A Pseudo-Bayesian Model-Based Approach for Noninvasive Intracranial Pressure Estimation

by

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Submitted to the
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Abstract

A noninvasive intracranial pressure (ICP) estimation method is proposed that incorporates model-based estimation within a probabilistic framework. A first-order subject-specific model of the cerebral vasculature relates arterial blood pressure with cerebral blood flow velocity. The model is solved for a range of physiologically plausible ICP values, and the resulting residual errors are transformed into likelihoods for each candidate ICP. The likelihoods are combined with a multi-modal prior distribution of the ICP to yield an a posteriori distribution whose mode is taken as the final ICP estimate. An extension to this method is proposed to harness the temporal evolution of past ICP estimates for reducing dependence on the multi-modal prior distribution. This approach combines ICP estimates computed with a uniform prior belief with predictions from a single-state model of cerebral autoregulatory dynamics. This method was tested on data from thirteen patients from Boston Children’s Hospital and yielded an ICP estimation bias (mean error or accuracy) of 0.3 mmHg and a root-mean-squared error (or precision) of 5.2 mmHg. These performance characteristics are well within the acceptable range for clinical decision making. The method proposed here therefore constitutes a significant step towards robust, continuous, patient-specific noninvasive ICP determination.

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<tr>
<td>ABP</td>
<td>Arterial blood pressure</td>
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<td>rABP</td>
<td>Radial ABP</td>
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<tr>
<td>cABP</td>
<td>Cerebral ABP</td>
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<td>Cerebral perfusion pressure</td>
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<td>nICP</td>
<td>Noninvasive ICP</td>
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<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
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<td>MCA</td>
<td>Middle cerebral artery</td>
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<td>PMF</td>
<td>Probability mass function</td>
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<td>tGMM</td>
<td>Truncated Gaussian mixture model</td>
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<td>IR</td>
<td>Inverse residual norm</td>
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<tr>
<td>PDA</td>
<td>Prior distribution adaptation</td>
</tr>
<tr>
<td>SaT</td>
<td>Seed and track</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SDE</td>
<td>(Sample) Standard deviation of error</td>
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<td>RMSE</td>
<td>Root mean squared error</td>
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Chapter 1

Introduction

Cerebrospinal fluid (CSF) surrounds and cushions human brain tissue. The hydrostatic pressure of the CSF is called intracranial pressure (ICP), and has classically been considered to range between 5 to 15 mmHg in healthy adults in the supine position [1]. The difference between cerebral arterial blood pressure (cABP) and ICP drives brain tissue perfusion, and thus elevated ICPs can impair cerebral blood flow and may exacerbate or even cause severe neural damage [2]. Such ICP elevations can occur in neuropathological conditions that include hydrocephalus, traumatic brain injury (TBI), hemorrhagic stroke, or brain tumors [2].

The clinical gold standard for ICP measurement involves drilling a hole through the skull to place a catheter into the CSF space. The catheter is connected to an external pressure transducer to measure the ICP relative to the atmosphere. Pressure transducers may also be placed in the parenchyma (brain tissue) with a slight loss in measurement accuracy [3]. Both these approaches are invasive, carry an associated risk of infection [4], and require neurosurgical expertise. ICP measurement is therefore used only for severely ill patients, and a larger pool of patients who may otherwise benefit from direct ICP measurement are not monitored [1]. This has prompted the development of noninvasive ICP (nICP) estimation schemes [4].

Despite significant research effort, reliable and continuous nICP estimation has remained elusive to the extent that authors of a recently published review article stated that 'none of the noninvasive methods demonstrates sufficient accuracy and
ease of use while allowing continuous monitoring in routine clinical use' [4]. Examples of nICP estimation methods include the use of transcranial Doppler (TCD) ultrasound to measure cerebral blood flow velocity (CBFV) indices [5], the application of external pressure on the eyeball to balance tissue pressure with ICP [6], and machine learning based methods [7]. Transcranial acoustic signal properties have been investigated for nICP estimation [8], as have physiologic model-based methods that relate subjects’ cABP with cerebral blood flow (CBF) [1, 9].

Physiologic model-based methods are attractive because in addition to generating nICP estimates, these methods can yield additional interpretable model parameter estimates. Kashif et al., for instance, have proposed an nICP estimation scheme that relates cABP with CBF in the middle cerebral artery (MCA) via a first-order, two-element model [1]. This model has three parameters: resistance to blood flow \( R \), compliance of the blood vessels and brain tissue \( C \), and the ICP \( I \). The authors propose real-time estimation of the \( \{R, C, I\} \) parameter set by using the CBFV as a surrogate for CBF and radial ABP (rABP) as a surrogate for cABP. Then, in addition to measuring the ICP noninvasively, their method yields \( R \) and \( C \) estimates that can assist in monitoring cerebrovascular autoregulation [10]. The training-free nature, combined with the ease of interpretation make the Kashif nICP estimation method very attractive for nICP estimation. There are, however, several challenges in adopting this approach in standard clinical practice. First, the rABP might not always be a faithful surrogate for the cABP since the arterial blood pressure profile can change significantly along the arterial tree [11]. Second, the CBFV waveform cannot often be recorded from the MCA; morphological differences between CBFV signals recorded from different vessels may alter the resulting nICP estimates. Moreover, the TCD probes are often hand-held, and this often leads to artifacts in the CBFV waveforms thereby compounding nICP estimation errors. In addition, there are (varying) time delays between the rABP and CBFV signals because they are recorded by separate devices at two different anatomical locations. Errors due to under-modeling may also contribute to unrealistic nICP estimates.

These challenges have motivated extensions and variations of the original Kashif
nICP estimation method. Fanelli et al. [12], for instance, have proposed a scheme based on the Kashif model that attempts to find an optimal time offset between the rABP and CBFV signals for nICP estimation. In a crucial preprocessing step, the authors also significantly reduce the mean rABP and CBFV levels via passband filtering. Thus, while their method generated accurate nICP estimates on clinical data (root-mean-squared error of 5.7 mmHg), the rationale behind passband filtering is not clear, and there still remains a need to develop robust nICP estimation methods centered around a physiologic model-based approach. This thesis proposes one such framework.

1.1 Proposed approach

In our approach, we employ the two-element Kashif model within a Bayesian framework. Specifically, we use the Kashif model to generate a likelihood distribution over candidate ICPs and possible time offsets between the rABP and CBFV waveforms. This two-dimensional likelihood distribution is then marginalized across the time offsets to generate a one-dimensional likelihood distribution only across the ICPs. This is then combined with an \textit{a priori} belief about the ICP to generate a posterior distribution whose mode is taken as the final nICP estimate.

In this approach, we use a prior distribution that generously models ICPs encountered in standard clinical practice, but that remains static across data records. We have developed a method, denoted the seed-and-track (SaT) approach, to reduce dependency on the static prior distribution. This method functions in a two-step process. A baseline nICP estimate is first established with the prior distribution in place for the initial part of a data record. Next, changes in the nICP are observed with only a uniform prior distribution. These changes are filtered and are subsequently added into the baseline (seed) ICP. The resulting nICP estimates have reduced dependence on the initial prior distribution.

Our proposed nICP estimation framework retains its interpretability due to the underlying physiologic model. Several possible time offsets are considered, which helps
address the challenge posed by unknown (and patient-specific) time offsets between the rABP and CBFV signals. Estimation is performed within a Bayesian framework, which helps increase the method’s resilience to both structured (for example differences between rABP and cABP morphology) and unstructured (for instance artifacts in CBFV signals) error sources.

We used data from thirteen patients from Boston Children’s Hospital (BCH) to validate our method. Initially, we unblinded ourselves to a subset of data from only three of these patients and developed our methodology using only these records. The resulting estimation framework was then tested on the remaining records in a blinded fashion (i.e. no algorithm parameters were altered after the initial development phase). Our proposed scheme achieved an estimation bias of 0.3 mmHg and a root-mean-squared error (RMSE) of 5.2 mmHg compared to invasive, gold-standard ICP measurements. These results are well within clinically acceptable error bounds, bringing us a step closer towards clinical translation of a reliable, continuous, and noninvasive ICP measurement modality.

1.2 Thesis structure

We first review the relevant physiology in Chapter 2. We then develop our proposed quasi-Bayesian approach in Chapter 3 where we employ a static prior distribution. We subsequently present the SaT approach in Chapter 4 before presenting the nICP estimation results with the SaT method on our clinical dataset in Chapter 5. We conclude the thesis in Chapter 6.
Chapter 2

Background

We begin this chapter by discussing relevant concepts of cerebrovascular physiology. This is followed by a brief summary of existing invasive and noninvasive ICP estimation methods. We then discuss the Kashif model and its associated nICP estimation method. We conclude the chapter by describing the clinical and experimental data used for developing and testing our proposed nICP estimation framework along with the preprocessing steps that are applied to these data.

2.1 Cerebrovascular physiology

The human brain is surrounded by CSF that is produced primarily by a specialized vascular mesh, the choroid plexus, that resides within the ventricular space (see Figure 2-1) [13]. In addition to providing mechanical support and buoyancy to brain tissue, the CSF is vital for homeostatic processes within the brain tissue [13]. CSF is one of three major intracranial constituents, with brain tissue and the cerebral vascular network (and the blood it contains) being the other major entities. The cerebral vasculature comprises a dense network of arteries, capillaries, and veins. The major arteries are illustrated in Figure 2-2.

The adult cranium itself is a rigid structure, and this rigidity results in a unique pressure-volume relationship within the intracranial space. This relationship is formally embodied in the Monro-Kellie doctrine that states that the nearly-incompressible
Figure 2-1: Intracranial ventricular spaces. Figure taken from [14].

Figure 2-2: Major cerebral arteries. Figure adapted from [15].

brain tissue is contained within the skull, and that the sum of the volume of intracranial compartments is constant [16]. Then, the ICP – the hydrostatic pressure of the CSF – may be plotted against the change in volume of one intracranial compartment [17]. In animals for example, fluid boluses may be injected inside the skull to produce a curve similar to the one shown in Figure 2-3. Typically, such pressure-volume curves have two regimes – a compensated and a decompensated regime [16]. In the compensated regime, increase of injected fluid is compensated for by decrease of intracranial blood volume, and thus the ICP remains low. The compensatory reserve reduces with increasing volumes of fluid boluses, and the curve transitions into the decompensated regime in which ICP rises steeply in response to even a slight in-
crease of injected volume. Increased ICP can cause or worsen neural damage, and thus it is important to monitor ICPs to ensure that patients do not transition from compensated to decompensated regimes.

Studies have been conducted to establish normal ICP ranges in both adults and in children. In one study, Gilland [18] performed lumbar punctures in fifteen healthy adult volunteers, and reported mean CSF pressures of 14 cmH$_2$O (11 mmHg) with a range from 9 to 20 cmH$_2$O (7 to 15 mmHg). In a subsequent study, Gilland et al. [19] monitored the CSF pressures of 31 healthy volunteers in ten-minute durations via lumbar punctures. They reported a mean pressure of 15 cmH$_2$O$^1$ (11 mmHg) with a range from 8 to 24 cmH$_2$O (6 to 18 mmHg). In this study, the authors also reported that intra-subject coefficients of variation (CV)$^2$ ranged between 3% and 14% for the ten-minute recording durations, whereas the inter-subject CVs for each minute ranged from 22% to 30%. More recently, Whiteley et al. [20] have reported that normal CSF pressures can exceed 20 mmHg in adults.$^3$

In newborn children, Welch [21] measured the ICP in 28 babies who were hospitalized for conditions other than those associated with abnormal ICPs. He reported a mean pressure of 4.5 (3 mmHg) ± 1.2 (SD) cmH$_2$O. The ICPs reported in this study

---

$^1$The authors used 0.15M NaCl whose density is close to that of pure water.

$^2$CV = SD/Mean × 100%

$^3$The studies cited above specifically measure the CSF opening pressure during lumbar puncture and not the ventricular CSF pressure.
Figure 2-4: Histogram of CSF opening pressure in children. Figure from [22].

were estimated by physically orienting the babies such that their fontanels became applanated (flat). At this point, the intracranial pressure was assumed to be at atmospheric pressure. The height from the midpoint of the clavicle to the fontanel was then measured and the associated hydrostatic pressure correction was applied to yield the estimated ICP. In another study, Avery et al. [22] measured the CSF opening pressure in 197 children (between 1 and 18 years of age). The subjects did not have any signs that would indicate abnormal CSF pressure. The authors reported that the 10th and 90th percentiles of measured CSF pressures were 11.5 to 28 cmH2O, respectively (8 and 21 mmHg). Figure 2-4 shows the histogram of opening pressures recorded by these authors.

Elevations beyond the normal ranges reduce cerebral perfusion pressure (CPP) – the difference between cABP and ICP – which can lead to severe cerebral ischemic injury [16]. Elevated ICPs, particularly those exceeding 22 mmHg, are therefore treated aggressively according to current clinical guidelines [23]. This necessitates accurate ICP measurement.

The clinical significance of CPP – and hence accurate ICP – monitoring is further augmented due to the concept of cerebral autoregulation. This concept is illustrated in Figure 2-5 and states that in steady state, CBF remains constant over a wide range of CPPs. This is brought about by vascular smooth muscle that acts on a range of factors including transmural pressure, blood flow, and blood oxygen or carbon dioxide.

