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ORIGINAL ARTICLE

Real-time estimation of cerebrospinal fluid system parameters via oscillating pressure infusion

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Abstract Hydrocephalus is related to a disturbed cerebrospinal fluid (CSF) system. For diagnosis, lumbar infusion test are performed to estimate outflow conductance, C_{out}, and pressure volume index, PVI, of the CSF system. Infusion patterns and analysis methods used in current clinical practice are not optimized. Minimizing the investigation time with sufficient accuracy is of major clinical relevance. The aim of this study was to propose and experimentally evaluate a new method, the oscillating pressure infusion (OPI). The non-linear model of the CSF system was transformed into a linear time invariant system. Using an oscillating pressure pattern and linear system identification methods, C_{out} and PVI with confidence intervals, were estimated in real-time. Forty-two OPI and constant pressure infusion (CPI) investigations were performed on an experimental CSF system, designed with PVI = 25.5 ml and variable C_{out}. The ARX model robustly estimated C_{out} (mean $C_{out,OPI} - C_{out,CPI} = 0.08$ µl/(s kPa), $n = 42$, $P = 0.68$). The Box–Jenkins model proved most reliable for PVI (23.7 ± 2.0 ml, $n = 42$). The OPI method, with its oscillating pressure pattern and new parameter estimation methods, efficiently estimated C_{out} and PVI as well as their confidence intervals in real-time. The results from this experimental study show potential for the OPI method and supports further evaluation in a clinical setting.

Keywords Normal pressure hydrocephalus · System identification · Outflow resistance · Outflow conductance · Intracranial pressure · Infusion test

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1 Introduction

Idiopathic normal pressure hydrocephalus (INPH) is a neurological disorder that primarily affects elderly patients with dilated ventricles of the brain and with symptoms of gait and balance disturbances, dementia and incontinence. The disease is associated with a disturbance in the cerebrospinal fluid (CSF) system [23]. CSF is produced in the ventricles and circulates through the ventricular system and cavities surrounding the brain and spinal cord, and is continuously reabsorbed into the venous bloodstream. Patients with INPH are treated by implantation of a CSF shunt system: a valve with a proximal tube in the brain and a distal tube to the abdominal cavity that changes the CSF system dynamics. Approximately three quarters of the

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patients improve [6, 24, 36]. To select patients for shunt surgery, several prognostic tests are performed, one of which is the artificial CSF infusion test the aim of which is to characterize the hydrodynamic properties of the CSF system [29]. Two needles are placed in the lumbar subarachnoidal space, connecting to the CSF system. One needle measures the pressure and the other is used for infusion or withdrawal of artificial CSF.

A particularly successful lumped-parameter model of the CSF system was developed in the seventies by Marmarou [28], described by the non-linear differential equation for intracranial pressure P_{ic} as

$$\frac{dP_{ic}}{dt} = kP_{ic}(-C_{out}(P_{ic} - P_r) + I_{ext}) \quad (1)$$

where C_{out} is the outflow conductance (being the reciprocal to the outflow resistance), k is the elastance coefficient, P_r is the resting pressure, regarded as a constant and I_{ext} is the external infusion or withdrawal of artificial CSF. By using the pressure and flow data together with the mathematical model of the CSF system, C_{out} and k can be estimated. These parameters are used both for diagnostic/prognostic and research purposes [15, 29]. There are both supportive studies regarding the predictive power of C_{out} [7, 33, 35] as well as negative [13, 24].

Different infusion patterns are used in current clinical practice [12, 18, 19, 30] but neither infusion pattern nor analysis method has been optimized for the CSF system. Although there has recently been some promising suggestions [4, 11], the presently established methods have their disadvantages, e.g. no real-time statistical value on the accuracy of the estimates, long investigation times or only one estimated parameter. Also, they do not attempt to model physiological variations, e.g. breathing and slow oscillating pressure variations known as B-waves. These variations are patient specific and will affect the accuracy and length of the individual patient investigation. To achieve similar estimation accuracy, patients with smaller physiological variations need a shorter investigation time while those patients with larger variations need a longer investigation time.

In this paper we further develop an extended [5] version of the non-linear differential equation of the CSF system and transform it via a non-linear change of variables into a linear time invariant (LTI) system, i.e. the system has a linear relationship between input and output and system characteristics that do not depend on time. With the CSF system written in the form of a LTI system, methods developed for parameter identification of such systems [21] can be utilized to find C_{out} and k. Due to the invasiveness and that patients have to lie still during the investigation, a reduction of the investigation time is of major clinical relevance. With a more efficient methodology this could be possible, since the LTI system no longer requires simple infusion patterns, and others can be found which optimally excite the system [21, 27]. Furthermore, the physiological variations can be explicitly modelled, which can improve the quality of the estimates and may also be of independent interest. A preliminary version of this technique in the present paper was suggested in [26].

The aim of this paper is to propose and experimentally evaluate a new method to assess CSF dynamics, by transforming the non-linear system into a LTI system and applying linear system identification techniques. The new method was named the oscillating pressure infusion (OPI) method.

