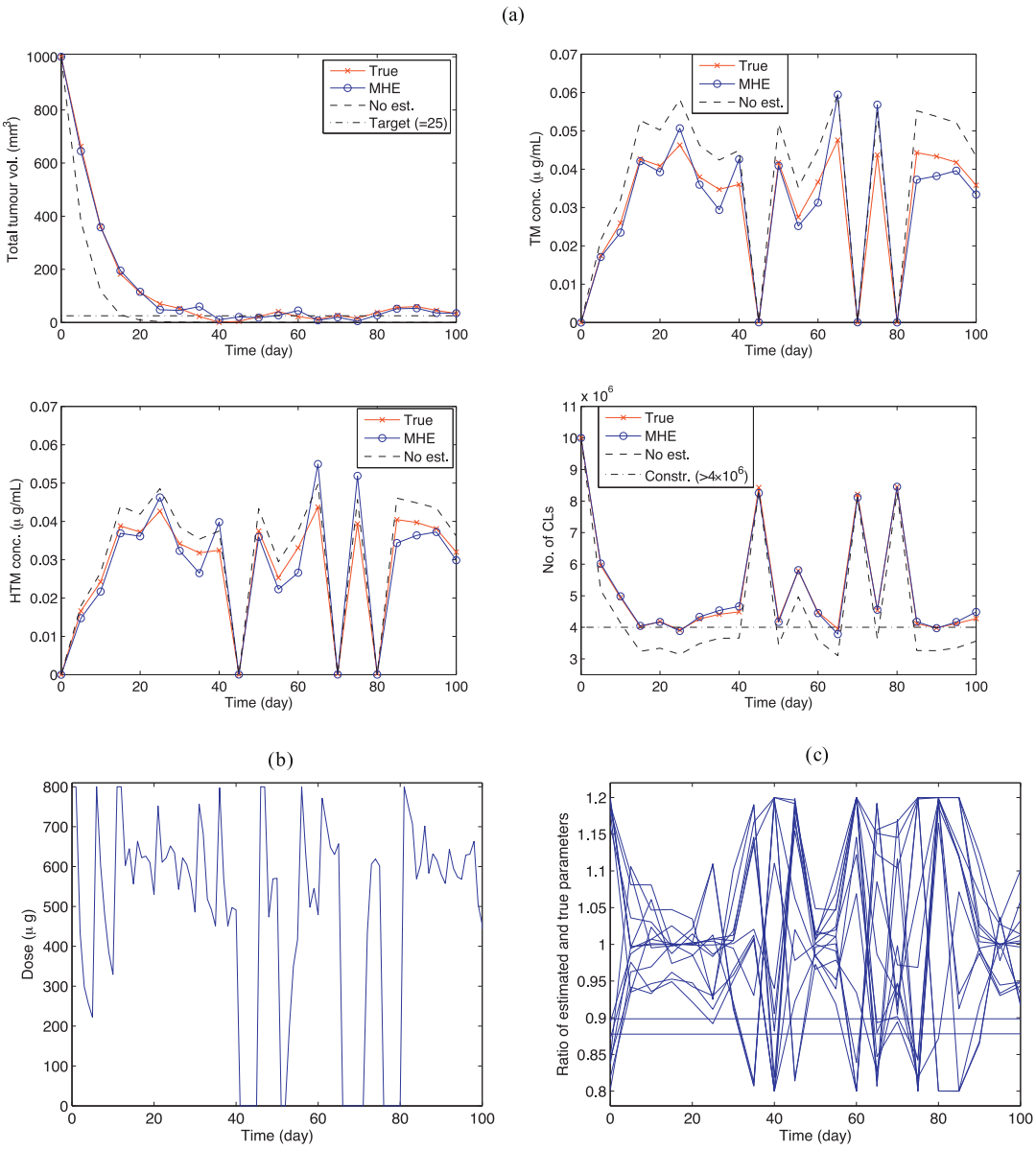

Fig. 3 – System profile for patient no. 19 with up to 20% parameter discrepancy: (a) state estimates through joint state and parameter estimation ($h = 2$ or ten days); (b) the profile of drug dose designed by MPC; (c) the ratio of estimated and true parameters.

recently particle filters [20–22]. These filters are sequential in the sense that they only infer the system states at the current time step by utilising the current measurement only. The past information is implicitly included via the use of *prior* distribution for the states. As such, these filters are efficient in terms of computation, which may be a necessity for industrial process control. However, these afore-mentioned filters are not directly applicable to constrained state estimation problems (e.g. states must be non-negative).

