Proceedings of the 17th World Congress
The International Federation of Automatic Control
Seoul, Korea, July 6-11, 2008

Nonparametric Prediction of Free-light Chain Generation in Multiple Myeloma Patients

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Abstract: Multiple Myeloma is a plasma cell cancer that produces excess Free Light Chains (FLC). Patients with this condition are treated with dialysis and chemotherapy. A previous compartmental model developed by Evans et al. [2006] described the removal of FLC through a hemodialysis membrane. In this model all rate constants were considered linear and the production of FLC a constant input function. It is known that the system rate constants and inputs are non-linear in nature due to the membrane dynamics and the use of chemotherapy to retard the production FLC producing cells. This study describes the use of maximum entropy deconvolution, in conjunction with a non-linear compartmental model, to recreate the FLC production rate in a non-parametric form, without the need for assumptions that are not supported by available data. Input functions are reconstructed from four different patients with a range of dialysis durations and FLC plasma concentrations to investigate the possible effects of chemotherapy on the underlying FLC production.

Keywords: deconvolution; maximum entropy; compartmental model; Multiple Myeloma; chemotherapy; dialysis.

1. INTRODUCTION

Multiple Myeloma (MM or Myeloma) is a cancer of the plasma cells which accounts for around 1% of all cancer cases in the UK. Approximately 3,750 people are affected by the condition annually (Cancer-Research [UK]). In the majority of patients the cancer results in an over-production of monoclonal light chains. The light chains are small proteins that join with heavy-chains to form immunoglobulins. Each immunoglobulin contains light and heavy chains; in Myeloma patients there is an abundance of light chains that are not bound to immunoglobulin, and these are termed Free Light Chains (FLC). 50% of Myeloma patients have renal failure that is not necessarily related to light chains. However, 10% of all Myeloma patients develop dialysis dependency and in this setting FLC are the major cause of renal failure. As the majority of FLC are removed via the urine, the extraction of FLC occurs predominantly through the reticuloendothelial system. Failure of the renal clearance results in light chains only being removed by the reticuloendothelial system and means their serum half-life changes from a few hours to $\approx$ 3 days [Pozzi, 1987, Bradwell et al., 2005].

The traditional treatment for MM is the use of chemotherapy to reduce the FLC producing cancer cells, and in patients with acute renal failure, plasma exchange is used to remove FLC directly from the bloodstream. Recently dialysis filters with large pore size have become available and these have been used to successfully treat patients with MM, by removing dramatically higher levels of FLC during dialysis than was previously the case [Hutchison et al., 2006].

Evans et al. [2006] developed a compartmental model that describes the kinetics of FLC and the effect of using large-pore dialysis filters on patients with MM. The model contained two compartments, representing plasma and ECF (Extracellular Fluid), with linear flows between compartments and removal from the system. The FLC production rate in this linear model was considered to be constant, but non-zero, during dialysis. This model was then used in conjunction with plasma FLC concentration measurements during dialysis to estimate suitable model parameters. However, the model exhibited discrepancies between simulation results and new data when extended to multiple dialysis sessions for a single patient. From simulations it became evident that the assumption of a constant production was not appropriate. Additionally, data were made available through the simultaneous measurement of venous and arterial lines, and through the quantification of the concentration of FLCs in the dialysate fluid. The additional dialysate data made it clear that removal of FLC due to dialysis was neither constant nor linear for the dialysis session implying that a modification to the linear model was required.

The objectives of this study are to elicit the FLC production and identify an improved description of FLC removal via dialysis. It will be shown that the FLC clearance can be estimated from plasma and dialysate FLC concentration. In order to estimate production there are several methods that may be employed. According to Charter and Gull [1987] these techniques can be classified as:

- Parametric [1]
- Mass-balance
- Deconvolution.