2 Methods

2.1 System identification

System identification is the process of building mathematical models of dynamical systems based on measured input and output data [21]. The system identification procedure for the CSF system can be described in three steps:

1. Experiment design to ensure sufficient information in the data (flow and pressure) for reliable statistical estimation, i.e. using an infusion pattern appropriate for the CSF system.
2. Select an appropriate mathematical model structure for both the CSF system and the physiological disturbances, as well as appropriate pre-filters for the measured signals.
3. From experimental or clinical data, estimate the parameters in the chosen model structure, and from these compute estimates of C_{out} and k.

The first step was investigated in [27], in which it was found that an infusion pattern that elevates the CSF pressure and regulates it according to an oscillating pattern provides persistent information about C_{out} and k. This paper focuses on the second and third steps.

2.2 CSF modelling

The Marmarou model of Eq. 1 was later extended to include a new parameter P_0, which some authors regard as an important parameter while others assume it to be zero [5]. However, that model does not explicitly consider any physiological variations. Using the extended model and including these variations, the differential equation describing the CSF system can now be written as

$$\frac{dP_{ic}}{dt} = k(P_{ic} - P_0)\left(-C_{out}(P_{ic} - P_r) + I_{ext} + I_{phys}\right) \quad (2)$$

where I_{phys} is the rate of volume variations in the system caused by the internal physiological variations. The parameter P_0 can be estimated by analysing the relationship between the amplitude of intracranial pressure pulsations and intracranial pressure [5, 20] and can thus be regarded as known.

From Eq. 2, it can be seen that the relationships between the input I_{ext} and the measured response P_{ic} is non-linear. Thus, standard system identification procedures [21] which assume a LTI system cannot be directly applied to the system given by Eq. 2.

2.2.1 A mathematical transformation

For this particular model of the CSF system a transformation of the non-linear differential equation (2) similar to the classical method of Bernoulli is possible. By introducing the virtual control signal u and a change of variables according to:

$$u = \frac{I_{ext}}{P_{ic} - P_0}, \quad x = \frac{1}{P_{ic} - P_0} - \frac{1}{P_r - P_0} \tag{3}$$

Equation 2 can be transformed into a first-order LTI system:

$$\frac{dx}{dt} = -k(P_r - P_0)C_{out}x - ku + w \tag{4}$$

where $w = -k\frac{I_{phys}}{P_{ic}-P_0}$ was treated as a lumped disturbance term. Note that it was assumed that P_0 is always less than P_r, and an infusion investigation always occurs at elevated pressure, i.e. $P_{ic} > P_r$, so the transformation is always well defined. System identification methods developed for LTI systems can now be directly applied to the CSF system. Note that this is not linearization about an operating point, but exact linearization by means of change of variables; therefore there is no loss of accuracy compared to the non-linear model. Using system identification procedures, a discrete time relationship between u and x can be obtained from which estimates of C_{out} and k can be calculated. See Supplementary material for detailed information.

To conform to conventional clinical nomenclature, the pressure volume index (PVI) was used in the results instead of k, where PVI = 1/0.4343k.

2.2.2 Prediction error method

In this study, the prediction error method (PEM) was used for the parameter estimation with the associated optimization performed with the Levenberg–Marquardt algorithm. PEM has the advantage that it can be used for many different model structures, and is known to correspond to the maximum likelihood parameter estimate [21]. Furthermore, it was computationally feasible to compute an estimate once per sample, i.e. every second, thus allowing real-time parameter estimation.

If there was sufficient information in the collected data, the PEM produces an estimated parameter covariance matrix [21]. See Supplementary material for more information on how the estimates for the standard deviation of the clinically relevant parameters C_{out} and PVI were assessed. These estimated reliability parameters were denoted ΔC_{out} and ΔPVI.

2.2.3 Pressure pattern

There are two approaches to specify an infusion investigation: by defining the infusion rate directly, or by defining a reference pressure pattern and achieving this reference via feedback control. As with a currently used method, constant pressure infusion (CPI), a pressure-regulated pattern will be used for the OPI method due to safety restrictions in intracranial pressure. Based on theoretical considerations [27] and knowledge of the CSF system dynamics, the pressure pattern was chosen to be persistently exciting, i.e. with a certain pressure increase and with oscillating variations with a range of frequencies around the expected bandwidth of the system whilst not exciting the system at frequencies where there are most physiological variations expected. The oscillating pressure pattern chosen for use in this study can be seen in Fig. 1.