In contrast, MHE [23,22] formulates the state/parameter estimation problem over a finite time horizon, making use of the information from multiple time steps in the past. The state constraints can be easily incorporated in MHE by devising a constrained optimisation problem. Specifically, at time step t, MHE attempts to solve the following problem over a time horizon of h steps (from $t-h+1$ to t):

$$\min_{\mathbf{x}_{t-h+1},\ldots,\mathbf{x}_t,\mathbf{p}} \left\{ V(\mathbf{x}_{t-h+1}) + \sum_{j=t-h+1}^{t-1} L_w(\mathbf{w}_j) + \sum_{j=t-h+1}^{t} L_v(\mathbf{y}_j - \mathbf{h}(\mathbf{x}_j, \mathbf{p})) \right\} \tag{12}$$

subject to $\mathbf{x}_{j+1} = \mathbf{f}\left(\mathbf{x}_j, \mathbf{p}, \mathbf{u}_j\right) + \mathbf{w}_j$ in addition to other constraints (if any) on the states and parameters. In the above formula, the first term summarises the information about $\mathbf{x}_{t-h+1}$ obtained from the past up to time $t-h$. Rigorously,

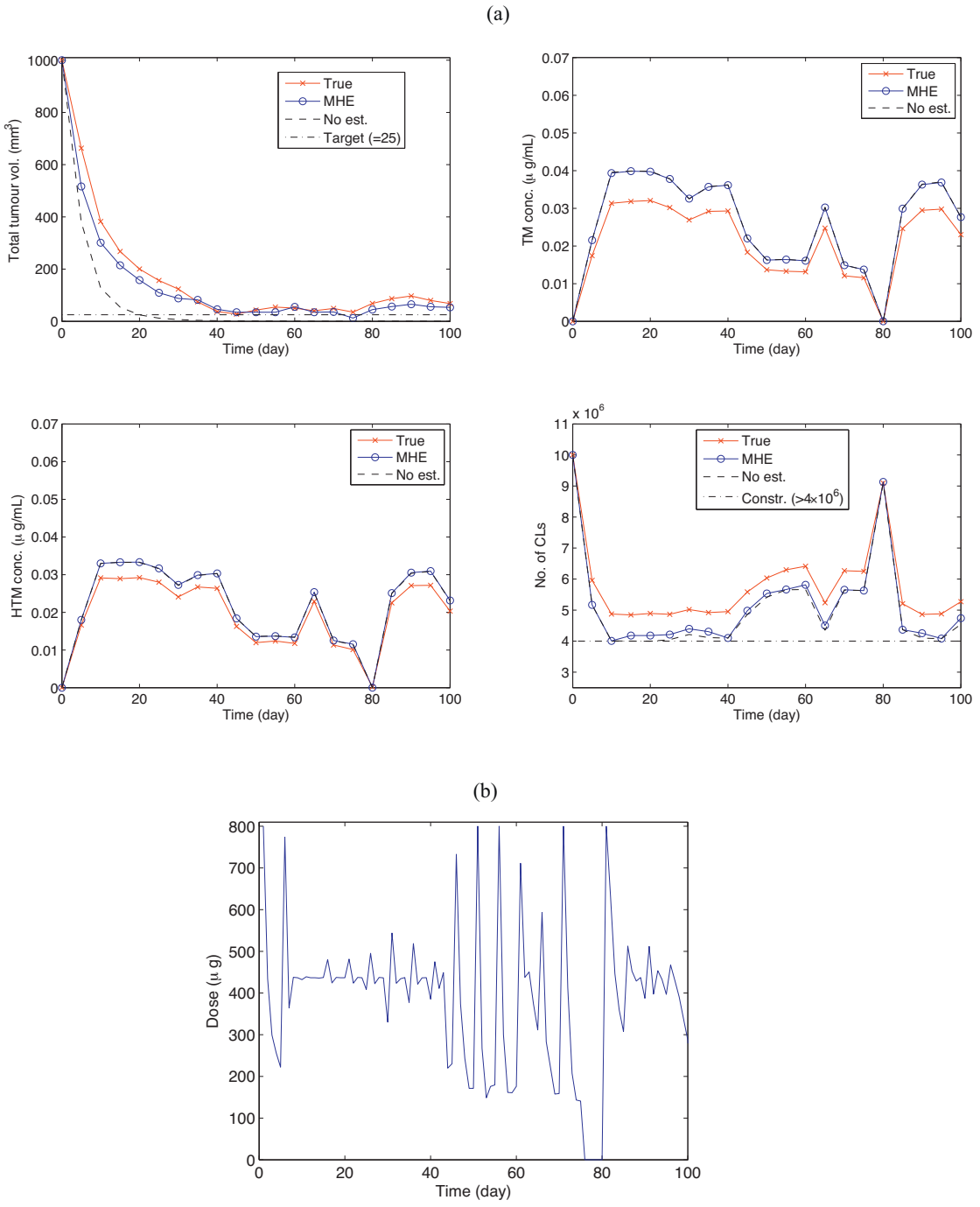

Fig. 4 – System profile for patient no. 19 with up to 20% parameter discrepancy: (a) state estimates without parameter estimation ($h = 2$ or ten days); except for tumour volume, the MHE estimates almost overlap with the prediction from the nominal model ("No est."). (b) the profile of drug dose designed by MPC.

$V(\mathbf{x}_{t-h+1})$ is the negative probability of $\mathbf{x}_{t-h+1}$ conditional on the measurement sequence $\{\mathbf{y}_1, \ldots, \mathbf{y}_{t-h}\}$. In the terminology of MHE, $V(\cdot)$ is called "arrival cost" and may be approximated by using an extended Kalman filter [23,22]. L_w and L_v are the negative log-likelihood functions, respectively: $L_w(\mathbf{w}) = -\log p_w(\mathbf{w})$, $L_v(\mathbf{v}) = -\log p_v(\mathbf{v})$, where p_w and p_v are the *pdf* for process and measurement noises