The parametric approaches rely upon a functional form to describe the input and therefore an appropriate form for the production to be known *a priori*. Mass-balance techniques require markers and cumulative measurements, in conjunction with numerical differentiation, to be used to infer the functional form of the input. Thus, in addition to performing extremely poorly with noise, due to the numerical differentiation, this method is infeasible for the dialysis treatment. Various forms of numerical deconvolution are available but are known to lack robustness in the presence of noise and with the often sparse and infrequent samples that are available in biomedical systems. Direct deconvolution was tried using the dialysis data, by interpolating additional data points. The results were unsurprisingly poor, resulting in inconsistent simulation results and unrealistic FLC production rates.

A deconvolution technique that has been successfully employed on biomedical data is maximum entropy [Charter and Gull, 1991, Madden et al., 1995]. This approach shall be described below but maximum entropy can be constructed as a regularization technique that can function under the criteria of high noise, sparse and irregular sampled data that is commonplace in biomedical signals, without the need to assume a functional form for the input signal. In addition, it shall be shown how a non-linear compartmental model can be integrated into the maximum entropy framework to produce simulation results that show excellent visual comparison with patient data. To the knowledge of the authors this is the first time this has been conducted.

This paper is broken into three broad sections: the first describing the pharmacokinetics model; the second outlines how the maximum entropy method is implemented for the dialysis data and in the final section results are given for application of the techniques to four MM patients.

2. THE MODEL

In order to estimate FLC production it is necessary to model the FLC kinetics *in vivo*. For this purpose the Evans et al. [2006] model has been extended to form a three compartment non-linear model. This model is depicted in Figure 1.

Rate constant k_{12} describes the flow of FLC across the capillary walls from plasma to ECF; k_{21} is the flow in the reverse direction. k_{21} is derived from k_{12} and compartmental volume ratios ($k_{21} = (V_2/V_1)k_{12}$) [Jacquez, 1996]. The

[1] Charter and Gull [1987] refer to this as Compartmental, it has been changed here to avoid confusion with the term Compartmental Model

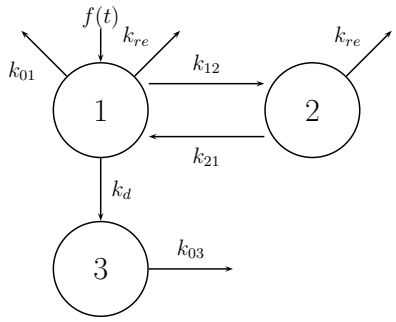

Fig. 1. Schematic of FLC dialysis Compartmental Model. Compartment 1 represents FLC in plasmas, 2 FLC in ECF and 3 the FLC in the dialyser.

rate constant k_{re} corresponds to the rate of the removal of FLC from plasma and ECF via the reticuloendothelial system. It is calculated from the half-life values of FLC when a patient's renal function has ceased [Bradwell et al., 2005]. k_{1e} estimates the rate of FLC removal via the urinary tract. It is provided here for completeness as in all patients considered renal function is negligible and therefore $k_{1e} = 0$. k_{03} is the rate of removal of FLC from dialyser via the counter current dialysate, assuming that the inflowing dialysate contains no FLC. This is feasible if dialysate is not recirculated; the value used for k_{03} is derived from the fixed flow rate of dialysate (0.5 L/min).

$$\begin{aligned}
\frac{\mathrm{d}q_1(t)}{\mathrm{d}t} &= -(k_{12} + k_{re} + k_{01} + k_d(t))q_1(t) \\
&\quad + k_{21}q_2(t) + f(t) \\
\frac{\mathrm{d}q_2(t)}{\mathrm{d}t} &= k_{12}q_1(t) - (k_{re} + k_{21})q_2(t) \\
\frac{\mathrm{d}q_3(t)}{\mathrm{d}t} &= k_d(q1(t), q3(t))q_1(t) - k_{03}q_3(t) \\
q_1(0) &= q_{10},\ q_2(0) = q_{20},\ q_3(0) = 0 \\
c_1(t) &= \tfrac{q_1(t)}{V_1},\ c_3(t) = \tfrac{q_3(t)}{V_3}
\end{aligned} \tag{1}$$