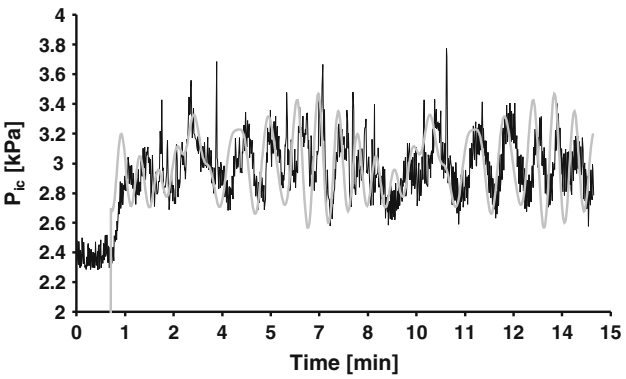

Fig. 1 The pressure response (*black line*) of the first 15 min of the patient investigation for the OPI method. The oscillating reference pattern (*grey line*) is 15 min in length and is continuously repeated

2.3 Experimental procedures

2.3.1 Infusion apparatus and the experimental set-up

The in-house developed infusion apparatus has been thoroughly described in previous papers [1, 2]. For the OPI method, a proportional-plus-integral controller was designed for the linearized system, and applied to the non-linear system using a technique known as exact feedback linearization [16] as previously described [26].

The experimental set-up used in this paper is shown in Fig. 2. The infusion apparatus was connected to the experimental set-up with Luer-lock connections. Seven different T304 stainless steel pipes were used yielding seven different C_{out} values. In order to simulate the physiological variations in the experimental set-up, six different 15-min patterns were selected from patients with lumbar resting pressure measurements, see Supplementary material. Irregularities such as coughing have been removed. These were broadly representative of possible physiological variations, from very little variation and slow breathing to more challenging variations such as B-waves.

2.3.2 Constant pressure infusion

The baseline for comparison was the CPI method, which is an established method in current clinical practice giving an estimate of C_{out} with confidence intervals [2]. The method does not provide an estimate of PVI. P_{ic} was regulated to six consecutive, predetermined pressure levels in steps of 0.4 kPa during 42 min of investigation time. Mean intracranial pressure was measured on each level, as well as the net flow needed to maintain the constant pressure. The conductance value, C_{CPI}, was then determined as the slope of the linear regression between net flow and corresponding mean pressure [2].

2.3.3 Investigation protocol for the experimental set-up

The investigation protocol consisted of six measurements, one per physiological variations pattern, on each of the seven pipes, for a total of 42 measurements. All measurements started with 10 min of resting pressure measurement. The order of CPI and OPI was randomly selected. Before the start of each new method, P_{ic} returned to resting pressure without regulation, had it not returned after 15 min, it was regulated back and was then allowed to stabilize for 5 min without regulation.

2.3.4 The procedure from data collection to estimation of parameters

Flow and pressure (i.e. input/output data) from the infusion investigation was transformed using Eq. 3. The transformed data was pre-filtered (10th order Butterworth low-pass filter) to focus on frequencies minimizing the prediction error [21]. The following cut-off frequencies were analyzed: 0.01, 0.05, 0.1, 0.2 Hz, chosen based on the

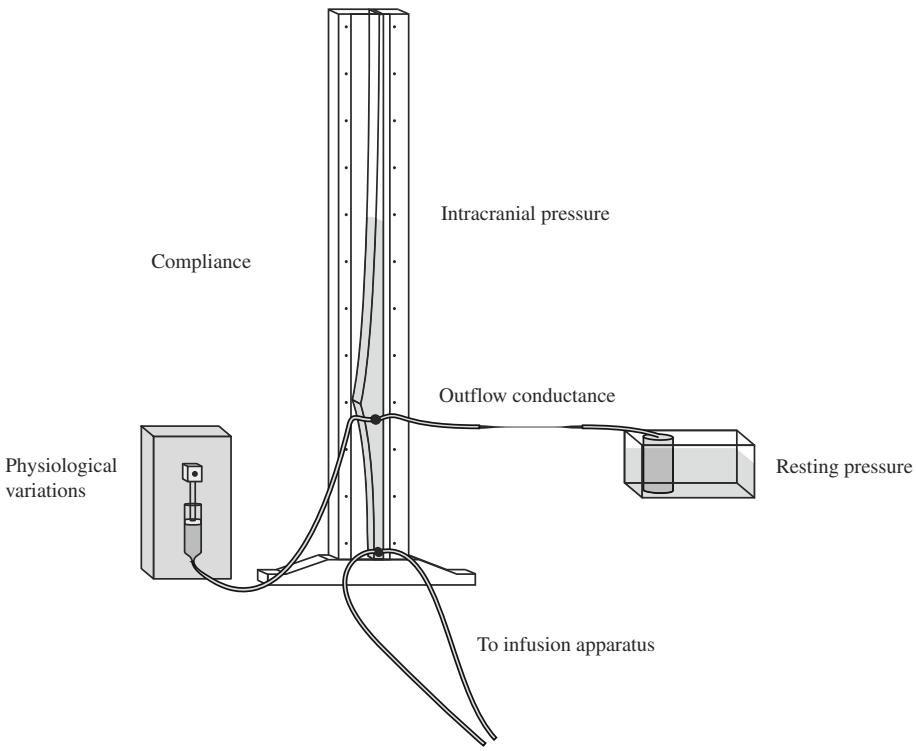

Fig. 2 The experimental set-up consists of a cavity formed in Polymetylmetakrylat shaped to model a PVI of 25.5 ml [32], and P_0 equal to zero. P_r was set to 1.56 kPa [32] and C_{out} was simulated using T304 stainless steel pipes. Physiological variations were added to the set-up through a separate pump

system and the typical dynamics of physiological variations. Three different model structures, ARX, ARMAX and Box–Jenkins (BJ), were used. The order of the disturbance-model polynomials for ARMAX and BJ were chosen from combinations of 5, 10, 15 and 20. Parameter estimation was started 2 min into the investigation.