discussed previously. Note that apart from the current states and parameters, MHE also obtains a sequence of "smoothed" past states from time $t-h+1$ to $t-1$. These smoothed past states, although not used for the purpose of predictive control, may be important information for post-analysis of the dynamic systems. In addition, the original MHE method only updates the states, not the parameters (i.e. removing $\mathbf{p}$ from the above optimisation problem). In the next section, the option of state estimation only will be empirically compared through case study with joint state/parameter estimation in terms of state accuracy and drug scheduling performance.

Table 3 – State estimation error in terms of RMSE. The results are averaged over 20 random repeats of simulation with up to 20% parameter discrepancy.

Method	Tumour vol.	TM conc.	HTM conc.	CL no. ($\times 10^5$)
State+Para.				
$h=1$	21.02	0.0099	0.0073	4.44
$h=2$	16.38	0.0081	0.0072	0.98
$h=4$	14.98	0.0073	0.0078	1.25
State only				
$h=1$	27.81	0.0388	0.0280	5.98
$h=2$	21.69	0.0382	0.0276	5.88
$h=4$	24.25	0.0389	0.0286	6.87

The solution to the optimisation problem in eq. (12) provides the estimate of current system states, which are required in Step 1 of the MPC scheme discussed in Section 3.1. The performance of MHE depends on the choice of the time horizon, h. In theory, longer time horizon carries more measurements and thus should give more accurate estimation. However, the dimension of the optimisation problem is $(h \times d_x + d_p)$ where d_x and d_p are the dimensions of the states and parameters, respectively. High dimensional optimisation tends to suffer from the issue of local optima, and thus in practice it may not always give better results than using a small h. This issue will be discussed together with the results subsequently.