All rate constants have units of mins^{-1} and are considered constant, with the exception of coefficient k_d, which is dependent on the concentration gradient across the filter membrane (see Section 2.2). A mathematical description of the system is given in (1). c_1 and c_3 represent the observed outputs of the system, i.e. the concentration measurements taken by clinicians (examples of which can be seen in figures 3 to 6). V_1 and V_3 are plasma and dialysate volumes respectively (see Section 2.1). A list of parameter for the patients considered can be found in Table A.

2.1 Patient Volume Estimates

In addition to removing toxins, the urinary system is also responsible for maintaining the body's volume levels. In patients with no renal function this is achieved through pressure difference (ultra-filtration) to force fluid out of the body during dialysis. This would have an effect on the clearance values, hematocrit and concentration measures. However, the dialysis session chosen had minimal, or no, ultra-filtration applied. It has therefore been assumed that the volumes remain constant throughout the simulations. In previous studies it had been assumed that all patients

had the mass of standard 75 kg male, with an estimated volume to match. For this analysis, anisotropic information has been gathered on the patients and a more realistic calculation is used to obtain an estimate for the volume of distribution [Lee et al., 2001] and the volume of distribution estimated as 14% of Total Body volume [Ward et al., 2006]. A list of patient volume can be found in Table A.

2.2 Dialysate Clearance

In the model presented in Evans et al. [2006] the dialysis removal rate (k_d) was considered constant over the dialysis session. However, from filter theory this is known not to be true (Jacquez [1996]); movement of particles across a semi-permeable membrane is driven by concentration and pressure gradients. In order to incorporate these features into the model in a parametric form would require values for key characteristics (e.g. membrane permeability) which are not available for FLC, so a more simplistic model is adopted.

The 'clearance' (cl) of a membrane is defined as the amount of liquid cleared by the filter per unit time. The 'gold standard' for this measurement is derived from the blood and dialysate concentration measurements, and the dialysate flow rate, see (2).

$$cl[n](L/min) = \frac{D_3[n]}{D_b[n]}Q_d, \quad k_d[n] = \frac{cl[n]}{V_b} \tag{2}$$

where $D_b[n]$ and $D_3[n]$ are the measured values of FLC concentrations in blood and dialysate at n^{th} sample; Q_d is the dialysate flow-rate (0.5 L/min in all dialysis sessions considered) and k_d represents the removal rate in min^{-1} and V_b is the blood volume.

The measurements provided by clinicians are given as concentrations in plasma. Plasma and blood concentrations are related through 3, where C_p and C_b are the FLC concentrations in plasma and blood respectively, and H is the Hematocrit (Lee et al. [1980]).

$$C_b = C_p(1 - H) \tag{3}$$

Equation (2) then becomes

$$k_d[n] = \frac{D_3[n]Q_d}{D_1[n](1 - H)V_1} \tag{4}$$

It should be recognised that the values for clearance calculated from the formulae, and therefore k_d, are not piecewise constant. For the purpose of the simulation a continuous representation was preferred for a more realistic clearance function and spline interpolation used.

In order to validate the values for k_d an analysis of concentration decreases in plasma during dialysis was conducted. If it is assumed that the chemotherapy a patient receives has completely stopped FLC production (i.e. $f(t) = 0$), an estimate can be made for the minimum value of k_d. If two adjacent data points are taken (e.g. $D_1(t)$ and $D_1(t + \tau)$) and an analytical form of the relationship between is available, a minimum value of k_d would be the value that enables the second data point to be reached given the first value as an initial condition. If