To evaluate the repeatability of the parameter estimates, the estimates of C_{out} and PVI at 15 min were computed for each of the 42 measurements. The standard deviation of estimates for all 42 measurements was computed, std C_{out} and std PVI, controlling for differences between pipes by subtraction of pipe mean estimates. This was done for each combination of filter cut-off frequency, model structure and model order. The percentage of estimation procedures that computed a reliable estimate of the confidence intervals was also recorded.

The combination that produced the lowest std C_{out}, and computed a reliable ΔC_{out} on all measurements, was selected and used for analysis of investigation time and for the comparison with C_{out} estimates obtained by the CPI method. The same procedure, lowest std PVI and reliable ΔPVI, was used for selecting a combination for estimation of PVI.

2.3.5 *Investigation time analysis*

For this analysis the investigation was considered ended when the maximum and minimum estimate of C_{out} stayed within 2 µl/(s kPa) and ΔC_{out} stayed below 2 µl/(s kPa) for the preceding 2 min of the investigation.

The Bland–Altman method and the paired *t*-test were used to compare the estimated parameters from the methods (OPI and CPI), $P < 0.05$ was considered statistically significant.

2.4 Patient study

One pilot investigation was performed on a patient. The local ethics committee approved all aspects of the investigation. After receiving written as well as oral information, informed consent was obtained from the patient. The patient had suspected INPH and underwent the infusion test of the preoperative investigation. The investigation protocol was similar to the one used for the experimental set-up. After the CPI measurement the relaxation time was 5 min followed by 1 min of regulation to reach resting pressure, and then another 5 min of relaxation before the start of the OPI method. The length of the new method was extended to 42 min (same as CPI). The combinations suggested from the experimental evaluation were used for estimation of C_{out} and PVI. P_0 was calculated [37] and used for the parameter estimation.

All data was collected during the investigations and analysed afterwards using Matlab® (The Mathworks, Inc., Boston, MA, USA) with the System Identification Toolbox.

3 Results

3.1 Experimental results

The method was evaluated over a range of model structures and a variety of disturbance patterns. Good repeatability was found for many combinations of filter cut-off frequency, model structure and model order, see Table 1 in the Supplementary material for detailed data. For different combinations, the percentage of experiments in which the algorithm could reliably estimate ΔC_{out} and ΔPVI varied between 0 and 100 percent. Typically, when a filter with a low cut-off frequency was used, it was difficult to estimate reliability for a high-order disturbance model, as one is fitting too many parameters to the given data.

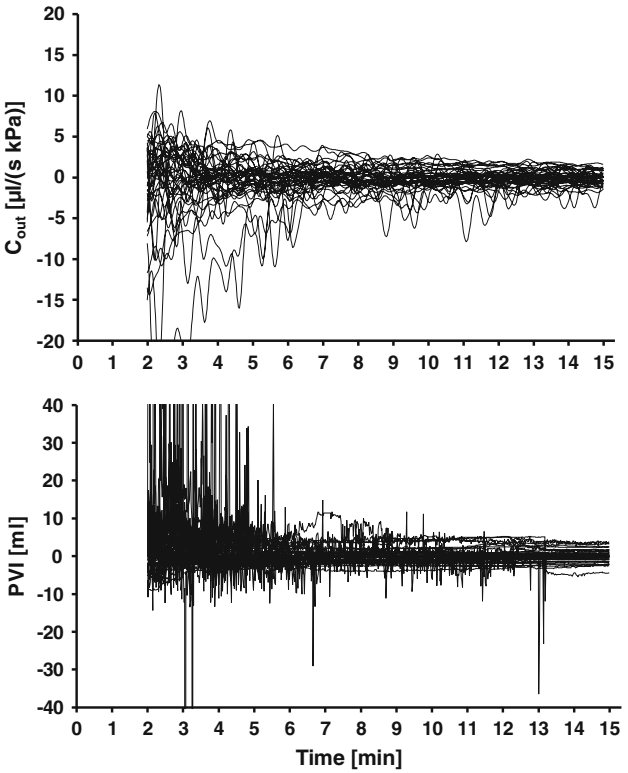

Fig. 3 Convergence and repeatability of estimates on the experimental set-up. The *curves* are obtained by subtracting the pipe mean estimates after 15 min from the estimates for all 42 measurements. C_{out} was estimated with an ARX model structure with a filter cut-off of 0.05 Hz, PVI was estimated with a Box–Jenkins model structure with a filter cut-off of 0.2 Hz and disturbance model polynomials $C(q)$ and $D(q)$ both fifth order