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[4] This was assumed to be the point at which the reference venous pressure is at atmospheric pressure.
concentration [10]. Blood vessels dilate as CPP decreases, and they constrict if CPP increases. Below a threshold CPP, the vessels become maximally vasodilated, which then establishes a linear pressure-flow relationship. Likewise, beyond an upper CPP threshold, blood vessels become maximally vasoconstricted, which then leads to a linear pressure-flow regime. Moreover, maintaining CPPs within the autoregulatory range has been shown to correlate with positive patient outcome; treatment options have been suggested that attempt to maintain such CPPs [16]. ICP monitoring, as a result, has attained great clinical significance, and we will now describe existing ICP measurement schemes.

2.2 Existing ICP measurement systems

An external ventricular drainage (EVD) system is the gold-standard ICP measurement method [4]. This is an invasive method in which a catheter is inserted into the ventricular space. The catheter is connected to an external pressure transducer (referenced to the atmosphere) that measures ICP continuously. CSF can also be drained out through the catheter to relieve elevated ICP, and the pressure sensor can be re-calibrated to ensure accurate readings. A downside of the invasive nature of this method is that it can cause infections – infection rates of 5% [3] and 10% [24]
have been previously reported.\textsuperscript{5,6}

Integrated (micro-transducer) sensing devices have been developed as an alternative to EVDs. These devices are predominantly inserted into the parenchyma (brain tissue), and are used by physicians when CSF drainage is not required \textsuperscript{4} or when targeting the ventricular system is complicated by cerebral edema, for example. These all-in-one devices use different sensing principles including fiber-optic \textsuperscript{25} and strain-gauge \textsuperscript{26} methods. Weigand and Richards \textsuperscript{3} have noted that (in children) intraparenchymal devices have lower infection rates than EVDs. Moreover, intraparenchymal micro-transducers have been reported to give measurements that closely match EVD measurements \textsuperscript{4}. Lescot \textit{et al.} \textsuperscript{27}, for example, reported that in a cohort of fifteen patients, the Codman (strain-gauge) device showed a drift of $0.1 \pm 1.6$ (1.96 SD) mmHg per 100 hours of monitoring, relative to EVD measurements, and that the device had an ensemble bias of 0.3 mmHg with limits of agreement (bias $\pm 1.96$ SD) of $-6.7$ and $7.1$ mmHg.

Implantable ICP sensors have also been proposed in the literature \textsuperscript{4,28,29}. Such devices, however, suffer from drawbacks that include drift and have therefore remained largely in the research phase \textsuperscript{4}.

Several noninvasive ICP estimation modalities have also been proposed in prior literature. Levinsky \textit{et al.} \textsuperscript{8} have proposed using transcranial acoustic signals for ICP (mean and pulsatility) estimation. A probe placed in one ear sends out a high frequency signal into the cranium and the attenuated signal is received at the other ear alongside head-generated acoustic signals. Features of the received signals are then extracted and are mapped to mean and pulsatile ICP values.

Increase in optic nerve sheath diameters has been shown to correlate with raised ICP \textsuperscript{30}. Raised ICP causes optic nerve sheath distension that can be detected via ultrasonography to provide spot assessments of acutely raised ICP. Ragauskas \textit{et al.} \textsuperscript{6} have also proposed a novel method wherein external pressure is applied on the eyeball to balance retro-orbital tissue pressure with ICP. This method is suitable for

\textsuperscript{5}Fried \textit{et al.} \textsuperscript{24} have noted that it is difficult to interpret infection rates quoted in the literature owing to varying definitions of infection.

\textsuperscript{6}The risk of infection has been shown to reduce with the use of antibiotic coated catheters \textsuperscript{24}. 

patients with healthy eyes and has an upper ICP measurement limit of around 25 mmHg [4]. Sensitive strain gauges have also been used to detect skull deformations induced by ICP pulsatility [31]. These deformations may be calibrated to provide nICP estimates. Additionally, methods have been proposed that use simultaneous ABP and CBFV recordings to estimate the ICP. These include machine-learning based approaches [7, 32], and also model-based approaches [1, 9].

Models of varying complexities have been developed to describe cerebrovascular hemodynamics. These models include multi-compartment, multi-parameter models [33, 34], that are able to describe complex cerebrovascular behaviors. Representing such complexity, however, comes at the cost of having to specify many model parameters that may be difficult to estimate in a simple, noninvasive, and patient-specific manner. Hu et al. [9], for instance, used a modified version of the model in [34] in conjunction with constrained nonlinear Kalman filters for nICP estimation and prediction. A downside of their proposed method is that it requires an offline training stage in which unknown model parameters must first be estimated from measured ABP, CBFV, and ICP. Kashif et al. [1], in contrast, proposed a two-element model of the cerebral vasculature that lends to a simple, training-free, and patient-specific nICP estimation algorithm. The method proposed in this thesis is based on the Kashif model, and we describe the model in detail in the subsequent section.

2.3 The Kashif model

Figure 2-6 depicts the two-element model of the cerebral vasculature proposed by Kashif et al. [1]. Here, arterial and brain tissue compliances have been lumped into the (dynamically varying) capacitor $C$, and the transmural pressure across the compliance element is set equal to the difference between the cABP, $p_a(t)$, and the ICP, $p_i(t)$. Resistance to blood flow is modeled by the (dynamically varying) resistance $R$. Also, venous pressure is assumed to be lower than the ICP. Thus, in accordance with the Starling resistor phenomenon [35], the pressure at the resistive termination is also set equal to $p_i(t)$. CSF production and absorption mechanisms have been ig-
Figure 2-6: Two-element model developed in [1]. cABP is represented as \( p_a(t) \), CBF as \( q(t) \), and \( R \) and \( C \) represent time-varying flow resistance and vascular/brain-tissue compliance, respectively. ICP is represented by \( p_i(t) \).

In this model, these processes happen over much longer timescales than the beat-to-beat time scales considered here. Within the context of the model, \( p_a(t) \) is related to \( q(t) \) according to

\[
q(t) = \frac{1}{R} (p_a(t) - p_i(t)) + C \frac{d}{dt} (p_a(t) - p_i(t))
\]  

(2.1)

This defining relation forms the basis of the Kashif nICP estimation algorithm that is presented next.

2.4 The Kashif nICP estimation algorithm

Kashif et al. make a series of simplifying assumptions to develop their model-based nICP estimation scheme. First, the ICP is assumed to be constant (= \( I \)) during an estimation window. Moreover, rABP is used as a surrogate for cABP since the latter cannot be obtained noninvasively in clinical practice. The CBF cannot be obtained noninvasively either, and thus the CBFV, \( q_v(t) \), is used as a substitute for CBF. Assuming that \( q(t) = \alpha q_v(t) \) over an estimation window, where \( \alpha \) is a constant
scaling factor, and substituting this into Equation 2.1,

\[ q_v(t) = \frac{1}{\alpha R'} (p_a(t) - I) + \frac{C'}{\alpha} \frac{d}{dt} (p_a(t) - I) \]

\[ = \frac{1}{R'} (p_a(t) - I) + C' \frac{d}{dt} (p_a(t) - I) \]

(2.2)

where \( R' \) and \( C' \) are scaled versions of \( R \) and \( C \). This shows that \( q_v(t) \) can indeed be used as a substitute of \( q(t) \). This scale invariance also suggests that small variations in TCD insonation angles only scale the resistance and compliance parameters without affecting the ICP, \( I \), to the extent that the two-element model is a reasonable approximation of the relevant cerebrovascular physiology. Thus, the Kashif method remains unaffected by variations in insonation angle as long as this angle is held constant over each estimation window.

With these assumptions, the ICP can be estimated in a three-step process. First, the compliance, \( C' \), is estimated by assuming that the blood flow through the resistor is negligible during the systolic pressure upstroke. As shown in Figure 2-7, we denote \( t_b \) and \( t_e \) as the starting and ending times of systole. Then,

\[ C'[p_a(t_e) - p_a(t_b)] = \int_{t_b}^{t_e} q_v(t) \, dt \]

(2.3)

An estimate \( \hat{C}' \) of \( C' \) can then be computed over a \( K \)-beat estimation window by stacking \( K \) such equations and solving for \( C' \) in a least-squared-error manner. Next, the resistance, \( R' \), is estimated by computing an estimate of the flow velocity through the resistance, \( \hat{q}_v^{R'}(t) = q_v(t) - \hat{C}' \frac{d}{dt} p_a(t) \). Since \( I = p_a(t) - R' \hat{q}_v^{R'}(t) \) and \( I \) is assumed constant over one estimation window, Kashif et al. evaluate \( \hat{q}_v^{R'}(t) \) at two time intervals \( t_1 \) and \( t_2 \)

\[ R' \left( \hat{q}_v^{R'}(t_1) - \hat{q}_v^{R'}(t_2) \right) = p_a(t_1) - p_a(t_2) \]

(2.4)

Again, a least-squared-error estimate \( \hat{R}' \) of \( R' \) can be computed over the \( K \)-beat
estimation window. Finally, the ICP can be estimated according to

\[
\hat{I} = \overline{p_a(t)} - \overline{R^v} \times \overline{q^v_b(t)}
\]  

(2.5)

where the overbars indicate time averaging over the data window.

The Kashif nICP estimation algorithm is attractive as it is model-based and nominally requires no training. Moreover, the model itself is extremely simple and leads to an elegant estimation algorithm. Kashif et al. validated this method using 35 hours of data from 37 patients, all suffering from traumatic brain injury (TBI). The authors computed nICP estimates in sixty-beat data windows, and achieved an estimation bias of 1.6 mmHg with an SDE of 7.6 mmHg. These results are extremely encouraging, particularly because the invasive reference ICPs exhibited significant variability (see Figure 2-8). The authors, however, did not have access to the height differences between the ICP and rABP pressure transducers, and thus they were unable to account
Figure 2-8: Distribution of ICPs in data used by Kashif et al. [1]. Data from 36 out of 45 records used by Kashif et al. were available.

for the hydrostatic pressure offset between rABP and ICP measurements. Moreover their data was recorded solely from TBI patients, and thus, they were unable to gauge their method’s performance on a wider range of pathologies.

A downside of the simplified nature of the Kashif model is that it may not capture all relevant signal dynamics or may not apply equally as well across different pathologies. Thus, under-modeling errors may creep into the nICP estimates. Also, this method generates point estimates of the ICP. It would be desirable, however, to also have associated metrics of estimation confidence. Certain additional challenges in applying this method to clinical data include:

- TCD devices measure the blood flow velocity in a cerebral blood vessel, and ideally an nICP estimation system should use a collocated ABP measurement. Such measurements are not possible noninvasively with current technology, and the Kashif estimation algorithm uses the rABP waveform instead. The human ABP waveform profile, on the other hand, changes along the arterial tree due to wave reflections from arterial branching sites, vessel taper, and terminal (arteriolar) impedance mismatch [11]. Thus, the rABP might not faithfully represent the cABP morphology. This could lead to nICP estimation errors.

- A related challenge is that it is not always possible to record CBFV signals
from the desired vessel (MCA). Lack of suitable acoustic windows (regions of the skull that allow ultrasound signals to propagate to and from the MCA), for instance, renders CBFV monitoring difficult to impossible in nearly 10% of individuals. This prevalence increases with increasing age [36]. Like ABP, the CBFV flow profiles also change with measurement location [11]. Thus obtaining the measurement location that is most conducive to accurate nICP estimation in a given individual remains a challenge.

- There is an unknown time delay between the rABP and the CBFV signals. This is because of two reasons: the signals are recorded by two separate devices that introduce independent processing delays; and, finite ABP wave propagation speeds imply that there is a physiologically induced time delay between the ABP waveform arriving at the MCA and the ABP waveform at the radial artery. While the device-induced delays can be measured and subsequently accounted for, the physiologically-induced time delays are patient-specific. Not accounting for these time delays can also lead to significant nICP estimation errors.7

- The Kashif algorithm involves differentiating the ABP signal (via finite differencing) in order to obtain \( \widehat{q}_{y} \). Clinically obtained ABP signals may contain noise that will be amplified by these differencing operations. This can worsen nICP estimation errors.

- The noisy nature of the CBFV signals poses yet another challenge. Human operators must manually position TCD transducers over narrow cranial acoustic windows and even the slightest movement can lead to severe artifacts in the derived CBFV (Figure 2-9). Moreover, it is worthwhile to note that the CBFV is derived from the spectrogram of the received TCD ultrasound signal [37] in a process that may involve several non-linear operations including hard thresholding and median filtering. Thus, the TCD CBFV estimates might not be faithful representations of the true maximum CBFV profiles, and the non-linear trans-

7Kashif et al. proposed aligning CBFV peaks with inflection points of the ABP systolic upstroke as a possible signal alignment strategy.
formations may make the estimated CBFV waveform envelope a non-smooth function of the backscattered ultrasound signal. This may further compound nICP estimation errors.

These challenges have prompted modifications to the original Kashif nICP estimation scheme. Frequency-domain solutions have been proposed to overcome time misalignment challenges [38, 39]. Most recently, Fanelli et al. [12] have proposed a time-domain modification to the Kashif algorithm that attempts to resolve the time misalignment challenge.

Fanelli et al. identify points where the rate of change of pressure, \( \frac{dp_a}{dt} \), for some small \( \epsilon \), is

\[ p_a(t) \approx R'_t \times q_a(t) + I \]  

(2.6)

The authors then fit a straight line over the selected points, and the y-intercept is taken as the ICP estimate. Moreover, the authors scan over a range of time delays between the rABP and the CBFV signals, and select the time delay that minimizes the variance in the least-squared error fit of Equation 2.6. This is a potential solution for the signal misalignment issue. The authors computed nICP estimates on nearly three hours of data from three patients. Although their data had limited ICP variability (it rarely exceeded 25 mmHg), that they achieved an estimation bias of \(-1.1\) mmHg, an SDE of 5.6 mmHg, and an RMSE of 5.7 mmHg is highly encouraging.
A downside of this method, however, is that the authors filter both $p_o$ and $q_o$ through an 80-tap passband FIR filter with cutoff frequencies at 0.5 and 12 Hz prior to nICP estimation. The rationale for applying this passband filter is not entirely clear. One possible explanation is that the filtered rABP better approximates cABP. The DC gain of this filter, however, is 0.66 and a reduction in mean ABP by 40% seems non-physiological. Likewise, the reason for reducing the mean CBFV levels is also not clear. Hence, a technique that can produce comparable results without such filtering is still desirable.