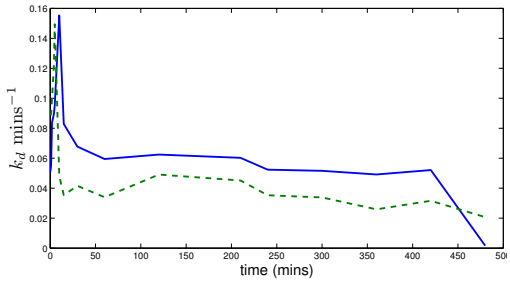

Fig. 2. k_d estimates from clearance (solid) and zero input (dotted).

the system described by Equation 1 is considered piecewise linear between data points, the minimum (constant) value for k_d can be found by solving equation 5 for k_d, where n is the sample at time point $t + \tau$.

$$D_1[n] = c_1(t + \tau; c_1(t), c_2(t), k_d[n]) \tag{5}$$

For the three compartment system $c_1(t)$ can be estimated from the $D_1[n - 1]$ measurement and $c_2(t)$ can be calculated from the previous value of estimated k_d . For sample n=1 (t=0) it is assumed that compartments 1 and 2 have had sufficient time to equilibrate, and therefore $c_1(0) = c_2(0) = D_1[1]$. An analytical solution can be found but the resulting expression is transcendental with respect to k_d, therefore a numerical approximation was used. Figure 2 shows k_d values generated from the clearance calculations and the lower bound. As can be seen the clearance calculation is close to the minimum value specified.

A similar process can be conducted to determine an upper bound on k_d if a upper value is known for FLC generation rate and considered constant over the period τ. A suitable upper bound for production has not yet been identified for the patients studied.

3. MAXIMUM ENTROPY SIGNAL RECOVERY

The use of maximum entropy to recover signal data originates in the domain of astrophysics (Skilling and Bryan [1984], Cornwell and Evans [1985]), where it is used to filter images to remove high-levels of noise. However, it has also been used in the recovery of biomedical signals (Charter and Gull [1987]). A comprehensive review can be found in Madden et al. [1995].

3.1 Entropy Measure

The 'entropy' in the title refers to the amount of uncertainty present in a signal. The concept behind maximum entropy is to produce an input signal that maximises the uncertainty, thus creating a signal that has the minimal assumptions whilst maintaining an acceptable fit to an observed output. Equation (6) is the standard representation for entropy (S)

$$S = \sum_{n=1}^{N} p_m \ln(p_m). \tag{6}$$

Entropy theory is concerned with estimating probability distributions and p_m (eqn. 6) represents the probability that a value m is attained (6). However, in signal reconstruction we are attempting to determine the value of the input function over a certain period of time. For this a modified version of entropy is considered. If the input signal is discretized into piecewise monotonic function, see (7), a similar function for the entropy can be used (8)

$$f(t) = \sum_{n=1}^{N} f_n I_n, \quad I_n(t) = \begin{cases} 1 \text{ if } t \in [t_n, t_{n+1}) \\ 0 \text{ elsewhere} \end{cases} . \quad (7)$$

Incorporating (7) into (6) yields an appropriate form for the entropy (S)

$$x_n = \frac{f_n}{\Sigma f_n}, \quad S = \sum_{n=1}^{N} x_n \, ln(\frac{x_n}{r_n}). \quad (8)$$

Where x_n presents the normalised value of the input at the n^{th} sample, and r_n is a base-line value that the production should take in the presence of no other information. In the case of biomedical signal processing this is normally taken to be a moving average to force the output signal to a smooth estimate. In addition, the values of x_n are assumed to be positive, since a negative production is infeasible. In the above equations r_n is calculated using a nearest neighbour average ($(x_{n-1} + x_{n+1})/2$). This encourages a smooth function to give a greater value of S, thus removing 'spikes' from the recovered input signal, which would not occur naturally. At the sample points $n = 0$ and $n = N$ the average is taken of adjacent samples, e.g. $(x_0 + x_1)/2$.

