Technical communique

A nonlinear observer for on-line estimation of the cerebrospinal fluid outflow resistance

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Abstract

Accurate estimates of the outflow resistance of the human cerebrospinal fluid system are important for the diagnosis of a medical condition known as hydrocephalus. In this paper we design a nonlinear observer which provides on-line estimates of the outflow resistance, to the best of our knowledge the first method to do so. The output of the observer is proven to globally converge to an unbiased estimate. Its performance is experimentally verified using the same apparatus used to perform actual patient diagnoses and a specially-designed physical model of the human cerebrospinal fluid system.

Keywords: Nonlinear observers; Biomedical systems; Parameter estimation

1. Introduction

Estimation of the outflow resistance of the cerebrospinal fluid (CSF) is an important problem in medical diagnosis. Patients with a condition known as Idiopathic Normal Pressure Hydrocephalus (INPH), a form of communicating hydrocephalus, are observed to have a disturbance to the hydrodynamics of the CSF system (Malm & Eklund, 2006).

It is well established that the symptoms of INPH can be reduced or eliminated by implanting a shunt, a small valve with an attached drainage tube, into the patient’s skull, thereby altering the system and increasing the CSF flow (Bergsneider, Black, Klinge, Marmarou, & Relkin, 2005).

The disease is difficult to diagnose and any such surgery has potential risks, so neurologists and neurosurgeons use a number of different diagnostic tests to decide whether or not the patient is likely to benefit from a shunt surgery. Estimation of the outflow resistance is one of the tests currently used, and higher than average resistance values are suggested to be an indicator for shunt surgery (Malm & Eklund, 2006).

The value of the resistance is not directly measurable, but must be inferred from measurements of fluid pressure, and an assumed hydrodynamical model. In this paper we propose a nonlinear observer which provides on-line estimates of the outflow resistance, to our knowledge the first method to do so.

All resistance estimation methods in current clinical use rely on off-line analysis of data (for examples, see Andersson, Malm, Backlund, and Eklund (2005), Czosnyka et al. (1990) and Marmarou, Shulman, and Rosende (1978)). Typically, artificial CSF is injected into the spinal column with a particular flow pattern. The resulting pressure variations are recorded. Following the experiment, certain standard formulas are applied, usually to the portions of the data in which the system has reached a steady state, and a resistance estimate is obtained.

A challenge with off-line estimation is that the physiological disturbances due to vasogenic blood volume variations in the craniospinal system are often large in comparison to the net
external inflow and CSF formation rate. The magnitude of such variations differs a lot between patients. This makes it difficult to choose an appropriate testing period in advance because patients with larger flow variations will require longer tests to achieve a reliable estimate.

Minimizing the test time benefits both the patient, who must endure shorter periods of discomfort, and the hospital, requiring less time of trained nursing staff. An on-line test allows the staff to monitor the progress of the estimated resistance, and end the test when it has converged to a stable value. This can allow shorter tests for patients with small flow variations, whilst ensuring sufficient data has been collected for those with large flow variations.

2. The cerebrospinal fluid system

Cerebrospinal fluid is generated by the body and introduced to the brain cavity at an approximately constant rate (Ekstedt, 1978). It provides physical support for the brain, and is believed to absorb and carry away toxic metabolic byproducts. It leaves the brain cavity by being reabsorbed into the bloodstream in the dural sinuses (Fishman, 1992).

The CSF system is an infinite-dimensional distributed parameter system, however it has been shown experimentally to be well approximated by a finite-dimensional lumped-parameter model in which the intracranial pressure, hereafter denoted \( P_{ic}(t) \), and other variables are assumed to be spatially invariant (Czosnyka, Czosnyka, Momjian, & Pickard, 2004; Marmarou, Shulman, & LaMorgese, 1975; Marmarou et al., 1978; Sivaloganathan, Tenti, & Drake, 1998). In this model, the flow out of the intracranial cavity due to absorption into the bloodstream, \( I_a \), is proportional to the difference between \( P_{ic} \) and the pressure in the dural sinuses, \( P_{ds} \):

\[
I_a(t) = (P_{ic}(t) - P_{ds})/R. \tag{1}
\]