One possible solution is to merge the model-based estimation approach with a probabilistic estimation framework. This can potentially introduce robustness in the resulting nICP estimates whilst retaining the physiologic interpretability offered by the model-centric paradigm. We propose one such method in this thesis. In our approach, we employ a discrete-time equivalent of the Kashif model to generate a likelihood distribution across a range of plausible ICP and time offset pairs. This distribution is subsequently marginalized across the time offsets and the resulting one dimensional likelihood distribution is combined with a preset prior belief about the ICP. We found that point estimates of the resulting a posteriori distributions are more robust nICP estimates than the point estimates of the likelihood distributions alone. In our initial approach, we held the prior distribution static over time. This can, however, limit the range of ICPs that can be reliably measured. Consequently, we developed a technique that helps reduce the dependence on the prior distribution, thereby increasing the range of ICPs that can be estimated over long recording durations. We tested this proposed approach on clinical and experimental data that were first preprocessed to extract noise-free segments. We describe the preprocessing stage next. This is followed by a description of our data.

## 2.5 Data preprocessing

Prior to nICP estimation, we applied a uniform set of preprocessing steps to all our data. A detailed description of these preprocessing steps is provided in Fanelli et al.
[40], and we only provide a summary here. First, a coarse time alignment step was applied between the rABP and the CBFV signals to account for time delays introduced by different measurement devices. This time offset was obtained by computing the cross-correlation between the rABP and the CBFV signals, and the lag with the highest cross-correlation coefficient was selected as the desired offset. Following this time offset correction step, the signals were resampled to a common 125 Hz to compensate for any underlying sampling frequency discrepancies. Finally, the baseline rABP was adjusted to account for differences in ICP and ABP transducer heights. These grossly time-aligned, height-corrected, and resampled signals were then passed to an additional noise filtering stage that is described next.

2.5.1 Signal pre-filtering

We incorporated a signal pre-filtering stage (Figure 2-10) into our method to guard against potential out-of-band noise. In our method, the ABP and CBFV trends are first extracted via a 256-tap moving-average filter.9 These trends are subtracted from the ABP and CBFV signals, respectively, and the resulting detrended signals are filtered by a 128-tap bandpass filter with cutoffs at 0.5 and 16 Hz. The trend removed in the first stage is then added back to the filter output to restore the original DC levels. This pre-filtering stage attenuates out-of-band signal noise only, and in-band noise is not eliminated. We developed a method to quantify the degree of in-band signal noise. This metric, denoted the waveform distortion metric, is described next.

2.5.2 Waveform distortion metric

Our simple waveform distortion metric assigns a flag to individual data windows. By default, we used non-overlapping twenty-beat data windows in this thesis. An estimation window is marked as noisy if the cross-correlation coefficient between any

---

8 A 5 mmHg hydrostatic pressure correction was applied when the transducer heights were not available.
9 MATLAB's \texttt{filtfilt} routine was used.
of the corresponding ABP and CBFV beats is below a threshold, $\xi$, set to 0.2. Figure 2-11 illustrates this procedure schematically and Figure 2-12 shows an example of the estimation windows marked as noisy in this manner. We will use this metric later in Chapter 4, when we track temporal changes in the ICP.

2.6 Data sources

We used two datasets for method development and validation. The first dataset was collected from pediatric patients at Boston Children’s Hospital (BCH), while the second was collected from five healthy male volunteers undergoing head-up tilt experiments at MIT. Details of the respective data collection protocols are presented in the following sections.

2.6.1 Boston Children’s Hospital

Data were collected at Boston Children’s Hospital (BCH) between February 2015 and June 2017. The data collection protocols were approved by the relevant Institutional Review Boards (IRB) at BCH and MIT, and informed consent was obtained from patients or their surrogates prior to data collection. Individual recording sessions lasted for nearly twenty minutes. Subjects’ rABP, CBFV, and (invasively measured)
ICP were recorded simultaneously. Important metadata including height differences between the location of the ICP and rABP transducers were also recorded for each recording session. Twenty data segments were manually extracted from three subjects (1, 7, and 14) for method development purposes. Data from the remaining patients were set aside for method validation.\textsuperscript{10} Table 2.1 summarizes the patient information for both development and validation datasets. Moreover, recording durations\textsuperscript{11} and the percentage of usable data\textsuperscript{12} are summarized in Tables 2.2 and 2.3.

\textsuperscript{10}Noise free data segments of the validation data were extracted automatically via an in-house software routine developed by Dr. Andrea Fanelli. This scheme selects extracts data segments in which both the ABP and CBFV signals are trustworthy.

\textsuperscript{11}CBFV signal durations were taken as the recording durations.

\textsuperscript{12}Fraction of records that was marked non-noisy by the in-house software.
Figure 2-12: Illustration of waveform distortion detection performance for $\xi = 0.2$. ABP and CBFV for a recording are plotted in (a) and (b), respectively. Estimation windows flagged as noisy are drawn in red, with dashed lines denoting window boundaries. ABP and CBFV of the two highlighted windows are plotted in (c) and (d), respectively.

2.6.2 Tilt-table experiments

We obtained noninvasive arterial blood pressure and CBFV recordings from five healthy adult volunteers who underwent head-up tilt experiments at MIT. Blood pressure was recorded noninvasively with the Nexfin monitor [41] that uses an inflatable finger cuff to obtain estimates of acral (finger) ABP that are then mathematically transformed to brachial arterial pressure [41, 42]. While we did not record invasive reference ICP measurements in this protocol, we expected that healthy adults in a supine position would have ICPs in the range $[10, 15]$ mmHg, and, that their ICPs would drop [43] to $[0, 5]$ mmHg during each head-up tilt.

Recording began with the subjects in the supine posture. The subjects were then raised to a head-up position after ten minutes, where they stayed for ten additional
Table 2.1: BCH patient demographics

<table>
<thead>
<tr>
<th>Subject</th>
<th>Gender</th>
<th>Age (Yrs)</th>
<th>Diagnosis</th>
<th>GCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>12</td>
<td>Stroke</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>16</td>
<td>Traumatic brain injury</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>14</td>
<td>Stroke</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>2</td>
<td>Hemorrhage</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>11</td>
<td>Brain tumor</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>18</td>
<td>Intraventricular hemorrhage</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>20</td>
<td>Hydrocephalus</td>
<td>14</td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>11</td>
<td>Traumatic brain injury</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>Male</td>
<td>7</td>
<td>Traumatic brain injury</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>Female</td>
<td>6</td>
<td>Hydrancephaly/Hydrocephalus</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>Male</td>
<td>4</td>
<td>Cerebrohepatopathy</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>Male</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>Male</td>
<td>25</td>
<td>Chiari malformation</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2.2: BCH data summary: Manually extracted data for development

<table>
<thead>
<tr>
<th>Subject</th>
<th>Recording sessions used for development</th>
<th>Data duration (hr:min)</th>
<th>[Min., Max.] ICP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>01:31</td>
<td>[11, 21]</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>00:40</td>
<td>[7, 10]</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>00:51</td>
<td>[9, 15]</td>
</tr>
<tr>
<td>Ensemble</td>
<td>11&lt;a</td>
<td>03:02</td>
<td>[7, 21]</td>
</tr>
</tbody>
</table>

*aComprise twenty data segments.

minutes. They were lowered down and the process was repeated again. The subjects’ hands were strapped to their chests at heart level throughout the duration of the recording thus ensuring that the distance from the Nexfin cuff to the tragus remained constant. This distance was recorded for each subject and was used subsequently to account for the hydrostatic pressure offset introduced by measuring the blood pressure at the chest level, rather than at the level of the tragus.

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### Table 2.3: BCH data summary: Automatically extracted noise-free data for testing

<table>
<thead>
<tr>
<th>Subject</th>
<th>Recording sessions</th>
<th>Total recording duration (hr:min)</th>
<th>Noise-free data duration (hr:min)</th>
<th>[Min., Max. ICP (mmHg)]&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
<td>12:03</td>
<td>02:19 (19%)</td>
<td>[8, 22]</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>02:25</td>
<td>00:44 (30%)</td>
<td>[9, 12]</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>01:43</td>
<td>00:21 (20%)</td>
<td>[7, 12]</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>01:15</td>
<td>00:25 (33%)</td>
<td>[8, 16]</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>01:31</td>
<td>00:09 (10%)</td>
<td>[5, 11]</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>02:17</td>
<td>00:26 (19%)</td>
<td>[8, 25]</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>03:35</td>
<td>00:27 (13%)</td>
<td>[8, 20]</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>00:23</td>
<td>00:08 (35%)</td>
<td>[6, 14]</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
<td>02:51</td>
<td>00:41 (24%)</td>
<td>[4, 21]</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>00:06</td>
<td>00:01 (17%)</td>
<td>[7, 7]</td>
</tr>
<tr>
<td>11</td>
<td>4</td>
<td>02:57</td>
<td>00:42 (24%)</td>
<td>[0, 16]</td>
</tr>
<tr>
<td>12</td>
<td>2</td>
<td>01:00</td>
<td>00:31 (52%)</td>
<td>[4, 8]</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
<td>00:22</td>
<td>00:10 (45%)</td>
<td>[4, 13]</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>57</strong></td>
<td><strong>32:28</strong></td>
<td><strong>07:05 (22%)</strong></td>
<td><strong>[0, 25]</strong></td>
</tr>
</tbody>
</table>

<sup>a</sup>Outliers excluded manually.

#### 2.7 Summary

This chapter provided a review of cerebrovascular physiology pertinent to ICP monitoring. We then reviewed existing ICP measurement techniques where we focused primarily on model-based nICP estimation. We outlined several challenges in applying such methods to clinical data thereby motivating our proposed approach. In the next part of the chapter we outlined the preprocessing steps that are applied to our data prior to nICP estimation. We also described the clinical and experimental data that we used for developing and validating our proposed approach. We will develop our proposed approach over the course of the next two chapters.
Chapter 3

Model-based, pseudo-Bayesian nICP estimation

We begin this chapter by formulating a discrete-time model of the relevant cerebrovascular physiology. Next, we develop an nICP estimation method based on this model. We show that this method generates nICP estimates with an acceptably low bias but with a clinically unacceptably wide standard deviation of error (SDE). This then leads to our formulation of the Bayesian estimation framework that is subsequently developed, and its possible design choices are discussed. We then present the nICP estimation results on both our clinical training data and on data from tilt-table experiments. The chapter concludes with analyses of the method’s sensitivity to signal noise, and to changes in the prior distribution.

3.1 Discrete-time model of the cerebral vasculature

In our nICP estimation approach of Section 3.2, we obtain least-squared-error estimates of the $R'$ and $C''$ parameters of the Kashif model (Equation 2.2). To obtain these estimates, we first convert the Kashif model into an equivalent discrete-time model. This can be done by approximating the derivative operation with backward
finite-differences so that

\[ q_v(nT) = \frac{1}{R'} [p_a(nT) - p_i(nT)] + \frac{C'}{T} [p_a(nT) - p_a((n - 1)T) - p_i(nT) + p_i((n - 1)T)] \]

where \( n \) is the sampling index, \( T \) is the sampling interval (= 8 ms for data sampled at 125 Hz), \( q_v \) is the CBFV, \( p_a \) is the ABP, and \( p_i \) is the ICP. Denoting the sampling instants with square brackets, we express our model as

\[ q_v[n] = \frac{1}{R'} (p_a[n] - p_i[n]) + \frac{C'}{T} (p_a[n] - p_a[n - 1] - p_i[n] + p_i[n - 1]) \]

\[ = b_0 (p_a[n] - p_i[n]) + b_1 (p_a[n - 1] - p_i[n - 1]) \]  \hspace{1cm} (3.1)

where \( b_0 = \frac{1}{R'} + \frac{C'}{T} \) and \( b_1 = -\frac{C'}{T} \).