3.2 Constraints

During the maximum entropy signal reconstruction the entropy of the input signal is maximised under the constraint that the output of the system should 'match' the real-data measurements. The most common form used to model this constraint is the χ^2 metric. This is given by:

$$\chi^2 = \sum_{i=1}^{N} \frac{(D_1[i] - c_1(\tau_i; f))^2}{\sigma_i^2}, \quad E(\chi^2) = N \quad (9)$$

where E donates the expected value, N the number of samples, and $D_1[n]$ and $c_1[n]$ are the measurements taken and the predicted value at the n^{th} sample, $t = \tau_i$. This can be seen as a weighted least squares estimator with weights of $\frac{1}{\sigma_i}$.

During application of the maximum entropy algorithm the input signal ($f(t)$) is modified to allow $E(\chi^2) \rightarrow N$ as the iterations increase (see Section 3.3). At each iteration $c_1(t)$ is calculated using a numerical solver (Facsimile, MCPA Software Ltd) for the new values of $f(t)$. This is then sampled at the appropriate points for the concentration measurements (e.g. $D_1[1], \ldots, D_1[N]$) and χ^2 is evaluated. In (9) σ_i represents the standard deviation of the noise present in the observations. For the FLC system the major contributor to noise is the error inherent in calculating the concentration of FLC. Herzum et al. [2005] conducted a study on the assay used and concluded that it exhibited a maximum coefficient of variation of approximately 7%. However, the accuracy of the sampling times in Herzum et al. [2005] study cannot be replicated in a hospital environment so the measurement error has been estimated at 10%. To compound matters, multiple experiments cannot be conducted to refine σ further. The patient and environment change in each experiment and repetition is infeasible. σ_i is calculated by $\sigma_i = \epsilon \; D_1[i]$, where ϵ is the measurement error (10%) and $D_1[i]$ is the i^{th} measurement of FLC in plasma.

3.3 Optimisation

In order to implement the maximum entropy signal recovery, the process can be viewed as an optimisation problem, given by:

$$\max_f S(f) \quad \text{s.t. } \chi^2(f) \leq N \qquad f_i \geq 0 \quad (10)$$

This optimisation can be achieved in numerous ways. The most common approach being to create the relevant Lagrangian function and minimise the inversion (see Eqn. (11)). The Lagrange multiplier (λ) discriminates between how much the χ^2 fit to the real data influences the change in the input function,

$$L(f, \lambda) = \chi^2(f) - \lambda S(f) \quad (11)$$

.

There are several algorithms available for solving this problem(see for example [Skilling and Bryan, 1984, Cornwell and Evans, 1985, Charter and Gull, 1987]). However, excellent results have been obtained using a Sequential Quadratic Programming (SQP) technique. The SQP algorithm is implemented in the fmincon method of MATLAB, which uses a Quadratic Programming subproblem coupled with calculation of the Hessian of the Lagrangian via the BFGS formula [Mathworks, 2007].

Madden et al. [1995] define a series of test functions, and an example model, that can be used to assess the performance of different deconvolution algorithms. In order to validate the implementation, Madden's functions 1,2 and 4 were executed to ensure that the maximum entropy algorithm was functioning correctly. The results produced were comparable with those seen in Madden et al. [1995] without the restrictive assumption made regarding the initial and final values of the input signal, i.e. in the Madden and Carter studies it was assumed that signal at $t = 0$ and for several points around final sampled point were known to be zero. This restriction was not required to produce equivalent results. In addition, the results were not 'smoothed' via post processing (e.g. averaging) as in the Madden study.