It is the outflow resistance, \( R \), which we wish to estimate. The CSF fluid is essentially incompressible, so a simple conservation of volume equation can be proposed:

\[
\frac{d}{dt} V_{CSF}(t) = I_f + I_{ext}(t) - I_a(t), \tag{2}
\]

where \( V_{CSF}(t) \) is the volume of CSF inside the brain cavity, \( I_f \) is the formation rate of CSF produced by the body, which is assumed constant (Ekstedt, 1978), and \( I_{ext}(t) \) is the external inflow of artificial CSF introduced during the experiment.

The pressure and volume of the brain cavity are related by a pressure-dependent compliance term \( f_c(P_{ic}(t)) \) like so:

\[
f_c(P_{ic}) \frac{d}{dt} P_{ic}(t) = \frac{d}{dt} V_{CSF}(t). \tag{3}
\]

In this paper a compliance function of the following form is assumed:

\[
f_c(P_{ic}) := 1/(k P_{ic}), \tag{4}
\]

where \( k \) is a positive constant, which varies from person to person. This form of compliance is common in the literature, and there exists experimental procedures to determine the value of \( k \), such as the bolus infusion test (Marmarou et al., 1978). In this paper we assume it is available.

We now introduce a new constant, the resting pressure, denoted \( P_r \). It is the steady state pressure reached due to \( I_f \) only:

\[
P_r = I_f R + P_{ds}. \tag{5}
\]

We cannot measure \( P_{ds} \), however \( P_r \) is available, being the value of \( P_{ic}(t) \) when \( I_{ext}(t) = 0 \).

Now, substituting (1), (2), (4) and (5) into (3) we obtain the following nonlinear differential equation for \( P_{ic}(t) \):

\[
\frac{d}{dt} P_{ic}(t) = -\frac{k}{R} (P_{ic}(t))^2 + \left( k I_{ext}(t) + \frac{k P_r}{R} \right) P_{ic}(t). \tag{6}
\]

This is the model we will use to design our observer. In the design we will make use of the fact that the change of variables \( x(t) = 1/P(t) \) and \( \theta = 1/R \) results in the following equation:

\[
\hat{x}(t) = -\hat{P}_{ic}(t)/P_{ic}^2(t) = k\theta - (k I_{ext}(t) + k P_r \theta) x(t). \tag{7}
\]

3. The observer

The objective is to obtain an estimate of the constant \( R \) in real-time, from measurements of the signals \( P_{ic}(t) \) and \( I_{ext}(t) \) and knowledge of the constants \( P_r \) and \( k \). We propose a nonlinear observer which generates coupled estimates of \( P_{ic}(t) \) and \( R \) based on the system (6). It is defined by the following equations\(^1\)

\[
\frac{d}{dt} \hat{x} = -k I_{ext} \hat{x} + \hat{\theta} \left( k - \frac{k P_r}{P_{ic}} \right) + c \left( \hat{x} - \frac{1}{P_{ic}} \right), \tag{8}
\]

\[
\frac{d}{dt} \hat{\theta} = -\gamma \left( k - \frac{k P_r}{P_{ic}} \right) \left( \hat{x} - \frac{1}{P_{ic}} \right), \tag{9}
\]

\[
\hat{P}_{ic}(t) = 1/\hat{x}(t), \quad \hat{R}(t) = 1/\hat{\theta}(t). \tag{10}
\]

The gains \( \gamma \) and \( c \) can be adjusted to tune convergence rates, and must satisfy the following inequalities:

\[
\gamma > 0, \quad c < k I_{ext}(t) - \delta \quad \forall t \geq 0, \tag{11}
\]

for some constant \( \delta > 0 \).