Equation 3.1 is our desired model, and we will employ it in our nICP estimation algorithm in the next section. Before proceeding to that section, however, we note that this model may be extended to an arbitrary order by increasing the number of poles and zeros. Such a model would be of the form

\[ q_v[n] = \sum_{k=1}^{K} a_k q_v[n - k] + \sum_{l=0}^{L} b_l (p_a[n - l] - p_i[n - l]) \]  \hspace{1cm} (3.2)

where the higher-order poles and zeros may be used to overcome undermodeling limitations. The nICP estimation schemes developed in this thesis can potentially be adapted to such higher-order models. We continue to use the first-order model, however, due to its physiological relevance and interpretability, and because the increasing degrees of freedom associated with higher-order models might make the resulting nICP estimates more sensitive to signal noise.
3.2 nICP estimation using the discrete-time model

We formulate our nICP estimation scheme by assuming that the ICP is equal to its mean in each estimation window, $I$, such that

$$p[n] \approx I$$

(3.3)

Substituting Equation 3.3 into Equation 3.1,

$$q_v[n] = b_0 (p_a[n] - I) + b_1 (p_a[n-1] - I)$$

(3.4)

In accordance with clinical practice, we now define the cerebral perfusion pressure, $p_c'[n] = p_a[n] - I$, and substitute $p_c'[n]$ in the expression above to obtain

$$q_v[n] = b_0 p_c'[n] + b_1 p_c'[n-1]$$

(3.5)

This equation assumes that we have access to the true cABP. In our method, however, we use rABP as a surrogate for cABP and thus we must account for possible time offsets between the recorded CBFV and rABP signals. To do so, we define the model $M_{I,d}$ where $q_v[n]$ is shifted by $d$ samples relative to the $p_c'[n]$.

$$M_{I,d} := q_v[n - d] = b_0^{I,d} p_c'[n] + b_1^{I,d} p_c'[n-1]$$

(3.6)

Then, for a range of physiologically plausible ICPs and time offsets, we compute least-squared-error estimates, $\hat{b}_k^{I,d}$, for the corresponding model, $M_{I,d}$. We start from $I = I_s$, where $I_s$ is set to $-10$ mmHg. This is because negative ICPs are physiologically possible, though quite rare, for patients in the supine posture. $I$ is increased in increments of $\Delta I = 1$ mmHg – a granularity deemed sufficient for clinical diagnostic and treatment purposes – and is stopped upon reaching the mean blood pressure, $\overline{p_a}$, because the mean ICP cannot exceed the mean ABP. Next, to determine the time offset range, we first detect the systolic and diastolic indices of the ABP and CBFV waveforms. Then, for each estimation window, we define the median samples
Figure 3-1: Illustration of time offset range formation. Systolic indices of the ABP and CBFV are marked by blue and red triangles, respectively. Diastolic indices of the ABP are marked by blue squares. $\Delta N_{rel}$ is the median offset from red to blue triangles.

It takes for the ABP wavelets to rise from their inflection points to their peak systolic values

$$N_{\text{rise,a}} = \text{median}(n_{\text{sys,a}} - n_{\text{dia,a}})/2$$

where $n_{\text{sys,a}}$ and $n_{\text{dia,a}}$ are the systolic and diastolic sampling indices of the ABP waveform in the estimation window, and the results are rounded to the nearest integer. Likewise, we define the offset (in samples) between the ABP and CBFV waveforms (see Figure 3-1) as

$$\Delta N_{rel} = \text{median}(n_{\text{sys,a}} - n_{\text{sys,q}})$$

where $n_{\text{sys,q}}$ are the systolic sampling indices of the corresponding CBFV waveform in that estimation window.\(^1\) Then, as illustrated in Figure 3-2, we vary $d$ in the range

$$d = \{\Delta N_{rel} - (N_{\text{rise,a}} - 1), \Delta N_{rel} - (N_{\text{rise,a}} - 2), \ldots, \Delta N_{rel} - 1\}$$

The individual least-squared-error estimates, $\hat{b}_k^{l,d}$, are then computed as

---

\(^1\)We detected diastolic points of the ABP signal using the *wabp* function [40], and then detected the ABP systolic indices by searching for peaks in the vicinity of the diastolic points. The diastolic and systolic indices of the CBFV waveform were then detected by searching in the vicinity of the corresponding ABP indices.
Figure 3.2: Time offset range. The input ABP and CBFV waveforms are plotted in blue and red, respectively, and the range over which the CBFV signal is shifted is plotted as a red band.

\[ \hat{b}^{I,d} = (\Phi^T \Phi)^+ \Phi^T q_v^d \]

where \( q_v^d = [q_v[2-d], ..., q_v[N-d]]^T \)

\[ \Phi^I = \begin{bmatrix} p_c[2] & p_c[1] \\ \vdots & \vdots \\ p_c[N] & p_c[N-1] \end{bmatrix} \]

\[ \hat{b}^{I,d} = \begin{bmatrix} \hat{b}_0^{I,d}, \hat{b}_1^{I,d} \end{bmatrix}^T \]

Here, the \(^+\) symbol represents a matrix pseudo-inverse. Also, for each \( M_{I,d} \), the corresponding predicted flow velocity, \( \hat{q}_0^{I,d} = \Phi^I \hat{b}^{I,d} \), the residual-error vector, \( \zeta^{I,d} = \hat{q}_0^{I,d} - q_v^d \), and the \( l_2 \) error norms, \( \zeta^{I,d} = \| \zeta^{I,d} \|_2 \) are computed.

We then select the \((I, d)\) pair that produces the smallest \( \zeta^{I,d} \) as our final nICP and time offset such that

\[ (\hat{I}_{ML}, \hat{d}_{ML}) = \arg\min_{I, d} \zeta^{I,d} \]

(3.11)

Also, we use \( \hat{b}_0^{ML}, \hat{d}_{ML} \) to compute the resistance and compliance estimates

\[ \hat{R}' = \left( \hat{b}_0^{ML}, \hat{d}_{ML} + \hat{b}_1^{ML}, \hat{d}_{ML} \right)^{-1} \]

(3.12)

\[ \hat{C}' = -T \hat{b}_1^{ML}, \hat{d}_{ML} \]

(3.13)

This procedure is illustrated in Figure 3.3 for one estimation window; the parameters
used in this method are tabulated in Table 3.1.

![Diagram showing nICP estimation using the discrete-time cerebral vasculature model. Segments of ABP and CBFV are passed to the model. The model coefficients $b_k$ are then solved for a range of physiologically plausible ICPs and time offsets. The corresponding model-predicted flow velocities for three ICP and time offset pairs are shown in red, overlaid on top of the actual flow-velocity (gray). (b) The residual-error curves across the ICPs and time offsets are shown. Minima at each time offset are drawn in red. (c) Top view of the minima from (b). The final ICP estimate, $\hat{I}_{ML}$, corresponding to the smallest $\zeta^I, d$, is drawn in green, and the actual ICP is plotted in black.]

Table 3.1: ICP scan range parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I_s$</td>
<td>-10.0</td>
<td>mmHg</td>
</tr>
<tr>
<td>$\Delta I$</td>
<td>1.0</td>
<td>mmHg</td>
</tr>
</tbody>
</table>
Table 3.2: nICP estimation results on clinical training data.

<table>
<thead>
<tr>
<th>Estimation windows</th>
<th>Bias</th>
<th>SDE</th>
<th>RMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>715</td>
<td>2.0</td>
<td>13.4</td>
<td>13.5</td>
</tr>
</tbody>
</table>

Figure 3-4: nICP estimation results for one data record. The ICP waveform, the mean ICP, and the nICP estimates are plotted in gray, black, and red, respectively.

3.2.1 nICP estimation results

We computed nICP estimates for our training data in non-overlapping windows of twenty cardiac beats. The resulting estimation bias, SDE, and RMSE for the resulting 715 estimation windows are listed in Table 3.2. The nICP estimates for one record are plotted in Figure 3-4 and histograms of the estimated model parameters are plotted in Figure 3-5. These results indicate that while the estimation bias of this method is acceptably small, there is a relatively large SDE. Also, the histograms in Figure 3-5 indicate that while the resistance estimates are positive, the compliance estimates can be negative for some estimation windows, which is not physiologically reasonable. This may happen when $\hat{b}_{0,ML} > 0$ and $\hat{b}_{1,ML} > 0$, or when $\hat{b}_{0,ML} < 0$ and $\hat{b}_{1,ML} > 0$. The occurrence counts of such estimation windows are listed in Table 3.3. Moreover, we stratified the estimation bias, SDE, and RMSE according to the signs of the compliance estimates. These are presented in Table 3.4.

To further investigate estimation windows with negative estimated compliances, we computed representative CPP and CBFV wavelets corresponding to the cases with positive and negative compliance estimates. Specifically, we selected the CPP
Figure 3-5: Histograms of the estimated model coefficients, $\hat{b}_0^{\text{ML}}, \hat{d}_0^{\text{ML}}, \hat{b}_1^{\text{ML}}, \hat{d}_1^{\text{ML}}$, and the derived resistance and compliance estimates.

The cardiac beats in each estimation window were then demeaned and were normalized to unit pulsatility. We averaged the resulting beats together, sample-by-sample, to yield representative ABP and CBFV beat pairs for each estimation window. Finally, ABP and CBFV beat pairs corresponding to estimation windows with $\hat{b}_0^{\text{ML}}, \hat{d}_0^{\text{ML}} > 0$ and $\hat{b}_1^{\text{ML}}, \hat{d}_1^{\text{ML}} > 0$ were resampled to the same length and were averaged to yield a representative beat pair. The process was repeated for estimation windows with $\hat{b}_0^{\text{ML}}, \hat{d}_0^{\text{ML}} > 0$ and $\hat{b}_1^{\text{ML}}, \hat{d}_1^{\text{ML}} < 0$ to yield a complementary beat pair, and these are plotted in Figure 3-6.

---

We manually inspected the two estimation windows with $\hat{b}_0^{\text{ML}}, \hat{d}_0^{\text{ML}} < 0$ and $\hat{b}_1^{\text{ML}}, \hat{d}_1^{\text{ML}} > 0$. One of these had very noisy CBFV, and the other was a borderline case with a slightly negative $\hat{b}_0^{\text{ML}}, \hat{d}_0^{\text{ML}} = -0.05 \text{ cm/s} \cdot \text{mmHg}$, and with $\hat{b}_1^{\text{ML}}, \hat{d}_1^{\text{ML}} = 1.0 \text{ cm/s} \cdot \text{mmHg}$. 

---
Table 3.3: Per-patient occurrence frequency of estimation windows with positive and negative compliance estimates. Signs of $\hat{\theta}_0^{ML}, \hat{\delta}_{ML}$ and $\hat{\theta}_1^{ML}, \hat{\delta}_{ML}$ are indicated in parentheses.

<table>
<thead>
<tr>
<th>Patient</th>
<th>$\hat{C}' &gt; 0$</th>
<th>$\hat{C}' &lt; 0$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$(+, -)$</td>
<td>$(-, -)$</td>
</tr>
<tr>
<td>1</td>
<td>410 (100%)</td>
<td>1 (0%)</td>
</tr>
<tr>
<td>7</td>
<td>79 (65%)</td>
<td>42 (34%)</td>
</tr>
<tr>
<td>14</td>
<td>177 (98%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Ensemble</td>
<td>666 (93%)</td>
<td>47 (7%)</td>
</tr>
</tbody>
</table>

Table 3.4: nICP estimation bias, SDE, and RMSE (mmHg) stratified by windows with positive and negative compliances. Signs of $\hat{\theta}_0^{ML}, \hat{\delta}_{ML}$ and $\hat{\theta}_1^{ML}, \hat{\delta}_{ML}$ are indicated in parentheses, respectively.

<table>
<thead>
<tr>
<th>Patient</th>
<th>$\hat{C}' &gt; 0$</th>
<th>$\hat{C}' &lt; 0$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$(+, +)$</td>
<td>$(-, +)$</td>
</tr>
<tr>
<td>1</td>
<td>$(5.1, 12.3, 13.3)$</td>
<td>$(-21.7, 0.0, 21.7)$</td>
</tr>
<tr>
<td>7</td>
<td>$(5.0, 14.4, 15.2)$</td>
<td>$(-11.0, 11.9, 16.1)$</td>
</tr>
<tr>
<td>14</td>
<td>$(-2.9, 11.6, 11.9)$</td>
<td>$(-24.5, 0.2, 24.5)$</td>
</tr>
<tr>
<td>Ensemble</td>
<td>$(3.0, 12.9, 13.2)$</td>
<td>$(-12.4, 12.0, 17.1)$</td>
</tr>
</tbody>
</table>

Figure 3-6: Representative ABP (blue) and CBFV (red) beat pairs and their unit SD bounds for estimation windows with (a) positive $\hat{\theta}_0^{ML}, \hat{\delta}_{ML}$ and negative $\hat{\theta}_1^{ML}, \hat{\delta}_{ML}$, and (b) positive $\hat{\theta}_0^{ML}, \hat{\delta}_{ML}$ and positive $\hat{\theta}_1^{ML}, \hat{\delta}_{ML}$.
3.2.2 Discussion

The results in the previous section show that the estimated compliance tends to be positive for estimation windows where the CBFV beats resemble high-pass filtered versions of the corresponding ABP beats, consistent with the two-element Kashif model. Likewise, the estimated compliance tends to be negative with positive $b_0^{\text{ML}}, d_0^{\text{ML}}$ and $b_1^{\text{ML}}, d_1^{\text{ML}}$ for estimation windows where the CBFV beats are low-pass filtered versions of the ABP beats. As an example, Figure 3-7 shows an estimation window in which an abnormally low CBFV pulsatility resulted in a negative compliance estimate. This low pulsatility may be because of systematic measurement inaccuracy in the CBFV, or it could also be the result of under-modeling. Also, we use the radial ABP as a surrogate for the cerebral ABP, and this might also be a contributing factor towards observing such cases.\(^3\)

The ensemble bias for this estimation method is reasonably low. The RMSE, however, is much larger. This suggests that we should consider incorporating an additional protection layer in our nICP estimation scheme. In our proposed method, this protection layer is in the form of an a priori belief about a subject’s ICP. We combine this prior belief with a likelihood distribution of ICPs that is derived from the residual-error norms, $\zeta^{I,d}$, and subsequently compute a point estimate of the resulting a posteriori distribution as our final ICP estimate. This Bayesian formulation is presented in the next section.

3.3 Incorporating prior information about the ICP

In order to incorporate prior information about the ICP and the model parameters, we note that in our setting there is little prior information available about $R'$, $C'$, and consequently, the model parameters, $b_k$. Therefore, we simplify our inference task by imposing a prior distribution only on the ICP, and we continue to estimate the model parameters $b_k$ as before. The framework developed here, however, is sufficiently flexi-

\(^3\)Although we may employ constrained least-squares optimization methods to eradicate cases with negative compliance estimates, the number of such cases was small in our training data. We therefore continued to employ unconstrained least-squares optimization to estimate $b_0$ and $b_1$. 