4. RESULTS

The results of the maximum entropy reconstructions can be seen in Figures 3 to 6. Each figure consists of two graphs. The top graph shows the results of applying the recovered input signal to the concentration in plasma, the dashed line the concentration in ECF, and the solid line donates the real data measurements with the circles indicating the sample point. In the lower of the two graphs

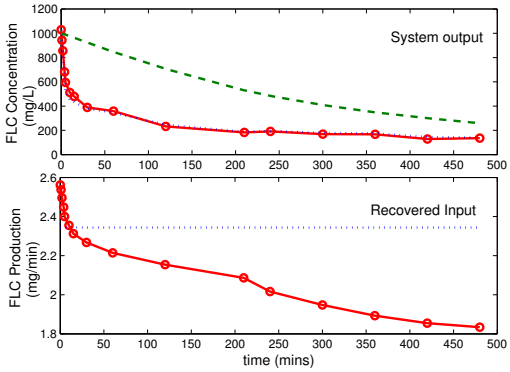

Fig. 3. Recovered FLC Input Signal Patient 1. Top (solid - measured data, dashed - FLC concentration in ECF, dotted - FLC concentration plasma). Bottom (solid - estimated input, dotted - initial estimate)

the predicted input signal is shown (solid-line). The dotted line donates the FLC production calculated from the initial plasma measurement, assuming the production is constant and the system is in steady-state at time $t = 0$. This is used as the starting value for production ($f(t)$) during the maximum entropy optimisation.

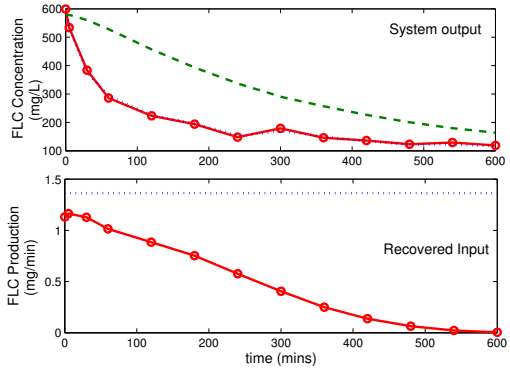

Fig. 4. Recovered FLC Input Signal Patient HD003. For legend see Fig. 3

Of the patients chosen, 3 and 4 received chemotherapy prior to the dialysis treatment. Patients 1 and 2 both had chemotherapy over 24 hours before dialysis treatment. As can been seen in Figures 3 and 5, the results suggest that the chemotherapy treatment appears to still be affecting the production rates in the system by reducing the FLC generation rate. In both these cases the production is not brought immediately down below the FLC production expected in a healthy individual (0.22 mg/min - Evans et al. [2006]). However, in patient 2 the production does reach normal levels in the later stages of dialysis ($t > 400$ mins).

Patient 3 (Fig. 5) had an extended dialysis session (12 hrs) allowing the chemotherapy effects to be observed over a longer period. As for patients 1 and 2 a drop in production is predicted by the simulation. However, a steep rise in the production rate between 0 and 200 mins is suggested. This is due to the rise in plasma concentration between 5 and 30 mins, as can be seen in the top graph of Figure. 5. It is not known precisely why this increase in FLC should occur, but it is seen in numerous patients and cannot be

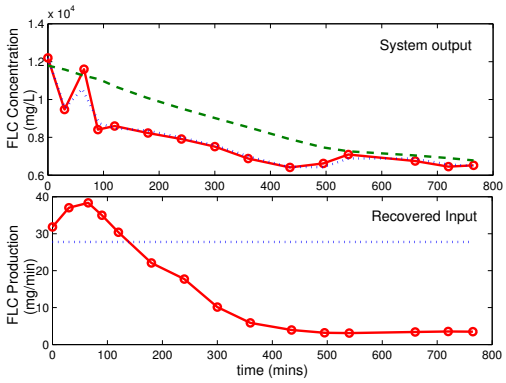

Fig. 5. Recovered FLC Input Signal Patient HD002. For legend see Fig. 3

explained by procedural abnormalities (e.g. changing of filter, or clearing of lines). The maximum entropy approach could accomodate this increase by reducing the constaints mentioned above but it is unlikely that this rise is due to FLC production unless there is possibly some form of delay in the effect of chemotherapy.