4. Results and discussions

In this section, the proposed MHE method is demonstrated through scheduling the delivery of TM to simulated tumour-bearing mice (referred to as "patient" hereafter). The patients are simulated by solving the ODEs as given in Section 2. The total simulation duration is fixed to 100 days, and the objective is to reduce the tumour volume to 25 mm^3 as rapidly as possible whilst satisfying the constraints on maximally allowable drug dose and the number of CLs. Each patient is simulated by subjecting the nominal model parameters in Table 2 to a certain deviation, creating model–patient mismatch. The MHE algorithm will then try to infer the correct system states and parameters from the measured total tumour volume, TM and HTM concentration, and the number of CLs. The measurements are corrupted by zero mean noise with diagonal covariance matrix $\mathbf{R} = \text{diag}[20\,;0.001\,;0.001\,;10^5]^2$, reflecting clinically realistic measurement error. The covariance matrix for the system noise is chosen as $\mathbf{Q} = \text{diag}[10\,;10\,;10\,;0.002\,;0.002\,;0.002\,;0.002\,;5\times10^4]^2$; this introduces approximately 1% random mismatch between the model and patients at each time step, on top of the mismatch due to parameter discrepancy. The sampling (measurement) interval is chosen as five days, whilst the drug is delivered each day. Hence the input signal is a vector containing five doses within each sampling interval. The control horizon, n in Eq. (11), is fixed to two sampling intervals (10 days). Therefore, the MPC aims to solve an optimisation problem of 10 dimensions at each sampling time step. All computation is carried out within the Matlab (R2011) environment whereby the optimisation problems are solved using the function `fmincon` from the Matlab Optimisation Toolbox. Computation time quoted is based on a desktop computer running Windows 7 system with an Intel Core Duo 3.00 GHz processor.

The first task is to study the effectiveness of MHE for state estimation, based on which MPC is used for scheduling the TM drug dose. To obtain reliable results, a set of 20 patients are simulated by randomly perturbing the nominal model parameters with up to 20% discrepancy. The state estimation accuracy is quantified by root mean squared error (RMSE). Two methods are compared: joint state/parameter estimation and state estimation only. The RMSE averaged over the 20 patients are summarised in Table 3. To better visualise the results, Figs. 3 and 4 show the profile of one representative patient where the two methods are both capable of effective reduction of the tumour volume whilst observing the constraint on the CL number. Note that due to the introduced randomness of the system, which is to emulate the un-modelled stochastic variation of the patient, a successful cure is not strictly defined as tumour volume below 25 mm^3 and CL number

Table 4 – State estimation error (RMSE) as a function of parameter discrepancy ($h=2$ in MHE).

Methods	Tumour vol.	TM conc.	HTM conc.	CL no. ($\times 10^5$)	No. of failures
20%					
State+Para.	16.38	0.0081	0.0072	0.98	0
State only	21.69	0.0382	0.0276	5.88	2
30%					
State+Para.	16.81	0.0081	0.0082	0.98	0
State only	32.06	0.0655	0.0359	12.3	8
40%					
State+Para.	17.11	0.0081	0.0082	0.99	0
State only	49.06	0.0948	0.0394	19.6	9
50%					
State+Para.	17.36	0.0086	0.0087	1.09	1
State only	98.68	0.1368	0.0467	30.5	11