**Remark 1.** It is impossible for \( P_{ic}(t) \) and \( R \) to be anything but positive numbers. In Section 4 it will be proved that \( \hat{x}(t) \) and \( \hat{\theta}(t) \) converge globally and asymptotically to \( 1/P_{ic}(t) \) and \( 1/R \), respectively, and hence \( \hat{P}_{ic}(t) \) and \( \hat{R}(t) \) will eventually be well defined. Although it is possible for \( \hat{x}(t) \) or \( \hat{\theta}(t) \) to cross zero early in the experiment, the experimenter can disregard these values as nonsensical, and wait for the convergence to take its course.

In connection with this observer, we make the following definition:

\(^1\) For the sake of brevity of expression, we will occasionally drop the \( (t) \) arguments from signals.
Definition 1. The persistence of excitation condition is said to hold if there exists positive constants \( \epsilon \) and \( \Delta \) such that
\[
\int_{t}^{t+\Delta_1} (P_{ic}(\tau) - P_r)^2 d\tau \geq \epsilon, \quad \forall t \geq 0.
\] (12)

Remark 2. Roughly speaking, this condition requires that the CSF pressure be different from the resting pressure, except possibly at isolated points. This requirement is intuitive, since if \( P_{ic}(t) \) is equal to \( P_r \), and thus constant, then Eq. (6) reduces to
\[
kI_{ext}(t)P_{ic} = 0,
\] (13)
which implies \( I_{ext}(t) = 0 \), since \( k \) and \( P_{ic} \) are positive. Clearly no information on the resistance can be derived from this relation.

Remark 3. Having nonzero artificial CSF inflow, \( I_{ext}(t) \), is a sufficient condition for (12) to be satisfied.

4. Main theoretical result

Theorem 1. Consider a nonlinear system (6) and an observer (8)–(10). Suppose \( P_{ic}(t) \) satisfies the persistence of excitation condition, and suppose the external inflow signal \( I_{ext}(t) \) and \( P_{ic}(t) \) are bounded functions, with \( P_{ic} \) bounded away from zero:
\[-K_1 \leq I_{ext}(t) \leq K_2, \quad 0 < K_3 \leq P_{ic}(t) \leq K_4, \quad \forall t \geq 0\]
for some numbers \( K_1, K_2, K_3, K_4 \).

If the chosen gains \( \gamma \) and \( c \) satisfy (11) then the states of the observer, \( \hat{x}(t) \) and \( \hat{\theta}(t) \), globally asymptotically converge to 1/\( P_{ic}(t) \) and 1/R, respectively.

Remark 4. The boundedness of the signals \( I_{ext}(t) \) and \( P_{ic}(t) \) is a technical requirement for our proof, and would always be satisfied in practice.

Proof of Theorem 1. Let us first observe that Eq. (6) is the famous Bernoulli equation and can be rewritten as the linear differential equation (7) after a change of variables.

We introduce the error variables \( e = \hat{x} - x, \hat{\theta} = \theta - \hat{\theta} \), and design a standard observer for \( x \) and \( \theta \):}
\[
\dot{\hat{x}} = -kI_{ext}\hat{x} + \hat{\theta}(k - kP_r x) + c(\hat{x} - x), \quad \dot{\hat{\theta}} = v,
\] (14)
where a constant \( c \) and a function \( v \) must be chosen so that the error dynamics
\[
\dot{e} = [c - kI_{ext}] e + (k - kP_r x)\hat{\theta}, \quad \dot{\hat{\theta}} = v,
\] (15)
are globally asymptotically stable. To this end, we introduce the Lyapunov function candidate
\[
V(e, \hat{\theta}) = \frac{1}{2} e^2 + \frac{1}{2\gamma} \hat{\theta}^2.
\]
Differentiating \( V(e, \hat{\theta}) \) along the solution of the error system (15) we obtain
\[
\dot{V} = [c - kI_{ext}] e^2 + \left[ \frac{1}{\gamma} v + (k - kP_r x) e \right] \hat{\theta}.
\]

If we choose \( v \) to be the following function
\[
v = -y(k - kP_r x) e = -y(k - kP_r x)(\hat{x} - x)
\] (16)
then
\[
\dot{V} = [c - kI_{ext}(t)]e^2(t),
\]
and if the constant \( c \) is chosen to satisfy (11), then \( \dot{V} \leq 0 \). It follows that the signals \( e(t) \) and \( \hat{\theta}(t) \) are bounded on \([0, \infty)\). Note that the system is time-varying, so stability cannot be proved using LaSalle’s principle. However, it will now be shown that the persistence of excitation condition guarantees stability.