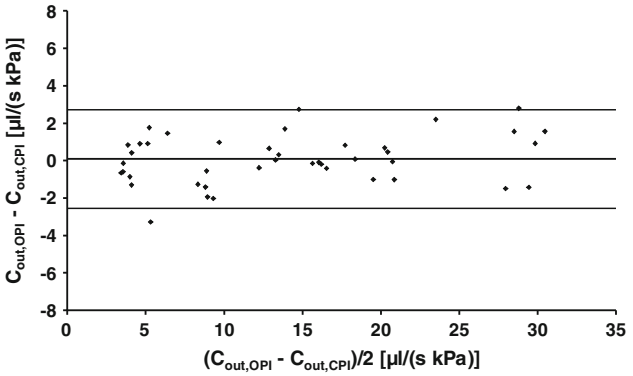

Fig. 4 Bland–Altman plot showing results from the experimental set-up investigations. The difference in C_{out} between the methods (OPI and CPI) is plotted against the mean of the two methods ($n = 42$). For OPI the C_{out} estimates were computed at the investigation times obtained by using the stopping criteria. Mean and two times standard deviation are shown

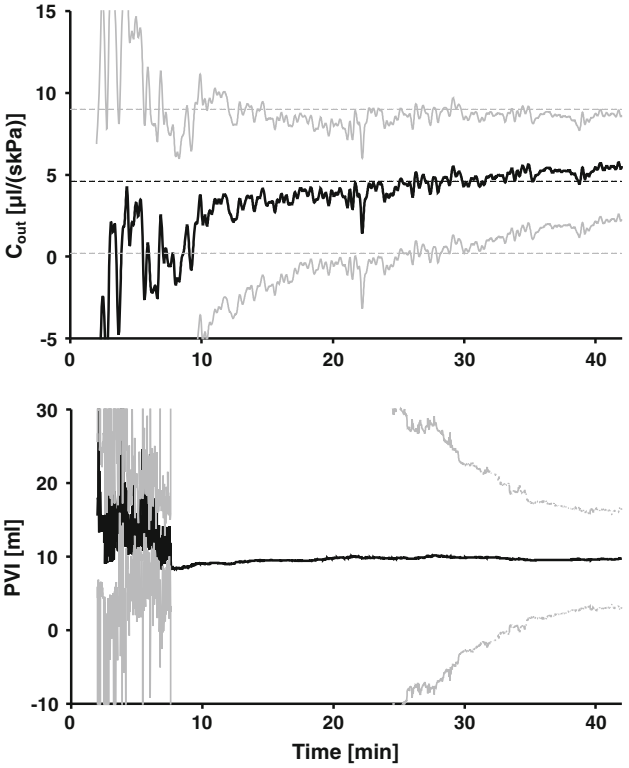

Fig. 5 The parameter estimates as a function of investigation time for the patient investigation. The *upper figure* shows C_{out} (*black line*) and $1.96\Delta C_{out}$ (*grey lines*). For reference, C_{CPI} and its corresponding confidence interval ($1.96\Delta C_{out}$) estimated after 42 min of investigation are shown (*dotted lines*). The estimated C_{out} confidence intervals of the OPI method approached the confidence interval value of the CPI method at approximately 20 min of investigation time. The *lower figure* shows the estimates of PVI and 1.96ΔPVI as a function of investigation time

For each parameter, C_{out} and PVI, the combination of filter and disturbance model was selected that produced the lowest standard deviation with the constraint that the covariance estimates could be reliably computed at all times. The best estimator for C_{out} was an ARX model structure with a filter cut-off of 0.05 Hz. The best estimator for PVI was a Box–Jenkins model structure with a filter cut-off of 0.2 Hz and disturbance model polynomials $C(q)$ and $D(q)$ both fifth order (see Supplementary material for details). Using these estimators, the repeatability and convergence are visualized in Fig. 3.

The results when applying the stopping criteria showed that the majority of the investigations required less than the 15-min investigation time with a median investigation time of 6.1 min. Using this stopping criteria and comparing C_{out} from the OPI method with that of the reference method, CPI, the two methods showed no significant difference (mean $C_{out,OPI} - C_{out,CPI} = 0.08$ µl/(s kPa), $n = 42$, $P = 0.68$) and no visual C_{out} dependence, see Fig. 4. For comparison with the experimental set-up design of PVI = 25.5 ml, the mean for all 42 PVI measurements was 23.7 ± 2.0 ml.