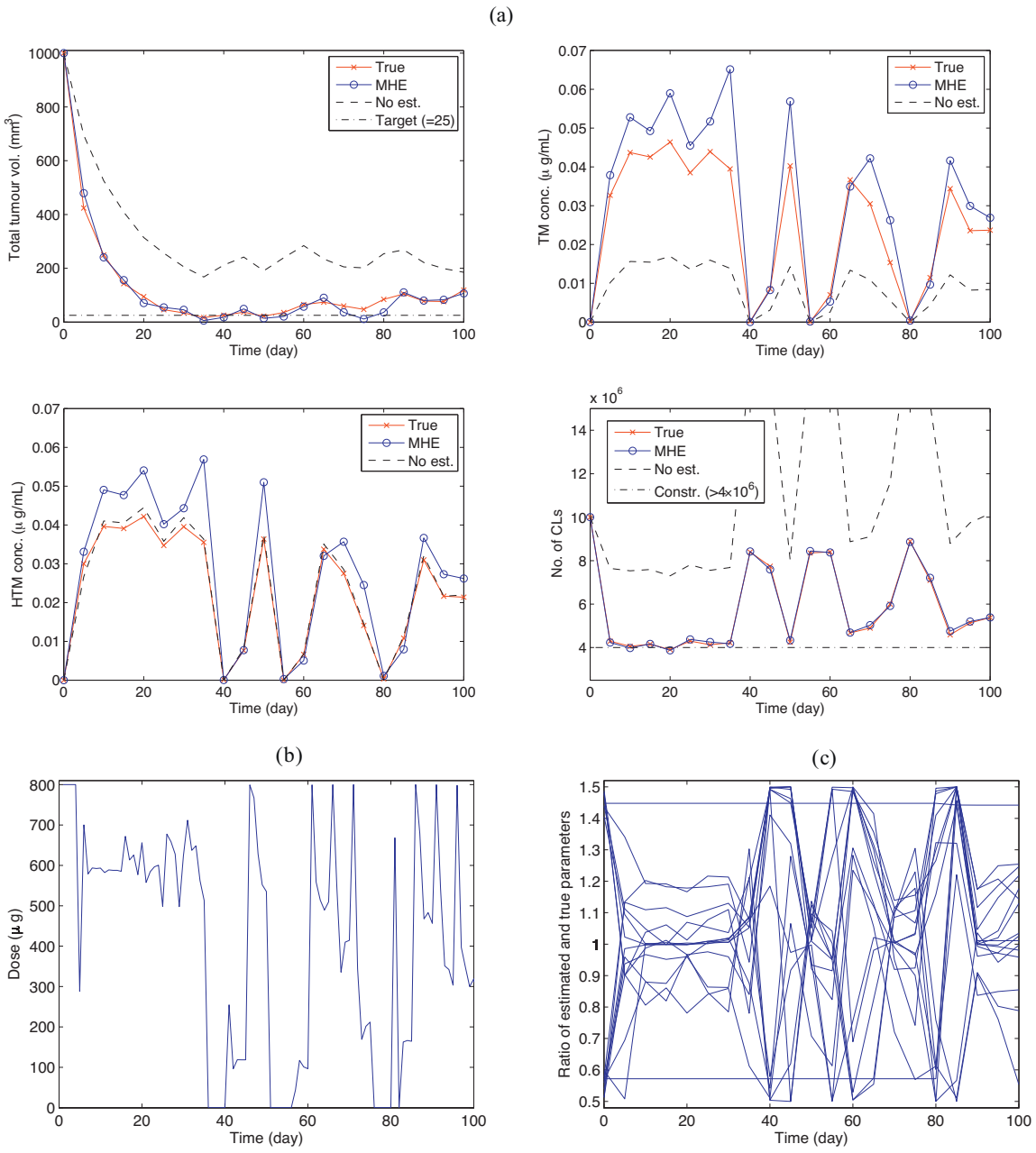

Fig. 5 – System profile for patient no. 9 with up to 50% parameter discrepancy: (a) state estimates through joint state and parameter estimation ($h = 2$ or ten days); (b) the profile of drug dose designed by MPC; (c) the ratio of estimated and true parameters.

above 4×10^6. Rather, the therapy is deemed unsuccessful only if above objectives are consistently unmet, which require certain subjective judgement.

Because of the parameter discrepancy, the states predicted by the model without any estimation effort ("No est." in the two figures) are significantly different from those of the patients. Note that the "no estimation" profiles in the two figures are not identical, because the scheduled drug doses, based MPC-MHE, are different. In Fig. 3(a), the model without adaptation dramatically over-predicts the effect of drug on killing tumour cells. If the chemotherapy were scheduled based on this nominal model, the dose would be insufficient to effectively reduce the tumour volume. Joint state/parameter estimation is effective to compensate for the model–patient mismatch. Similar observation can be derived from Fig. 4, which, however, also indicates the partial success of state estimation without considering parameters. Except for tumour volume, the profiles obtained from MHE almost overlap with those without estimation. The drug scheduled with joint estimation is more aggressive and kills the tumour cells more rapidly: the designed dose, in particular within the first 40 days, is higher than that with state estimation only (see part (b) of the two figures). The joint estimation scheme infers the number of CLs more accurately, a fact that allows MPC