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Figure 3-7: Estimation window with a noisy CBFV signal that is laden with ripples and that has low pulsatility. The resulting compliance estimate is negative with $\hat{b}_0^{\text{ML}}, \hat{a}_\text{ML} > 0$ and $\hat{b}_1^{\text{ML}}, \hat{a}_\text{ML} < 0$.

able to incorporate basic prior information about $R'$ and $C'$ via constrained/regularized least-squares optimization routines.\footnote{Enforcing sophisticated prior distributions simultaneously on $R$, $C$, and $I$ might require iterative and computationally-intensive Markov chain Monte Carlo Bayesian system identification approaches such as the one proposed in [45].}

This (pseudo) Bayesian formulation requires both a prior belief about the ICP, and also a likelihood distribution that must be derived from the observed ABP and CBFV signals. The prior distribution, for instance, can be formed via statistical analysis of patients’ ICPs, and physicians can be given the option to adjust the prior distribution at the bedside. In our formulation, we obtain the likelihood distribution by appropriately transforming the calculated model residual-error norms, $\zeta^{I,d}$. An $a$ posteriori distribution of ICPs is then generated and a corresponding point estimate, such as the mode, is then chosen as our final $nICP$ estimate. We describe these steps in detail in the following sections.

### 3.3.1 Prior distribution selection

We evaluated two prior distributions for the mean ICP. The first is a uniform distribution over all ICPs in the range $I_{\text{range}} = \{I_s : \Delta I : \overline{p}_s\}$, where $I_s$ and $\Delta I$ are set as in Section 3.2, namely $I_s = -10$ mmHg and $\Delta I = 1$ mmHg. Then, the probability of
a candidate ICP is

\[
Pr(I) = \begin{cases} 
\frac{1}{|I_{\text{range}}|}, & I \in I_{\text{range}} \\
0, & I \notin I_{\text{range}} 
\end{cases} 
\]  

(3.14)

where \(|I_{\text{range}}|\) denotes the number of elements in the set \(I_{\text{range}}\).

In addition, we also used a (truncated) Gaussian mixture model (tGMM) with two components to represent low and high ICPs, respectively. This model is of the form

\[
Pr(I) = \begin{cases} 
\frac{1}{S} \times \sum_{k=1}^{2} w_k \frac{1}{\sqrt{2\pi}\sigma_k} \exp \left\{ -\frac{1}{2} \left( \frac{I - \mu_k}{\sigma_k} \right)^2 \right\}, & I \in I_{\text{range}} \\
0, & I \notin I_{\text{range}} 
\end{cases} 
\]  

(3.15a)

\[
w_1, w_2 \in [0, 1], \text{ subject to the constraint } w_1 + w_2 = 1, \]  

(3.15b)

Here \(S\) is chosen such that \(\sum_{I \in I_{\text{range}}} Pr(I) = 1\).

We selected a representative subset of 46 twenty-beat estimation windows from the clinical training dataset to derive the parameters for the tGMM distribution, and found the mean ICP and standard deviation to be 13.6 and 2.8 mmHg, respectively. This low standard deviation corresponds to a lack of heterogeneity in ICPs encountered and measured in standard clinical practice. Consequently, we set \(\mu_1 = 13.6\) mmHg to model low ICPs, and set \(\sigma_1 = 10\) mmHg—a value larger than the ICP standard deviation in the 46 estimation windows—to model greater variance in ICPs. Using our best judgment, we then set \(\mu_2 = 50\) mmHg and \(\sigma_2 = 20\) mmHg to model high ICPs. Also, we set \(w_1 = 0.8\) and \(w_2 = 0.2\) by noting that the mean ICP exceeded 30 mmHg in 20% of the data records used by Kashif et al. [1] (see Figure 2-8). These parameters are summarized in Table 3.5, and both the resulting uniform and tGMM prior distributions are plotted in Figure 3-8.
Table 3.5: Summary of prior distribution parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu_1$, $\sigma_1$</td>
<td>13.6, 10.0</td>
<td>mmHg</td>
</tr>
<tr>
<td>$\mu_2$, $\sigma_2$</td>
<td>50.0, 20.0</td>
<td>mmHg</td>
</tr>
<tr>
<td>$w_1$, $w_2$</td>
<td>0.8, 0.2</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure 3-8: tGMM prior distribution (solid) with the parameters of Table 3.5. A uniform belief over the ICPs (dashed) is also plotted.

### 3.3.2 Likelihood model

Having described the prior distribution, we now describe the likelihood distribution model. We chose to generate likelihood distributions by appropriately transforming the model residual-error norms, $\zeta_{I,d}$, in a two-stage process. First, we transform the residual-error norms into likelihoods over the two-dimensional space of ICPs and time offsets. Next, we marginalize this two-dimensional likelihood probability mass function (PMF) into a one-dimensional PMF over possible ICPs.

We evaluated two possible schemes for the first (likelihood generation) stage. The first scheme assigns a likelihood to each $(I, d)$ pair according to the inverse of the corresponding model residual-error norm. That is,

$$
\mathcal{L}(I, d) = \frac{1}{S} \times \frac{1}{\zeta_{I,d}} \quad (3.16a)
$$

$$
S = \left( \sum_{I, d} \frac{1}{\zeta_{I,d}} \right)^{-1} \quad (3.16b)
$$

This model, denoted as the inverse-residual-norm (IR) model, assigns high probability...
Figure 3-9: (a) Residual-error norms computed for an estimation window and (b) the corresponding likelihood using the IR model of Equation 3.16a. (c) Slices of the likelihood surface at \( d = 0 \) for the IR model, and for the exponential model (Equation 3.17a) with \( p = 1 \) and \( p = 2 \), respectively.

to an \((I, d)\) pair with low residual-error norm (indicating a good fit to the underlying model) and low probability to a pair with high residual-error norm.

The second scheme models the likelihood function as a decaying exponential of the \( p^{\text{th}} \) order:

\[
\mathcal{L}(I, d) = \frac{1}{S} \times \exp \left\{ - \left( \frac{\zeta_{I, d}}{m} \right)^p \right\} \\
(3.17a)
\]

\[
m = \min_{I, d} \zeta_{I, d} \\
(3.17b)
\]

\[
p \in \mathbb{Z}_{>0} \\
(3.17c)
\]

\[
S = \left( \sum_{I, d} \exp \left\{ - \left( \frac{\zeta_{I, d}}{m} \right)^p \right\} \right)^{-1} \\
(3.17d)
\]

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As illustrated in Figure 3-9, this scheme functions similarly to the IR model albeit with exponentially decaying tails. A multitude of other likelihood functions based, in some form, on the inverse of the residual norm can be conceived. We will, however, focus on IR and the exponential models.

After generating the two-dimensional likelihood distribution, \( \mathcal{L}(I, d) \), we then transform it into a one-dimensional distribution over ICP only. This can be done by marginalizing \( \mathcal{L}(I, d) \) over the time offsets according to

\[
\mathcal{L}(I) = \sum_d \mathcal{L}(I, d) \quad (3.18)
\]

We also evaluated a different scheme (denoted the minimization scheme) wherein the likelihood curve corresponding to \( \hat{d}_{ML} \) (Equation 3.11) was selected such that

\[
\mathcal{L}(I) = \frac{1}{S} \times \mathcal{L}(I, \hat{d}_{ML}) \quad (3.19a)
\]

\[
S = \sum_I \mathcal{L}(I, \hat{d}_{ML}) \quad (3.19b)
\]

where \( \hat{d}_{ML} \) was first selected via a joint optimization over \( I \) and \( d \)!

The final likelihood PMFs generated in this manner are illustrated in Figure 3-10.

3.3.3 Final nICP estimate

Once we have obtained the prior and likelihood distributions, the next step is to generate an \textit{a posteriori} ICP distribution according to

\[
\Pr(I|p_0, q_0) = \frac{1}{S} \times \Pr(I)\mathcal{L}(I) \quad (3.20a)
\]

\[
S = \left( \sum_I \Pr(I)\mathcal{L}(I) \right)^{-1} \quad (3.20b)
\]
Figure 3-10: (a) Likelihood surface for an estimation window with the second-order exponential model of Equation 3.17a. (b) The resulting one-dimensional likelihoods over possible ICPs obtained using the marginalization (solid) and minimization (dashed) schemes, respectively.

We then take a point estimate (see Figure 3-11) such as the mean, median, or mode of the posterior PMF as our final ICP estimate, where

\[
\hat{I}_{\text{Mean}} \triangleq \sum_{I} I \times \Pr(I|p_a, q_v) \\
\hat{I}_{\text{Median}} = \sum_{I=I_m} \Pr(I|p_a, q_v) = \frac{1}{2} \\
\hat{I}_{\text{Mode}} = \arg\max_{I} \Pr(I|p_a, q_v)
\]

(3.21a) (3.21b) (3.21c)

3.4 Results on training dataset

We computed nICP estimates for the training dataset in twenty-beat non-overlapping windows. Several design choices were evaluated, and the resulting bias, SDE, and RMSE are listed in Table 3.6. Here, the marginalization and minimization schemes have been abbreviated as Mar. and Min., respectively. A Bland-Altman analysis [46] of one of these configurations for the mode estimator is shown in Figure 3-12. The estimation results for one data segment with the same configuration are plotted in
Figure 3-11: Illustration of the estimation algorithm on one data window. The residual-error norms for a range of ICPs and time offsets are computed. These are transformed (using the second-order exponential model in this example) into a likelihood distribution that is then marginalized across the time offsets. The resulting likelihood is then multiplied by the prior PMF to yield the a posteriori PMF whose mode (green dotted line) is picked as the final nICP estimate. The actual ICP (solid black line) is also shown. The process is repeated for each estimation window.

Figure 3-13. Additionally, we computed nICP estimates without scanning over the time offset range. In this case, the time offset, $d$, was set to zero, and the resulting estimation scheme did not require marginalization or minimization.

3.5 Discussion

The results illustrate various aspects of the algorithm. We focus first on the mode estimator and subsequently analyze the other estimators’ performance. For the mode, the results remain unaffected by the choice of the likelihood model for $d = 0$ when the uniform prior belief is used. This is because for the uniform prior belief and with $d = 0$, the mode estimator selects the ICP with highest likelihood regardless of the probability landscape across the remaining ICPs. The likelihood generation models only affect the probability magnitudes assigned to each ICP and thus, the ICP that
Table 3.6: Results on training data (Bias, SDE, RMSE), mmHg

<table>
<thead>
<tr>
<th>Prior</th>
<th>Likelihood model</th>
<th>IR</th>
<th>$p = 1$</th>
<th>$p = 2$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mode</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$d = 0$</td>
<td>Uniform</td>
<td>(5.9, 15.4, 16.5)</td>
<td>(5.9, 15.4, 16.5)</td>
<td>(5.9, 15.4, 16.5)</td>
</tr>
<tr>
<td></td>
<td>tGMM</td>
<td>(1.4, 3.5, 3.8)</td>
<td>(1.6, 3.5, 3.9)</td>
<td>(2.5, 4.3, 5.0)</td>
</tr>
<tr>
<td>Mar.</td>
<td>Uniform</td>
<td>(0.2, 14.6, 14.6)</td>
<td>(−0.1, 14.7, 14.7)</td>
<td>(0.5, 14.7, 14.7)</td>
</tr>
<tr>
<td></td>
<td>tGMM</td>
<td>(0.9, 3.5, 3.7)</td>
<td>(0.9, 3.6, 3.7)</td>
<td>(1.2, 4.1, 4.3)</td>
</tr>
<tr>
<td>Min.</td>
<td>Uniform</td>
<td>(2.0, 13.4, 13.5)</td>
<td>(2.0, 13.4, 13.5)</td>
<td>(2.0, 13.4, 13.5)</td>
</tr>
<tr>
<td></td>
<td>tGMM</td>
<td>(1.3, 3.6, 3.8)</td>
<td>(1.3, 3.6, 3.9)</td>
<td>(1.8, 4.2, 4.5)</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$d = 0$</td>
<td>Uniform</td>
<td>(9.0, 5.3, 10.4)</td>
<td>(6.3, 6.0, 8.7)</td>
<td>(5.3, 8.2, 9.7)</td>
</tr>
<tr>
<td></td>
<td>tGMM</td>
<td>(2.1, 3.4, 4.0)</td>
<td>(1.8, 3.5, 3.9)</td>
<td>(2.3, 4.3, 4.9)</td>
</tr>
<tr>
<td>Mar.</td>
<td>Uniform</td>
<td>(7.3, 5.1, 8.9)</td>
<td>(3.7, 5.8, 6.9)</td>
<td>(1.5, 7.4, 7.5)</td>
</tr>
<tr>
<td></td>
<td>tGMM</td>
<td>(1.5, 3.5, 3.8)</td>
<td>(1.0, 3.5, 3.7)</td>
<td>(0.8, 4.1, 4.2)</td>
</tr>
<tr>
<td>Min.</td>
<td>Uniform</td>
<td>(7.3, 4.8, 8.8)</td>
<td>(4.4, 5.3, 6.9)</td>
<td>(2.5, 6.7, 7.2)</td>
</tr>
<tr>
<td></td>
<td>tGMM</td>
<td>(1.7, 3.5, 3.9)</td>
<td>(1.4, 3.5, 3.8)</td>
<td>(1.3, 4.0, 4.2)</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$d = 0$</td>
<td>Uniform</td>
<td>(10.9, 4.9, 11.9)</td>
<td>(6.9, 5.4, 8.8)</td>
<td>(5.1, 7.2, 8.8)</td>
</tr>
<tr>
<td></td>
<td>tGMM</td>
<td>(4.1, 3.5, 5.4)</td>
<td>(3.3, 3.6, 4.8)</td>
<td>(3.2, 4.4, 5.4)</td>
</tr>
<tr>
<td>Mar.</td>
<td>Uniform</td>
<td>(9.9, 5.0, 11.1)</td>
<td>(4.9, 5.4, 7.3)</td>
<td>(2.0, 6.6, 6.9)</td>
</tr>
<tr>
<td></td>
<td>tGMM</td>
<td>(3.5, 3.6, 5.0)</td>
<td>(2.3, 3.6, 4.3)</td>
<td>(1.6, 4.2, 4.4)</td>
</tr>
<tr>
<td>Min.</td>
<td>Uniform</td>
<td>(9.7, 4.7, 10.8)</td>
<td>(5.4, 5.0, 7.3)</td>
<td>(2.7, 6.0, 6.6)</td>
</tr>
<tr>
<td></td>
<td>tGMM</td>
<td>(3.6, 3.5, 5.0)</td>
<td>(2.6, 3.5, 4.4)</td>
<td>(2.0, 4.0, 4.5)</td>
</tr>
</tbody>
</table>