3.2 The patient investigation

The parameters of C_{out} and PVI were estimated from the patient data using the same filters and model structures selected in the experimental study. The results are shown in Fig. 5. The patient had a low C_{out} typical for INPH patients. P_r was 2.2 kPa and P_0 was calculated to be 1.8 kPa. The estimated C_{out} of the OPI method ($C_{out} = 5.5$ and $\Delta C_{out} = 1.6$ µl/(s kPa) at 42 min) approached the CPI results ($C_{cpi} = 4.6$ µl/(s kPa)). PVI and ΔPVI were estimated to approximately 9.7 and 3.4 ml, respectively, at the end of the investigation. The CPI method does not produce a PVI estimate.

4 Discussion

The introduction of the mathematical transformation of the non-linear CSF system into a LTI system enables the use of system identification methods for LTI systems [21]. In this paper several different model structures have been evaluated. The results show that the method was able to reliably estimate C_{out} (compared with CPI) and PVI with a reduced investigation time. This experimental study demonstrates potential and recommends further work in a clinical setting.

Identifying a non-linear system often requires solutions specific to the problem, e.g. assuming steady state behaviour (CPI [2], static constant infusion [18]) or using curve fitting of mathematical expressions based on analytical solutions related to a simple enough input pattern (bolus [30], dynamic constant infusion [12]). Approaches with

sinusoidal infusion patterns have been used, but in those cases with an assumption of a piecewise linear model [9, 10]. An adaptive observer was designed allowing arbitrary inputs but only provided estimates of C_{out} [1, 25]. Thus, the non-linear aspect of the CSF system has limited the methods and analyses used. The transformation introduced in this paper changes this. No approximation is involved since the linearization is exact by way of a non-linear change of variables. This eliminates restrictions resulting from having a non-linear model, and the extensively developed methods for identification of LTI systems can be applied.

The currently used infusion methods all have their respective benefits when compared to each other. The best features from each method were also implemented in the OPI method. As with CPI the pressure is regulated during the infusion, avoiding the risk of dangerously high pressure. Instead of the static pressure levels of CPI, the OPI method uses a dynamic pressure regulation pattern with a pre-set mean pressure increase and an oscillating variation. This creates a persistently exciting system [27] yielding information about both parameters of interest at all times. Thus, as with dynamic constant infusion and the bolus method, PVI can also be estimated.

A major advantage with the OPI method is that it enables real-time estimation of C_{out} and PVI as well as their respective confidence intervals. This allows one to end the investigation when sufficient data is recorded. The results indicate that a significant time reduction can be achieved with the OPI method where in some cases (for the experimental set-up) a reliable estimate was computed in less than 5 min. Taking the ARX model, using the estimates as given with time reduction and comparing it with the results from the CPI method using the Bland–Altman method, see Fig. 4, there was no significant difference between the two methods and the confidence interval was within clinically acceptable limits [2, 8].

The original model of the CSF system lacks a description of the physiological variations. It is known that failing to model disturbances can lead to large biases in system parameter estimates [21]. This effect can be significant if the disturbances occur in similar frequency bands to the system dynamics, which is the case for B-wave variations. To enable the system identification algorithm to accurately distinguish between responses to the infusion input and physiological variations, it is important that the infusion pattern contains a broad range of frequencies. Furthermore, quantification of the physiological variations can by themselves have a clinical importance in the investigation of INPH patients. It has previously been suggested that increased activity in rhythmic oscillations in P_{ic} can be used to select patients that are likely to improve from shunting [14, 22, 31, 34]. The linearization of the CSF model makes it straightforward to explicitly model these variations, see Eq. 4, which has not been previously considered for the CSF system. A potential problem can be non-stationary behaviour of the physiological variations and pressure-dependent complexity of the P_{ic} signal [17]. The modelling of physiological variations and their effect on the system identification will be a major part of the analysis in a future patient study.

Since this was an experimental study on a phantom, it is likely that somewhat different filter and model order will be optimal for clinical use; however, the present study was based on clinically recorded physiological variations and gives valuable knowledge about the respective performance of different choices. The chosen range for the pre-filter cut-off frequency and the model order were based on the notion that they gave a reasonable interval with respect to the frequency spectrum of the typical physiological variations and the expected time constant of the CSF system. The results for the experimental set-up show that, depending on filter cut-off frequency, the basic ARX model is robust and consistently produces ΔC_{out} estimates and estimates C_{out} with good repeatability. A pre-filtering cut-off removing most of the disturbances (but also some of the compliance information) produces a good estimate of C_{out} since it is a steady state parameter, however, low cut-off removes valuable information and ΔC_{out} increases. For PVI there is benefit in using a richer model of the physiological variations, as indicated by the results for BJ compared to ARX. Several different model structures can be used with similar results (see Table 1 in Supplementary material). In applied clinical use, it would be possible to use multiple model structures and estimations, both for C_{out} and PVI, but also several for each parameter, and then choose in real-time from those one that produces a stable estimate and small confidence intervals.