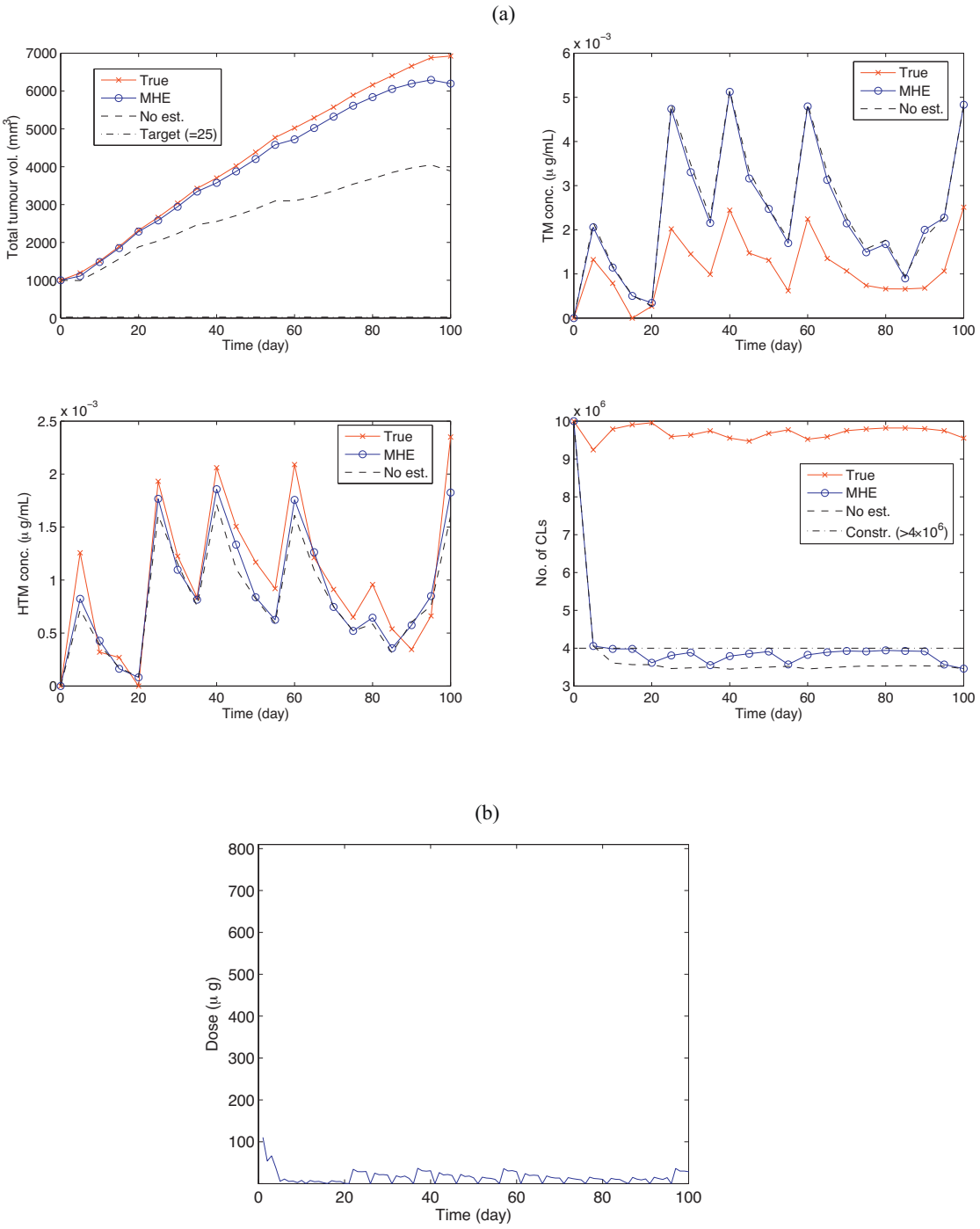

Fig. 6 – System profile for patient no. 18 with up to 50% parameter discrepancy: (a) state estimates without parameter estimation ($h = 2$ or ten days); (b) the profile of drug dose designed by MPC.

to use a proper dose whilst observing the constraints on the patient's health. In contrast, state-only method significantly under-estimates the number of CLs, and thus it can only tolerate a lower dose.