Figure 3-12: (a) Bland-Altman plot for the automatically determined time offset range with the mode estimator for the exponential likelihood model ($p = 2$). The tGMM prior belief was used and the time offsets were marginalized. Bias (solid) and 2 SDE lines (dashed) are plotted. The corresponding histogram of estimation bias is also shown in (b).
Figure 3-13: Estimation results for one data segment corresponding to the Bland-Altman plot in Figure 3-12. The ICP waveform, the mean ICP, and the nICP estimates are plotted in gray, black, and red, respectively.

has the highest likelihood remains unchanged. Moreover, scanning over the time offset range leads to considerable reduction in the bias for the uniform prior. The advantage gained from scanning over multiple time offsets persists even when the tGMM prior distribution is used. Also, the tGMM prior distribution itself can be seen to improve both bias and RMSE. The magnitude of improvement brought about by the tGMM distribution, however, is affected by the choice of likelihood model. This is because the IR model produces a flatter ICP distribution compared to the exponential models for $p = 1$ and $2$ (see Figure 3-9), thereby allowing the prior distribution to dominate. Similarly, marginalized likelihoods are relatively obtuse compared to the likelihood PMFs generated by the minimization scheme. This allows the prior distribution to exert greater influence when the marginalization strategy is used. The differences in results generated by the marginalized and minimized likelihoods, however, are less significant than the differences brought about by the choice of IR and exponential models.

These observations persist across all three estimators. Of the three estimators, however, the mode is least dependent on the ICP scan range, whereas the mean depends most strongly on the scan range. This manifests in the form of increased positive bias for the mean estimator because the mean is computed over an ICP scan range that is predominantly positive. That the median and mean estimators have greater dependence on the scan range helps them outperform the mode in reducing
the RMSE when the uniform prior is used. Thus, the median or mean might be appropriate estimators in cases when a prior distribution is not available. Moreover, the dependence on the scan range is reduced for both mean and median estimators when the exponential likelihood model is used because the likelihoods generated with these models are less obtuse than the ones generated by the IR model.

The results at this point have helped establish the importance of scanning over multiple time offsets. Moreover, we observed that the tGMM prior belief is important for generating accurate results. The marginalization and minimization schemes were also shown to produce comparable results, and the mode estimator was shown to be most desirable as it is least-dependent on the scanning range. These results, however, have not established the relative advantages and disadvantages of the IR model versus the exponential models. Moreover, the ICPs encountered in this dataset are very homogeneous. Thus to gain further insight, we tested the method on data from tilt-table experiments. The resulting nICP estimates are presented in the following section.

3.6 nICP estimation in tilt-table experiments

We analyzed the nICP estimation method’s performance on data from all five tilt-table experiment subjects to gain a better understanding of the relative advantages and disadvantages of the likelihood distribution models. While the overall data collection procedure was described in Chapter 2, here we reiterate that healthy adults in a supine position are expected to have ICPs in the range \([10, 15]\) mmHg and that their ICPs are expected to drop to \([0, 5]\) mmHg during each head-up tilt. This expected physiologic change can potentially allow us to test the method’s performance on a wider range of ICPs than the ones encountered in the clinical training dataset.

We analyzed the tilt-table recordings in non-overlapping twenty-beat data windows and used the mode as our final nICP estimate with the tGMM prior distribution. The same likelihood models were tested as in the previous section, and the likelihoods were marginalized over the time offset range. For each likelihood model, the nICP
estimates for each subject were resampled to a common length, and the resampled estimates were averaged sample-by-sample to produce an average nICP trend. The resulting nICP trend for each likelihood model is shown in Figure 3-14.

The head-up tilts result in reductions in nICP as per our expectation. The reduction magnitudes, however, are affected by the choice of the likelihood model. The IR model produces the smallest reductions as it is unable to dominate the tGMM prior belief. The depression magnitudes increase for the exponential likelihood models with increasing $p$. As shown by the wider SD bounds in the figure, however, a downside of using the exponential likelihood models is that the nICP estimates are subject to more variability. Thus, while the exponential models are better able to capture ICP trends by exercising greater influence on the posterior distribution, the resulting nICP estimates can become sensitive to structured and unstructured uncertainties in the underlying ABP and CBFV signals. This suggests that we should analyze the proposed framework's sensitivity to signal noise. Such an analysis is presented in the following section.

3.7 Sensitivity to noise in input signals

Our proposed nICP estimation framework uses ABP and CBFV signals as input. Of these, the CBFV signal is more prone to noise and motion artifacts. Consequently, we investigated the effect of CBFV signal noise on the resulting nICP estimates. In our analysis, we added zero-mean Gaussian IID noise to the CBFV signals in our clinical training dataset, and we analyzed the change in mode estimates of the resulting likelihood distributions. We performed this analysis in non-overlapping twenty-beat estimation windows with the pre-filtering stage of Section 2.5.1 in place. Moreover, we used the second-order exponential likelihood model, and we marginalized the likelihood distributions across the time offsets. This process was repeated five times for each record, and this is illustrated for one estimation window in Figure 3-15. Also, Table 3.7 presents the resulting nICP estimation results with the uniform prior distribution and the mode estimator. We performed this analysis with the tGMM prior.
Figure 3-14: Mean nICP trends (solid) obtained for the tilt-table experiments with (a) the IR model, (b) the exponential likelihood model with $p = 1$, and (c) the exponential likelihood model with $p = 2$. Unit SD bounds are also shown (dotted). Vertical tilts result in nICP depressions whose magnitudes and variability are affected by the choice of the likelihood model.

distribution in place, and the corresponding nICP estimation results are summarized in Table 3.8.

Figure 3-15 shows that while the pre-filtering stage of Section 2.5.1 was able to remove significant out-of-band noise from the data, the in-band noise could not be removed, and this affected the likelihood distributions in two ways. First, increasing noise variance increases the nICP estimation uncertainty, and this manifests itself as a progressive flattening of the likelihood distributions. Second, the mode estimates of the likelihood distributions tend to decrease with increasing noise in the CBFV signal, resulting in the negative shift in bias seen in Table 3.7. Statistical signal processing techniques can potentially be used to remove in-band noise to further mitigate effects
Figure 3-15: Empirical sensitivity analysis method. (a) One instance of noisy CBFV (blue) for a noise variance of 25 cm$^2$/s$^2$ is plotted. The pre-filtering stage of Section 2.5.1 removes a significant amount of out-of-band noise, leading to the filtered CBFV (black) that is then passed to the nICP estimation routine. (b) The likelihood distributions generated via the second-order exponential model for the original (non-noisy) CBFV (black), and for noisy CBFV signals with noise variances of 1, 25, and 100 cm$^2$/s$^2$ (five instances each) are plotted in green, blue, and red, respectively. The respective modes are also marked.

Table 3.7: [Minimum, Maximum] bias, SDE, and RMSE (mmHg) obtained with the uniform prior distribution for different CBFV noise variances. Five instances were generated for each noise-variance.

<table>
<thead>
<tr>
<th>Noise variance (cm$^2$/s$^2$)</th>
<th>Bias</th>
<th>SDE</th>
<th>RMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>0.5</td>
<td>14.7</td>
<td>14.7</td>
</tr>
<tr>
<td>1</td>
<td>[0.3, 0.5]</td>
<td>[14.7, 14.8]</td>
<td>[14.7, 14.8]</td>
</tr>
<tr>
<td>25</td>
<td>[-0.2, 0.0]</td>
<td>[14.7, 14.9]</td>
<td>[14.7, 14.9]</td>
</tr>
<tr>
<td>100</td>
<td>[-1.2, -1.0]</td>
<td>[14.9, 15.0]</td>
<td>[15.0, 15.0]</td>
</tr>
</tbody>
</table>

Table 3.8: Results corresponding to Table 3.7 for the static tGMM prior distribution. Results are in mmHg unless indicated otherwise.

<table>
<thead>
<tr>
<th>Noise variance (cm$^2$/s$^2$)</th>
<th>Bias</th>
<th>SDE</th>
<th>RMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>1.2</td>
<td>4.1</td>
<td>4.3</td>
</tr>
<tr>
<td>1</td>
<td>[1.2, 1.2]</td>
<td>[4.1, 4.1]</td>
<td>[4.2, 4.3]</td>
</tr>
<tr>
<td>25</td>
<td>[1.0, 1.0]</td>
<td>[3.8, 3.9]</td>
<td>[4.0, 4.0]</td>
</tr>
<tr>
<td>100</td>
<td>[0.8, 0.8]</td>
<td>[3.6, 3.6]</td>
<td>[3.7, 3.7]</td>
</tr>
</tbody>
</table>

of signal noise. Such methods, however, are not developed in this thesis. Furthermore, the results in Table 3.8 exhibit an increasingly negative shift in bias. This is primarily because the likelihood distributions become increasingly flat with increasing noise
variance, thereby ceding greater influence to the tGMM prior distribution. Table 3.8 indicates that the nICP estimation results did not change significantly even for a noise variance as large as $100 \text{ cm}^2/\text{s}^2$ when the tGMM distribution was in place. While this is encouraging, it also suggests that we must also investigate the estimation method’s sensitivity to change in the tGMM distribution’s parameters. Such an analysis is presented in the next section.

### 3.8 Sensitivity to change in tGMM parameters

Our results in the previous section showed that it is important to analyze our method’s sensitivity to changes in tGMM prior distribution parameters. Of the parameters, the mode, $\mu_1 = 13.6 \text{ mmHg}$, is most important because our clinical training data lies within its purview. Thus, we evaluated the effect of changing $\mu_1$ on the resulting bias, SDE and RMSE for the static tGMM prior distribution. We postulated that the sensitivity to $\mu_1$ would also be governed by the choice of likelihood models. Consequently, we evaluated both the IR and the second-order exponential models. In our analysis, we marginalized the likelihood distributions across the time offsets. The resulting bias, SDE and RMSE are plotted in Figure 3-16 for a range of $\mu_1$.

The results in these figures are encouraging as they illustrate that the RMSE remains largely invariant to changes in $\mu_1$ despite the linear relationship between $\mu_1$ and the estimation bias. Moreover, the RMSE sensitivity is smaller for the second-order exponential likelihood model than for the IR likelihood model. This therefore suggests that the combination of the tGMM prior distribution and the second-order exponential likelihood model might be an appropriate choice for noninvasively estimating ICPs encountered in standard clinical practice.

### 3.9 Summary

We presented a model-based, (pseudo) Bayesian nICP estimation scheme. The first-order continuous-time model of Kashif et al. [1] was initially converted into a discrete-
time model. Next, a range of physiologically plausible mean ICPs and time offsets were substituted into the model, and the remaining model parameters were estimated in a least-squared-error sense. We showed that the candidate ICP corresponding to the least-residual-error norm had a low bias, but a large standard deviation of the error compared to the true ICP. Thus, we adopted a Bayesian approach in which we transformed the model residual error norms of each ICP and time offset pair into a likelihood distribution that we then combined with a prior belief. Point estimators of the resulting posterior distribution of ICPs were then taken as the final nICP estimates.

We tested this method on our clinical training dataset comprising twenty data segments from three patients and we evaluated several design choices. The nICP estimates on this training dataset were well within the desired clinical accuracy when

Figure 3-16: nICP estimation results obtained by varying the mode, \( \mu_1 \), of the tGMM prior distribution. Results with the IR (blue) and second-order exponential likelihood models (red) are shown.
the tGMM prior distribution was used. The method was further tested on data from five healthy subjects who underwent tilt-table experiments. The results here showed that the second-order exponential likelihood model produced results that closely matched our postulated ICP behavior. This, however, came at the expense of greater variance in the estimates. Thus, in cases where the ABP and CBFV signals are suspected to be corrupted by artifacts or noise, the IR likelihood model may be preferred over the exponential models. Likewise, the exponential models may be preferred in cases where the ABP and CBFV signals are more trustworthy.

We also conducted an empirical analysis of the nICP estimation method's sensitivity to noise in the CBFV signals. We found that the estimation results did not change significantly with noise in the CBFV signals when the tGMM prior distribution was in place. We then investigated the effect of changing the tGMM distribution’s mode, $\mu_1$, on the estimation results, and we found that while the bias varies linearly with $\mu_1$, the RMSE remains largely unaffected. This is encouraging and it suggests that the the tGMM prior distribution, particularly in combination with the second-order exponential likelihood model, might be an appropriate choice for noninvasive ICP estimation.