The results from the pilot investigation were promising. Estimates of both parameters converge to stable values within 15 min compared to the 42 min, which is the standard for the current method of CPI to estimate C_{out}. The estimate of C_{out} was close to that obtained by the CPI method for the selected combination (see Fig. 5). The resting pressure is not part of the CPI analysis while it was used in the OPI analysis, which could lead to a systematic difference in the estimates. However, previous studies with repeated CPI tests have shown a variation of similar size [2, 8]. The parameter P_0 has an effect on the CSF system identification [11]. It was by design set to zero for the experimental set-up and therefore set to zero in the system identification. For the patient, it was calculated and used in the parameter estimates, but further investigation in a large patient material is needed for evaluating its importance.

It is known that system identification with a feedback controller and large disturbances can produce a bias in the

estimates. This bias can be removed if a sufficiently rich model of the disturbances is used. Alternative estimation methods such as instrumental variables may also be useful and should be further investigated. With respect to the lumped model for the CSF system, it is based on certain assumptions, e.g. the pressure independency of C_{out}, and the pressure-dependent compliance. Most of these have been verified [3, 30] and it is the most common model used for infusion tests. It is important to note that the new transformation does not add any new assumptions to the model. As can be noted in Fig. 1, there is a phase shift between the measured P_{ic} and the pressure pattern. The pump characteristics, i.e. pump velocity, were limited due to medical safety considerations. This means that not just any reference pressure pattern can be selected. However, the system identification procedure uses recorded pressure and flow and is thus not dependent on the phase shift against reference pressure.

5 Conclusions

In this paper we have presented a new way of performing infusion investigations called OPI. This incorporates the transformation of the commonly used non-linear model of the CSF system into a first-order LTI system, a new pressure regulated infusion pattern, and new parameter estimation methods to estimate C_{out} and PVI. It has been shown to give results not statistically different than the currently used CPI method for the experimental set-up of the CSF system. A significant time reduction can be expected as well as real-time estimates on both C_{out} and PVI. This experimental study and pilot investigation demonstrate potential for the OPI method and support proceeding with further evaluation in a clinical setting.

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References

1. Andersson K, Manchester IR, Andersson N, Shiriaev AS, Malm J, Eklund A (2007) Assessment of cerebrospinal fluid outflow conductance using an adaptive observer—experimental and clinical evaluation. Physiol Meas 28:1355–1368
2. Andersson N, Malm J, Backlund T, Eklund A (2005) Assessment of cerebrospinal fluid outflow conductance using constant-pressure infusion—a method with real time estimation of reliability. Physiol Meas 26:1137–1148
3. Andersson N, Malm J, Eklund A (2008) Dependency of cerebrospinal fluid outflow resistance on intracranial pressure. J Neurosurg 109:918–922
4. Andersson N, Malm J, Wiklund U, Eklund A (2007) Adaptive method for assessment of cerebrospinal fluid outflow conductance. Med Biol Eng Comput 45:337–343
5. Avezaat CJ, van Eijndhoven JH, Wyper DJ (1979) Cerebrospinal fluid pulse pressure and intracranial volume-pressure relationships. J Neurol Neurosurg Psychiatry 42:687–700
6. Boon AJ, Tans JT, Delwel EJ, Egeler-Peerdeman SM, Hanlo PW, Wurzer HA, Avezaat CJ, de Jong DA, Gooskens RH, Hermans J (1997) Dutch normal-pressure hydrocephalus study: prediction of outcome after shunting by resistance to outflow of cerebrospinal fluid. J Neurosurg 87:687–693
7. Borgesen SE (1984) Conductance to outflow of CSF in normal pressure hydrocephalus. Acta Neurochir (Wien) 71:1–45
8. Borgesen SE, Albeck MJ, Gjerris F, Czosnyka M, Laniewski P (1992) Computerized infusion test compared to steady pressure constant infusion test in measurement of resistance to CSF outflow. Acta Neurochir (Wien) 119:12–16
9. Brinker T, Beck H, Klinge P, Kischnik B, Oi S, Samii M (1998) Sinusoidal intrathecal infusion for assessment of CSF dynamics in kaolin-induced hydrocephalus. Acta Neurochir (Wien) 140:1069–1075
10. Charlton JD, Johnson RN, Pederson NE, Mann JD (1983) Assessment of cerebrospinal fluid compliance and outflow resistance: analysis of steady-state response to sinusoidal input. Ann Biomed Eng 11:551–561
11. Cieslicki K, Czepko R (2010) Can infusion tests be recommended for patients with giant hydrocephalus? Neurol India 58:78–84
12. Czosnyka M, Batorski L, Laniewski P, Maksymowicz W, Koszewski W, Zaworski W (1990) A computer system for the identification of the cerebrospinal compensatory model. Acta Neurochir (Wien) 105:112–116
13. Delwel EJ, de Jong DA, Avezaat CJ (2005) The prognostic value of clinical characteristics and parameters of cerebrospinal fluid hydrodynamics in shunting for idiopathic normal pressure hydrocephalus. Acta Neurochir (Wien) 147:1037–1042 discussion 1042-3
14. Eklund A, Agren-Wilsson A, Andersson N, Bergenheim AT, Koskinen LO, Malm J (2001) Two computerized methods used to analyze intracranial pressure B waves: comparison with traditional visual interpretation. J Neurosurg 94:392–396
15. Eklund A, Smielewski P, Chambers I, Alperin N, Malm J, Czosnyka M, Marmarou A (2007) Assessment of cerebrospinal fluid outflow resistance. Med Biol Eng Comput 45:719–735
16. Glad T, Ljung L (2000) Control theory: multivariable and nonlinear methods. Taylor and Francis, New York
17. Hornero R, Aboy M, Abasolo D (2007) Analysis of intracranial pressure during acute intracranial hypertension using Lempel-Ziv complexity: further evidence. Med Biol Eng Comput 45:617–620
18. Katzman R, Hussey F (1970) A simple constant-infusion manometric test for measurement of CSF absorption. I. Rationale and method. Neurology 20:534–544
19. Kosteljanetz M (1985) Resistance to outflow of cerebrospinal fluid determined by bolus injection technique and constant rate steady state infusion in humans. Neurosurgery 16:336–340
20. Lenfeldt N, Andersson N, Agren-Wilsson A, Bergenheim AT, Koskinen LO, Eklund A, Malm J (2004) Cerebrospinal fluid pulse pressure method: a possible substitute for the examination of B waves. J Neurosurg 101:944–950
21. Ljung L (1999) System identification—theory for the user, 2nd edn. Prentice Hall, Upper Saddle River, NJ
22. Lundberg N (1960) Continuous recording and control of ventricular fluid pressure in neurosurgical practice. Acta Psychiatr Scand 36(Suppl 149):1–193
23. Malm J, Eklund A (2006) Idiopathic normal pressure hydrocephalus. Pract Neurol 6:14–27