The estimated parameters, given in Fig. 3(c), are not perfectly aligned with the true parameters. This is not surprising given the fact that a total of 16 parameters need to be estimated. The sensitivity of the measurements with respect to some parameters may be too low to allow any update of these parameters (e.g. the two straight horizontal lines in Fig. 3(c)). In addition, the high-dimensional optimisation problem may have many local optima, each of which may give similar values of the objective function. What is important is to allow the parameters to vary so that the model can better adapt to the measurement. In the literature, similar results have been reported whereby excellent state estimation can be achieved with relatively lower quality in parameter estimation [20,32].

Table 3 confirms the overall better performance when considering the states and parameters simultaneously in MHE. This table also shows the trend of RMSE with regard to the time horizon for estimation. In theory, a longer horizon contains more measurements and should result in higher accuracy, and this is the case when h is increased from one to two. However, in this specific example, when further increasing the horizon to four time steps, the RMSEs do not consistently decrease for joint state/parameter estimation, and actually deteriorate for state estimation only. Notice that $h=4$ corresponds to a non-linear constrained optimisation problem with $4\times 8+16=48$ dimensions for joint estimation (32 dimensions for state estimation only). Such problems tend to have many local optima and may require more advanced optimisation algorithms than those available in the Matlab built-in function `fmincon`. In addition, the computation time for MPC+MHE with $h=4$ already takes around 18 h on average for each patient with joint estimation (around 10 h for state estimation only), whilst the corresponding computation time with $h=2$ is two hours (one hour for state estimation only). Therefore, $h=2$ is adopted for the subsequent study in this paper.

Next, the impact of the magnitude of parameter discrepancy is investigated, and the results are summarised in Table 4. Estimating state only is very sensitive to the increase in parameter discrepancy, since no mechanism is available to explicitly account for this mismatch. The large estimation error, reflected by RMSE, leads to more patients with failed treatment. In contrast, the joint estimation scheme is more robust to the model–patient mismatch: the RMSEs increases slowly with the increase of parameter discrepancy and only one patient is not successfully treated when the parameters are subject to 50% deviation. The profile of this patient, given in Fig. 5, shows a satisfactory profile of tumour reduction until around 80 days, where tumour regression occurs. This may be explained by the over-estimate of drug concentration (see TM and HTM profiles in the figure), which would predict that less-than-optimal drug should be delivered, reducing the tumour killing efficacy. The state only method fails in this patient in a similar manner (profile not shown for the sake of conciseness).

Finally, Fig. 6 illustrates an extreme case where MPC completely fails because the model parameters are not updated (i.e. state estimation only). The primary reason of the failure is that the model inflates the drug's effect on killing CLs, and thus to keep CL number above the lower limit, the dose is far from sufficient. It may be argued that in clinical practice, the small drug dose and the large error between measurement and estimation would strongly indicate model–patient mismatch, and thus suggest to refine the model via parameter updating or switch to experience-based scheduling. In either case, the treatment results would be significantly more favourable than those shown in Fig. 6.

5. Conclusions

This paper investigates the application of feedback control methodology, in particular MPC, for optimal dosing of chemotherapy to aid cancer treatment. The main challenge that has been addressed is the lack of measurement of the complete system states, coupled with the unavoidable parameter uncertainty giving rise to model–patient mismatch. Moving horizon estimation, an optimisation-based approach originating from the community of process control, is utilised to jointly estimate the states and parameters. The potential of the MPC-MHE method for cancer treatment is demonstrated through scheduling the dose of chemotherapy for simulated tumour-bearing patients (mice). The results highlighted the importance of handling model–patient mismatch to enable successful model-aided cancer treatment. The promising results on simulation is a strong motivation for following this route toward ultimate clinical application, and this is being investigated.

Conflict of interest

None.

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