In conclusion, the results obtained from our proposed method are well within clinically acceptable error bounds. While the estimation RMSE was shown to be largely invariant to changes in the prior distribution’s mode particularly with the second-order exponential likelihood model, it is still desirable to further reduce the dependence on the tGMM prior distribution. This may be achieved, for instance, if the tGMM distribution is used only in the initial stages of the algorithm to establish a baseline nICP. Once this baseline has been established, we may start using a uniform prior distribution instead. Estimated changes in the resulting nICPs may then be appropriately filtered, and these may then be added incrementally to our initial baseline to produce the final nICP estimates. We develop this approach further in the next chapter.
Chapter 4

Longitudinally tracking the ICP

The estimation methods presented in Chapter 3 were shown to produce nICP estimates with clinically acceptable accuracy, albeit on a limited dataset. In the approaches, however, the prior distributions were held static over time. This restriction can potentially be relaxed by leveraging information about nICP estimates computed in previous estimation windows. In this chapter, we first explore a method (denoted PDA) to incrementally update the tGMM prior distribution. This exploration leads to our proposed approach (denoted SaT) in which we estimate nICP changes from one estimation window to the next and incrementally add these changes to a baseline nICP estimate. We present the methods' nICP estimation results on both the clinical training dataset and on the head-up tilt experiments. We then compare the methods' performances on a synthetic dataset and we show that the SaT method performs better than the PDA approach. We conclude the chapter by analyzing the SaT method's sensitivity to signal noise and to changes in the tGMM prior distribution.

4.1 Incrementally translating the prior distribution

Our first approach involves adapting the parameters of the tGMM prior distribution by analyzing trends of past nICP estimates. In this prior distribution adaptation (PDA) approach, we adapt the modes, $\mu_1$ and $\mu_2$, of the tGMM prior distribution defined in Equation 3.15 while the respective standard deviations and mixture weights
remain unchanged. At each update step, we change both modes by the same amount, thereby incrementally translating the initial tGMM distribution. Specifically, for the \((m + 1)^{th}\) estimation window, we denote the tGMM prior distribution's vector of modes as \(\mu[m + 1] = [\mu_1[m + 1], \mu_2[m + 1]]^T\). We define the vector of past nICP estimates,

\[
\mathbf{I}[m + 1] = [\hat{I}[m - (M_{\text{trend}} - 1)], \ldots, \hat{I}[m - 1], \hat{I}[m]]^T
\]  

(4.1)

where \(\hat{I}[r]\), for \(r \in \{m - (M_{\text{trend}} - 1), \ldots, m - 1, m\}\), denotes the nICP estimate of the \(r^{th}\) estimation window, and \(M_{\text{trend}}\) is an integer parameter. We then perform a weighted least-squares regression to obtain a straight-line approximation of the values in \(\mathbf{I}[m + 1]\). That is, for a line segment of the form \(y = \alpha_{m+1} x r + \beta_{m+1}\), we solve

\[
\begin{bmatrix}
\hat{\alpha}_{m+1} \\
\hat{\beta}_{m+1}
\end{bmatrix} = (P^T WP)^+ (P^T P) \mathbf{I}[m + 1]
\]

(4.2)

\[
P = \begin{bmatrix}
m - (M_{\text{trend}} - 1) & 1 \\
m - (M_{\text{trend}} - 2) & 1 \\
\vdots & \vdots \\
m - 1 & 1 \\
m & 1
\end{bmatrix}
\]

\[
W = \begin{bmatrix}
1/\sigma_i^2[m - (M_{\text{trend}} - 1)] & 0 & \cdots & 0 \\
0 & 1/\sigma_i^2[m - (M_{\text{trend}} - 2)] & \cdots & 0 \\
\vdots & \ddots & \ddots & \vdots \\
0 & 0 & \cdots & 1/\sigma_i^2[m]
\end{bmatrix}
\]
Table 4.1: Parameter choices of the PDA method.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$M_{Step}$</td>
<td>3</td>
</tr>
<tr>
<td>$M_{Trend}$</td>
<td>6</td>
</tr>
<tr>
<td>$\delta$</td>
<td>1, 2, ..., $M_{Step}$</td>
</tr>
</tbody>
</table>

Here, the weighting matrix $W$ comprises the reciprocals of the posterior distribution variances

$$\sigma^2_r = \sum_{I \in I_{Range}} \left( I - \tilde{I}_{Mean}[r] \right)^2 \times \Pr_r(I|p_a, q_v)$$

$$\tilde{I}_{Mean}[r] = \sum_{I \in I_{Range}} I \times \Pr_r(I|p_a, q_v) \quad (4.3)$$

where $\Pr_r(I|p_a, q_v)$ denotes the posterior nICP probability distribution for the $r^{th}$ estimation window.

The estimated parameters $\tilde{\alpha}_{m+1}$ and $\tilde{\beta}_{m+1}$ can now be used to obtain new tGMM modes. In our formulation, we use an update equation of the form

$$\mu[m + 1] = \mu[m] + \delta \tilde{\alpha}_{m+1} \cdot \begin{bmatrix} 1 & 1 \end{bmatrix}^T \quad (4.4)$$

where $\delta$ is a tunable parameter governing the adaptation rate.

These prior-distribution updates can be performed after each estimation window (spanning only twenty cardiac cycles in our implementation). Doing so, however, can induce the nICP estimates to drift. We therefore performed one update after every $M_{Step}$ estimation windows, where $M_{Step}$ was set to three. Moreover, we set $M_{Trend}$ to six. For the twenty-beat estimation windows used in the thesis, these choices of $M_{Step}$ and $M_{Trend}$ correspond to 60 and 120 cardiac cycles, respectively. In addition, we evaluated several values of $\delta$ in unit increments. These parameter values are summarized in Table 4.1, and the resulting nICP estimation approach is schematically depicted in Figure 4-1.

This method's advantage is that it incorporates the adaptation procedure within
the pseudo-Bayesian nICP estimation scheme of Chapter 3. Moreover, the method is flexible in that the adaptation rate can be altered by adjusting the value of $\delta$, or by changing $M_{\text{Step}}$ and $M_{\text{Trend}}$. Also, this method acts on nICP trends observed over the relatively longer timescale of $M_{\text{Trend}}$ estimation windows. The seed-and-track approach that we present next, aims to instead use window-by-window changes observed in the nICP estimates. These window-by-window changes are filtered, and are added into a baseline nICP to yield the final nICP estimates.

### 4.2 Seed-and-track (SaT) approach

In this section, we present an alternative method to reduce the dependence on the tGMM prior distribution. We begin by noting that the PDA scheme developed in the previous section incrementally translates the tGMM distribution by observing trends in the past nICP estimates. These trends are extracted via weighted least-squares regression analysis in what is effectively a noise filtering procedure. Drawing inspiration from Kalman filtering, however, we can also attempt to iteratively filter
out the noise.

4.2.1 Iterative noise filtering framework

Kalman filtering is reviewed in Appendix A. Here we only state that its prerequisites include a state-space model relating the system’s present state to its state at the next epoch, an output model that relates the system’s state to its observed output, and a prior belief about the system’s starting state. The state estimate from the previous epoch is used to predict the current state. This predicted state is then updated using the currently observed output, and the process is repeated for all successive epochs. The initial prior belief is used only in the first iteration to initialize the filtering process.

Following our approach in the previous section where our tGMM prior adaptation rule (Equation 4.4) was based on the ICP trend and not on the actual ICP values themselves, we wish to develop a Kalman-filter-like method to estimate the change in ICP between successive estimation windows, \( \Delta I[m + 1] = I[m + 1] - I[m] \). To develop this approach, we note that the simple, two-element model of Kashif et al. [1] does not explicitly model cerebrovascular autoregulatory phenomena. These phenomena occur over time scales of twenty to sixty beats, and they modulate the cerebrovascular resistance, compliance, and the ICP. Since the Kashif model does not explicitly represent these phenomena, the model cannot be used to predict \( R, C, \) and \( I \). In our method, instead of integrating complex nonlinear descriptions of cerebrovascular autoregulation into the Kashif model, we model the inter-estimation-window ICP dynamics as an autoregressive (AR) random process driven by white noise. This modeling choice allows us to retain the largely training-free, computationally-simple and real-time nature of our existing nICP estimation method. Our autoregressive process model is of the form

\[
\Delta I[m + 1] = \gamma_m \Delta I[m] + v[m]
\]

where \( v[m] \) is an IID white noise sequence with power \( \sigma_v^2 \). The (possibly time-varying)
parameter $\gamma_m$ is such that $|\gamma_m| < 1$ for model stability. This parameter describes the inter-estimation-window ICP trend, with values close to +1 modeling rapidly rising or falling ICPs, and values close to 0 modeling relatively stable ICPs.

The model in Equation 4.5 is useful because we can potentially obtain robust ICP-change estimates, $\hat{\Delta I}[m+1]$, by combining the model-predicted ICP changes with the changes observed in our nICPs. In principle, we can then update our tGMM prior distribution via an equation similar to Equation 4.4. Alternatively, $\hat{\Delta I}[m+1]$ can simply be added into our previous nICP estimate, $\hat{I}[m]$, to yield the next, filtered, nICP estimate

$$\hat{I}[m+1] = \hat{I}[m] + \hat{\Delta I}[m+1]$$

(4.6)

Importantly, once a baseline ICP has been established, we can use the uniform prior belief to estimate nICP changes and rely on the prediction model to filter out the resulting errors. This is in contrast to the PDA scheme presented earlier in which we extracted the trend in nICPs computed with the tGMM distribution in place. A downside of completely abandoning the tGMM prior for the updating scheme, however, is that for larger values of $\gamma_m$, estimation windows with severe signal degradation can induce drifts in the estimated nICPs. Consequently, we will incorporate the distortion-detection scheme of Section 2.5.2 into our SaT method.\(^1\)

The SaT method itself comprises two stages. The first stage – the seed-acquisition stage – acquires a baseline nICP. This baseline is then fed to the second stage – the tracking stage – that uses the uniform prior belief to reduce the dependence over the tGMM distribution. The nICPs are estimated for all subsequent estimation windows with the uniform prior. Changes in these estimates are then filtered, and are added into the baseline nICP to compute the final nICP estimates. In the following description, we denote the nICPs computed with the uniform prior as $\hat{I}_u[m]$, their variances as $\sigma^2_u[m]$, and we continue to denote the final nICP estimates as $\hat{I}[m]$.

\(^1\)The distortion-detection scheme may also be incorporated into the PDA method. We found, however, that doing so, possibly because of the tGMM distribution, did not significantly change the nICP estimation results of the PDA method for the clinical training data.
4.2.2 Seed-acquisition stage

The seed-acquisition stage is depicted in Figure 4-2; it establishes a baseline ICP estimate. In this stage, the pseudo-Bayesian method of Chapter 3 is applied to successive estimation windows, starting from the first window. We evaluated both the IR and the exponential-likelihood models ($p = 2$), and used the mode estimator alongside the tGMM prior. In our method, we marginalize the likelihood distribution across the time offsets. We also compute the mode of the marginalized likelihood distributions, $\hat{I}_L[m]$, and the associated variances, $\sigma^2_L[m]$. Then, the first $M_{seed} (= 5)$ estimation windows that are not marked noisy by the distortion-detection scheme are selected and their nICP estimates (obtained with the tGMM prior) are averaged to yield the seed, $I_{Seed}$, such that

$$I_{Seed} = \frac{1}{M_{seed}} \sum_{m \in \text{Selected}} \hat{I}[m]$$

(4.7)

Here the summation is across the windows that are not marked as noisy, and the averaging is done to reduce the chances of a highly erroneous initial seed being passed to the tracking stage. Moreover, we denote the mode and variance of the likelihood distribution of the final selected estimation window as

$$I_{L, ref} = \hat{I}_L[m_{TS}]$$

$$\sigma^2_{L, ref} = \sigma^2_L[m_{TS}]$$

where $m_{TS}$ is the last selected estimation window's index.

The output of the seed-acquisition stage is passed to the tracking stage. The tracking stage computes nICP estimates with a uniform prior distribution. It then employs the prediction model of Equation 4.5 to filter out noise in observed inter-estimation-window nICP changes. These filtered changes are added back to $I_{Seed}$ to yield the final nICPs.
4.2.3 Tracking stage

The tracking stage starts from \( m \geq m_{TS} \), and the pseudo-Bayesian nICP estimation scheme is again applied. For the pseudo-Bayesian scheme, we use the same design options that were used in the seed-acquisition stage with two exceptions. First, the uniform prior distribution is used instead of the tGMM distribution. Second, for noisy estimation windows, \( \hat{L}_L[m] \) is set to \( \hat{L}_L[m - 1] \), and \( \sigma^2_L[m] \) is set to \( \epsilon \), where \( \epsilon \) is small.\(^2\) Doing so implicitly arrests any drifts induced by a series of noisy estimation windows.

\(^2\)We set \( \epsilon = 10^{-9} \).
windows and this will become clearer upon examining the filtering framework.

Our filtering task is to generate filtered ICP-change estimates by combining observed and model-predicted changes in ICP for \( m \geq m_{TS} \). In the following description, we denote the observed nICP changes as \( \Delta I[m + 1] \). Their variances are denoted as \( \sigma^2_{\Delta I}[m + 1] \). We denote the model-predicted ICP changes as \( \Delta I[m + 1|m] \) and their variances as \( \sigma^2[m + 1|m] \). Likewise, the filtered ICP-change estimates are denoted as \( \tilde{\Delta} I[m + 1] \) as their variances as \( \sigma^2_{\Delta I}[m] \).