Integrating the Lyapunov function over an interval \([t_k, t] \) we get the following:
\[
\frac{1}{2} [e^2(t) - e^2(t_k)] + \frac{1}{2\gamma} [\hat{\theta}^2(t) - \hat{\theta}^2(t_k)]
\]
\[
= \int_{t_k}^t \rho(\tau) e^2(\tau) d\tau
\] (17)
with \( \rho(t) = c - kI_{ext}(t) < -\delta \).

From this equation and the boundedness of \( e(t), \hat{\theta}(t), \) and \( \rho(t) \), it follows that \( e(t) \in L_2[0, \infty) \). Furthermore, it follows from (15) that \( \hat{\theta}(t) \) is also bounded. Therefore, it follows from Barbalat’s lemma that \( e(t) \to 0 \) as \( t \to \infty \).

Now, for a particular pair of times \((t_k, T_k)\), Eq. (17) can be rearranged like so:
\[
\hat{\theta}^2(T_k) - \hat{\theta}^2(t_k) = 2\gamma \int_{t_k}^{T_k} \rho(\tau)e^2(\tau)d\tau - \gamma[e^2(T_k) - e^2(t_k)].
\]

Consider an increasing sequence of pairs of times \((t_k, T_k)\), with \( t_k \to \infty \) and \( T_k > t_k \) for each \( k \). Since \( \rho(t) \) is bounded, \( e(t) \in L_2[0, \infty) \) and \( e(t) \to 0 \), the right hand side of the above equation goes to zero as \( t_k \to \infty \). It follows from the Cauchy convergence criterion that \( \hat{\theta}(t) \) converges to a constant value.

It shall now be shown by contradiction that if \( \hat{\theta}(t) \) converges to a constant, it must converge to zero. Suppose that \( \hat{\theta}(t) \to \hat{\theta}^* \neq 0 \) and examine the dynamics of \( \hat{\epsilon}(t) \):
\[
\dot{\hat{\epsilon}}(t) = [c - kI_{ext}(t)]e(t) + k[1 - P_r x(t)]\hat{\theta}(t).
\]

We first note that \( k \) is a positive number, and by the assumption on \( I_{ext}(t), [c - kI_{ext}(t)] \) is bounded, and we have just proved that \( e(t) \to 0 \). Hence, if \( \hat{\theta} \to \hat{\theta}^* \), then
\[
\dot{\hat{\epsilon}}(t) \to k\hat{\theta}^*[1 - P_r x(t)].
\] (18)

Now, the persistence of excitation condition (12) is equivalent to the existence of an \( \epsilon_1 > 0 \) such that
\[
\int_{t}^{t+\Delta} [1 - P_r x(t)]^2 d\tau \geq \epsilon_1, \quad \forall t \geq 0.
\] (19)

Furthermore, it follows from the boundedness of \( P_{ic}(t) \) that \( x(t) \) is bounded, and so it follows from (7) and the boundedness of \( I_{ext}(t) \) that \( |\hat{x}(t)| \) is bounded.

From the boundedness of \( |\hat{x}(t)| \) and (19), it follows that there exists positive constants \( \epsilon_2 \) and \( \Delta_2 \) such that for every \( t > 0 \) there exists an interval \([t_1(t), t_2(t)] \subset [t, t+\Delta] \) of length \( \geq \Delta_2 \),
such that either \([1 - P_r x(t)] < -\varepsilon_2\) or \([1 - P_r x(t)] > \varepsilon_2\) for all \(t \in [t_1(t), t_2(t)]\).