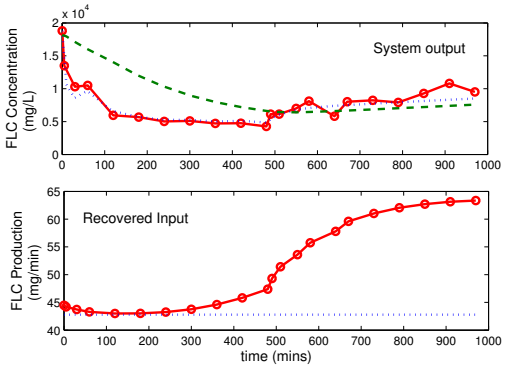

Fig. 6. Recovered FLC Input Signal Patient HD001. For legend see Fig. 3

For the final patient, (Fig. 6) plasma concentration data are available for an extended 16 hour period, including a 6 hour dialysis session, which started at $t = 0$,and 10 hours off dialysis. As with the previous patients we see a predicted drop during the initial phase of dialysis ($t < 100$ mins). However, in the later stages of dialysis a rise in production can be seen which continues in the off-dialysis period, suggesting a recovery of the FLC producing tumour cells after the chemotherapy treatment.

Whilst efficiency of the deconvolution technique was not a major consideration when conducting this analysis it should be noted that the maximum entropy implementation converged in around 20-30 iterations, taking approximately 1-2 minutes [2] when executed against the above data sets (i.e. 11 - 16 data points).

5. CONCLUSION

It has been shown that the maximum entropy technique provides an effective method of deconvolving an input signal from a nonlinear compartmental model without the

[2] The machine used was running Windows XP (Single 3.2 GHz processor, 1 Gb ram)

need for assuming a functional form for the input. The input produced appears biologically feasible, in terms of its magnitude and profile, and contains characteristics that are in-line with the limited knowledge of the chemotherapy effects on FLC producing tumours.

In Stec and Aitkinson. [1981] dialysis dynamics are described in relation to fluid flow which account for a fast and slow acting compartmental transfer. This could be incorporated into the compartmental model (Fig. 1) by splitting the ECF compartment in two with differing rate constants between fast and slow compartments. This may more accurately model the FLC kinetics whilst introducing a minimal number of extra parameters. The method should be extended to identify the amount of uncertainty and possible error in the input signal generated if the information is to be used during diagnosis and treatment. This will also require the sensitivity of the model to changes in volume and Hematocrit due to dehydration and subsequent re-hydration that occur during dialysis treatment. A follow-up study will be conducted to investigate the input predicted over multiple dialysis sessions. This may allow for the input signal to be parameterised with respect to the chemotherapy treatment (dose and frequency), which will enable a greater range of predictive simulations to be conducted in order to assist treatment.

Finally, whilst a performance time of 1-2 mins (see Section 4) is suitable for a small scale trial, if the concept is to be automated and extended to multiple sessions and patients an alternative implementation environment should be found. For example, a non-interpreted language, preferably an OS native optimisation routine should be found to conduct the maximum entropy fit.

ACKNOWLEDGEMENTS

This research was funded by EPSRC studentship.

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Appendix A. PATIENT PARAMETERS

Table A shows the values used for rate constants and volumes during the simulations. The parameters were obtained from selecting a dialysis session that maintained a consistent FLC concentration indicating a constant input signal. Parameter estimation, using FACSIMILE (Facsimile, MCPA Software Ltd), was then performed assuming all rates constants and production are constant. The volume ratio of plasma and ECF is 1:3 (Ward et al. [2006]). For all patients $k_{re} = 0.00016(min^{-1})$ and no renal ($k_{1e} = 0$).

Patient Parameters			
Patient	$k_{12}(min^{-1})$	$V_1(L)$	$V_2(L)$
1	0.07	2.1	7.1
2	0.02	2.2	6.9
3	0.01	1.9	6.5
4	0.05	2.545	12.0