24. Malm J, Kristensen B, Karlsson T, Fagerlund M, Elfverson J, Ekstedt J (1995) The predictive value of cerebrospinal fluid dynamic tests in patients with idiopathic adult hydrocephalus syndrome. Arch Neurol 52:783–789
25. Manchester IR, Andersson K, Andersson N, Shiriaev AS, Eklund A (2008) A nonlinear observer for on-line estimation of the cerebrospinal fluid outflow resistance. Automatica 44:1426–1430
26. Manchester IR, Andersson K, Eklund A, Shiriaev AS (2007) Experimental testing of a method for on-line identification of the cerebrospinal fluid system. Conf Proc IEEE Eng Med Biol Soc 2007:2843–2846
27. Manchester IR, Andersson K, Eklund A, Shiriaev AS (2007) Identifiability of the parameters of a nonlinear model of the cerebrospinal fluid system. In: Xia X, Camisani-Calzolari F (eds) Proceedings of the 7th IFAC symposium on nonlinear control systems, International Federation of Automatic Control, Laxenburg, Austria, Pretoria, South Africa. doi:10.3182/20070822-3-US-00164
28. Marmarou A (1973) A theoretical model and experimental evaluation of the cerebrospinal fluid system. Ph.D. thesis, Drexel University
29. Marmarou A, Bergsneider M, Klinge P, Relkin N, Black PM (2005) The value of supplemental prognostic tests for the preoperative assessment of idiopathic normal-pressure hydrocephalus. Neurosurgery 57:17–28
30. Marmarou A, Shulman K, Rosende RM (1978) A nonlinear analysis of the cerebrospinal fluid system and intracranial pressure dynamics. J Neurosurg 48:332–344
31. Raftopoulos C, Chaskis C, Delecluse F, Cantraine F, Bidaut L, Brotchi J (1992) Morphological quantitative analysis of intracranial pressure waves in normal pressure hydrocephalus. Neurol Res 14:389–396
32. Shapiro K, Marmarou A, Shulman K (1980) Characterization of clinical CSF dynamics and neural axis compliance using the pressure-volume index: I. The normal pressure-volume index. Ann Neurol 7:508–514
33. Sorteberg A, Eide PK, Fremming AD (2004) A prospective study on the clinical effect of surgical treatment of normal pressure hydrocephalus: the value of hydrodynamic evaluation. Br J Neurosurg 18:149–157
34. Stephensen H, Andersson N, Eklund A, Malm J, Tisell M, Wikkelso C (2005) Objective B wave analysis in 55 patients with non-communicating and communicating hydrocephalus. J Neurol Neurosurg Psychiatry 76:965–970
35. Tans JT, Boon AJ (2002) How to select patients with normal pressure hydrocephalus for shunting. Acta Neurochir Suppl 81:3–5
36. Tullberg M, Jensen C, Ekholm S, Wikkelso C (2001) Normal pressure hydrocephalus: vascular white matter changes on MR images must not exclude patients from shunt surgery. AJNR Am J Neuroradiol 22:1665–1673
37. Wåhlin A, Ambarki K, Birgander R, Alperin N, Malm J, Eklund A (2010) Assessment of craniospinal pressure-volume indices. AJNR Am J Neuroradiol. doi:10.3174/ajnr.A2166