Considering (18), this means that the derivative of \(e(t)\) is always held \(\varepsilon_2\) away from zero over an interval of length \(\Delta_2\). It follows that \(e(t)\) cannot converge to zero. So there is a contradiction, therefore the only possibility is that \(\hat{\theta} = 0\).

It has been proven that \(e \to 0\) and \(\hat{\theta} \to 0\) and therefore \(\hat{x} \to x\) and \(\hat{\theta} \to \theta\). By substituting the formula for \(v\), (16) and changing back to the original coordinates \(P_{ic}(t) = 1/x(t)\) in the observer equations (14) we obtain the observer in Section 3. This completes the proof of the theorem. \(\square\)

5. Experimental results

The observer was tested on an infusion apparatus which was built by the Department of Biomedical Engineering and Informatics at Umeå University Hospital, and is used daily for clinical diagnosis at the Department of Neurology.

In place of the human patient was an experimental set-up consisting of a water tower specifically designed for testing new methods of outflow resistance estimation. The tower has a plexiglass cavity shaped to model a compliance constant of \(k = 0.0889\) ml\(^{-1}\). The resting pressure \(P_r\) was simulated by an overflow tank placed at a level of 10.69 mm Hg. To simulate the various physiological fluctuations, pressure recordings were taken from an INPH patient during lumbar resting pressure measurement. Using the known compliance of the set-up, flow patterns could be calculated which were then incorporated into the set-up using a separate pump.

The outflow resistance was simulated using a T304 stainless steel pipe. The infusion apparatus was connected to the water tower using a double lumen catheter (BD CareflowTM, BD Critical Care Systems Pte Ltd, Singapore), where the two lumens were used for pressure measurement and fluid infusion/withdrawal respectively. A diagram of the water tower is shown in Fig. 1. The inflow pattern, depicted in Fig. 2, was generated in closed loop by a proportional feedback law to regulate the pressure, \(P_{ic}(t)\), to follow a step pattern, in spite of physiological disturbances. This is a standard method of inflow generation used in clinical practice at the University Hospital in Umeå, from which an estimate for \(R\) is calculated using the averaged steady-state values of \(P_{ic}(t)\) and the net flow rate on each level.

The estimates of pressure and outflow resistance generated by the observer are shown in Figs. 3 and 4. The pressure shows the step pattern expected. The resistance estimate converges to the value calculated by an established off-line estimation method.

The experiment begins at \(t = 600\) s, before which the inflow is zero, \(P_{ic}\) equals the resting pressure, and the persistence of excitation condition is not satisfied. The observer was implemented in such a way that evolution of the estimate of \(R\) is halted during such periods to prevent divergence, hence the flat section in Fig. 4.

Fig. 5 shows the difference between the measured pressure value and the pressure value estimated by the observer. Note that the measurement noise in this system is very small. The difference recorded is almost entirely due to the simulated physiological disturbances.

It is important to note that this data comes from a standard infusion test performed for off-line analysis, which runs for about 45 min (2700 s from 600 to 3300 s). The proposed observer can be seen to converge close to the established value in around 15 min (900 s from 600 s to 1500 s).
6. Conclusion

In this paper we have proposed a nonlinear observer which provides on-line estimates of the outflow resistance of the cerebrospinal fluid system.

An on-line system has the potential to make a significant impact on clinical practice, since the large variation in physiological disturbances from person to person makes it difficult to choose in advance a test period for use with off-line estimation methods. Minimizing the time of infusion tests is important for both patient comfort and efficient use of hospital resources.

A proof that the output of the observer converges to an unbiased estimate has been provided. Experiments conducted with a standard diagnostic apparatus and a specially-designed physical model of the human CSF system resulted in the estimate converging in one third the time of the standard test in current clinical use.

The proposed observer will be further validated in a clinical study, and future theoretical development will be focused on the simultaneous estimation of resistance and compliance, and providing second-order statistics of the resulting estimates.

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