Assuming that likelihood distributions of successive estimation windows are statistically independent, the observed nICP change (with the uniform prior) and its variance\(^3\) are

\[
\Delta \hat{I}[m + 1] = \hat{I}_L[m + 1] - \hat{I}_L[m] \\
\sigma^2_{\Delta I}[m + 1] = \sigma^2_L[m + 1] + \sigma^2_v[m] 
\]

(4.8)

where \( \hat{I}_L[m_{TS}] \) and \( \sigma^2_L[m_{TS}] \) are initialized to \( I_{L,ref} \) and \( \sigma^2_{L,ref} \), respectively. Likewise, the model-predicted ICP change and its variance are

\[
\Delta I[m + 1|m] = \gamma_m \Delta I[m] \\
\sigma^2[m + 1|m] = \gamma_m^2 \sigma^2_{\Delta I}[m] + \sigma^2_v 
\]

(4.9)

where the prediction is made using the filtered change estimate, \( \Delta \hat{I}[m] \), of the previous window. To initialize this computation at \( m = m_{TS} \), we set \( \Delta \hat{I}[m_{TS}] \) and \( \sigma_{\Delta I}[m_{TS}] \) to 0 mmHg.

Once both model-predicted and observed ICP changes and their variances have

\(^3\)This is an upper bound on the true variance because, by virtue of the independence assumption, the covariance term has not been included. We compensated for this by using relatively large values of \( \sigma^2_v \).
been computed, they are combined such that

\[ x = \frac{\sigma^2[m + 1|m]}{\sigma^2[m + 1|m] + \sigma^2_{\Delta I}[m + 1]} \]

\[ \sigma^2_{\Delta I}[m + 1] = x \sigma^2_{\Delta I}[m + 1] \]

\[ \Delta I[m + 1] = (1 - x) \Delta I[m + 1|m] + x \Delta \hat{I}[m + 1] \]  \hspace{1cm} (4.10)

The resulting filtered change, \( \Delta I[m + 1] \), is added to \( \hat{I}[m] \) to yield the final nICP estimate,

\[ \hat{I}[m + 1] = \hat{I}[m] + \Delta \hat{I}[m + 1] \]  \hspace{1cm} (4.11)

where \( I_{\text{seed}} \) is used instead of \( \hat{I}[m_{\text{TS}}] \) in the first iteration.

In this formulation, Equation 4.10 can be seen to merge the predicted and observed estimates of the inter-estimation-window ICP change by assigning greater weight to the estimate with lesser variance. This method is attractive as it reduces dependence on the tGMM prior distribution after the initial seed-acquisition stage. To explore this method further, we computed nICP estimates for several design choices, and the results alongside the nICP estimation results of the PDA approach of Section 4.1 are presented in the following section.

### 4.3 Results

We computed nICP estimates for the clinical training dataset in non-overlapping twenty-beat data windows with both the PDA and SaT schemes. Both the IR and exponential-likelihood model \( (p = 2) \) were evaluated, and the time offsets were marginalized. The parameters for both schemes were varied, and the resulting bias, SDE, and RMSE were calculated. The results are listed in Tables 4.2 and 4.3 where the results corresponding to the unmodified pseudo-Bayesian method are also listed in the first row of each table. Figures 4-3 and 4-4 illustrate the estimation results of the two methods for two records. Also, we computed nICP estimates on the head-up tilt data with both methods using the procedure outlined previously in Section 3.6.
Table 4.2: PDA results. (Bias, SDE, RMSE) in mmHg.

<table>
<thead>
<tr>
<th>Likelihood model</th>
<th>( \delta )</th>
<th>IR</th>
<th>( p = 2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(0.9, 3.5, 3.7)</td>
<td>(1.2, 4.1, 4.3)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>(0.8, 3.6, 3.7)</td>
<td>(1.1, 4.2, 4.4)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>(1.0, 3.6, 3.7)</td>
<td>(0.9, 4.6, 4.7)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>(1.0, 4.8, 4.9)</td>
<td>(1.0, 5.6, 5.6)</td>
<td></td>
</tr>
</tbody>
</table>

Table 4.3: SaT results. (Bias, SDE, RMSE) in mmHg. \( \sigma^2 \) is in mmHg^2.

<table>
<thead>
<tr>
<th>Likelihood model</th>
<th>( \gamma_m )</th>
<th>( \sigma^2 )</th>
<th>IR</th>
<th>( p = 2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(0.9, 3.5, 3.7)</td>
<td>(1.2, 4.1, 4.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>(0.8, 3.5, 3.6)</td>
<td>(1.0, 4.1, 4.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-.1</td>
<td>25 (0.8, 3.5, 3.6)</td>
<td>(1.0, 4.0, 4.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+.8</td>
<td>25 (0.6, 4.1, 4.1)</td>
<td>(0.8, 4.7, 4.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>49 (0.5, 4.8, 4.8)</td>
<td>(0.6, 5.5, 5.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The corresponding estimates are plotted in Figures 4-5 and 4-6.

4.4 Discussion

The results of the PDA method indicate that the larger values of \( \delta \) introduce greater variability in the resulting nICP estimates. This observation can be used to our advantage to offset the limitations of the IR likelihood model. As was shown earlier in Chapter 3, nICP estimates with the IR likelihood model depend highly on the tGMM prior distribution. Employing the PDA scheme with an appropriate value of \( \delta \) can, however, help reduce this dependency.

The SaT approach produced similar results to the PDA scheme on the clinical training dataset. Specifically, increasing values of the process noise variance, \( \sigma^2 \), lead to reduced dependence on the initial seed points. Similarly, increasingly positive values of \( \gamma_m \) lead to decreased reliance on the initial seed points. The parameter \( \gamma_m \) may be interpreted as follows. A small negative value indicates the tendency of nICP estimates to return back to the starting baseline following an initial perturbation. Such a \( \gamma_m \) best models the ICPs in our dataset, where the ICP values remain static over time. On the other hand, increasingly positive values of \( \gamma_m \) model the situation where the ICP may rise or fall rapidly. While we do not encounter such situations in our clinical training dataset, we notice that the resulting nICP estimates with such a \( \gamma_m \) are still within clinically acceptable error bounds. This suggests that we might be
Figure 4-3: Estimation results with the exponential likelihood model \((p = 2)\). The ABP (a) and CBFV (b) waveforms are also shown. Results of the PDA scheme corresponding to \(\delta = 2\) (orange) are plotted in (c). Likewise, the estimates of the SaT approach for \(\sigma_\nu^2 = 49\) mmHg\(^2\) and \(\gamma_m = 0.8\) (orange) are shown in (d). In both plots, the ICP waveform, the mean ICP, and the nICP estimates with the unmodified pseudo-Bayesian scheme are plotted in gray, black, and blue, respectively.

able to capture greater variability in the ICPs than we could with the static tGMM prior distribution whilst retaining clinically acceptable accuracy.

Finally, we note that the nICP estimates on the head-up tilt experiments illustrate that both PDA and SaT approaches produced nICP estimates with a greater drop in the head-up tilt phases compared to the original scheme of Chapter 3. Importantly, we note that the PDA scheme with \(\delta = 2\), and the SaT approach with \(\gamma_m = 0.8\) resulted in estimates with desirable accuracy on both the clinical training dataset, in which the ICPs were relatively constant, and on the tilt-table experiments, in which the ICPs have step-like changes. These results provide further evidence that our tracking methods may allow us to robustly estimate ICPs over a wider range
Figure 4-4: Estimation results for another record for the same settings as in Figure 4-3. Larger values of $\delta$ or $\gamma_m$ introduce greater variability in the nICP estimates.

than was previously possible with the static tGMM prior distribution. To further explore the methods’ tracking ability, we introduced synthetic trends in the ABP and ICP signals of our clinical training data, and we computed nICP estimates. This is presented in the next section.

4.5 nICP estimates on synthetic trends

We generated a synthetic dataset to further evaluate our methods’ ability to track ICPs over a wider range of transiently varying ICPs than before. In this dataset, we added a trend to the ABP signals of the clinical training data and left the CBFV unchanged. Then, within the confines of the linear, two-parameter Kashif model, because the CBFV was left unaltered, the CPP must not change either. This would only be possible if the ICP were to change by the same amount as the ABP. Thus,
Table 4.4: Comparison of the PDA and SaT approaches

<table>
<thead>
<tr>
<th><strong>PDA method</strong></th>
<th><strong>SaT method</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduces dependence on the static tGMM distribution by updating prior distribution</td>
<td>Reduces dependence by filtering changes observed in nICPs computed via a uniform prior belief</td>
</tr>
<tr>
<td>Adaptation-rule is not model-based</td>
<td>Tracking stage is based on a single-state model with possibility of using higher-state models</td>
</tr>
<tr>
<td>Easily integrates into the pseudo-Bayesian method</td>
<td>Tracking stage must be interfaced with the pseudo-Bayesian method</td>
</tr>
<tr>
<td>Less susceptible to drifts</td>
<td>Requires drift-arrest scheme for larger $\gamma_m$</td>
</tr>
</tbody>
</table>

we also added the same trend to the actual ICP waveforms. We then computed nICP estimates with the unmodified method of Chapter 3, and with the PDA and SaT approaches. That is, we used the original CBFV waveforms alongside synthetically modified ABP and ICP waveforms such that

$$p_{a,\text{mod}}(t) = p_a(t) + p_{\text{trend}}(t)$$

$$p_{i,\text{mod}}(t) = p_i(t) + p_{\text{trend}}(t)$$

where

$$p_{\text{trend}}(t) = \begin{cases} 
0, & t \leq T_{\text{trend}} \\
\Delta P_{\text{trend}} \times \frac{(t-T_{\text{trend}})}{T_{\text{trend}}}, & T_{\text{trend}} < t \leq 2 T_{\text{trend}} \\
\Delta P_{\text{trend}}, & 2 T_{\text{trend}} < t \leq 3 T_{\text{trend}} \\
\Delta P_{\text{trend}} \times \frac{(4 T_{\text{trend}} - t)}{T_{\text{trend}}}, & 3 T_{\text{trend}} < t \leq 4 T_{\text{trend}} \\
0, & t > 4 T_{\text{trend}} 
\end{cases}$$

(4.12)
Here $\Delta P_{trend}$ was set to 20 mmHg and $T_{trend}$ was set to 5 minutes to mimic a typical plateau wave that might be seen in patients with traumatic brain injury (TBI) [47]. The trend, $p_{trend}(t)$, was designed to facilitate a better understanding of our methods' ability to track longitudinal changes in ICP and is plotted in Figure 4-7. In records whose duration was shorter than 4 $T_{trend}$ minutes, however, we clipped $p_{trend}(t)$ accordingly. We then evaluated the second-order exponential-likelihood model, with the marginalization scheme in place. For the PDA method, $\delta$ was set to two. Moreover, we used $\gamma_m = 0.8$ and $\sigma^2 = 49$ mmHg$^2$ for the SaT approach. The resulting bias, SDE, and RMSE for the three schemes are presented in Table 4.5. Moreover, Bland-Altman plots and histograms of the estimation bias for the three methods are plotted in Figure 4-8, and nICP estimates for two records are plotted in Figure 4-9.

The estimation results on the synthetic data demonstrate that the SaT approach performs better than both the PDA and the unmodified pseudo-Bayesian methods. For the SaT method, however, the ability to follow ICPs is effectively governed by...
Figure 4-6: nICP estimates for head-up tilt experiments with the (a) unmodified pseudo-Bayesian method and (b) with the SaT approach for the IR likelihood model with $\gamma_m = 0.8$, and $\sigma^2_\gamma = 49$ mmHg$^2$. The corresponding plots for the exponential model with $p = 2$ are plotted in (c) and (d), respectively.

the noise in both ABP and CBFV signals – nICP posterior distributions obtained via noisy input signals have larger variances, and thus, have less influence in the tracking stage. Therefore, we analyzed the SaT method’s sensitivity to signal noise and to the tGMM distribution’s mode. This is presented in the following section.

### 4.6 Sensitivity analysis

We investigated the effect of CBFV signal noise on the SaT method’s performance following the procedure outlined in Section 3.7. The results are summarized in Table 4.6. Likewise, we investigated the SaT method’s sensitivity to change in the tGMM distribution’s mode following the procedure in Section 3.8. The estimation bias, SDE,
and RMSE of the SaT method are shown in Figure 4-10.

These analyses indicate that the SaT method’s nICP estimates remain relatively stable in presence of signal noise. This is brought about both by the influence of the tGMM distribution in the seed-acquisition stage, and due to the subsequent model-based nICP-change filtering that gives less influence to change estimates with a large associated variance. Likewise, we notice that estimation RMSE remains relatively unaffected by changes in the tGMM distribution’s mode. In fact, the RMSE curve here is less convex than the corresponding curve in Figure 3-16 owing to the reduced dependence of the SaT method on the tGMM distribution.

### 4.7 Summary

This chapter presented two methods for reducing the dependence of the nICP estimates on the static tGMM prior distribution. The first method uses trends observed
Figure 4-8: Bland-Altman plots for the synthetic data for (a) the unmodified pseudo-Bayesian scheme, (b) PDA scheme, and (c) with the SaT method. The respective histograms of estimation bias along with unit SD lines are plotted in (d), (e), and (f), respectively.

in past nICP estimates to apply incremental shifts to tGMM component modes. The second method is instead based on a single-state model of inter-estimation-window ICP changes. After establishing a baseline nICP using the static tGMM prior distribution, this method then observes the change in nICP estimates measured via the uniform prior belief. These observed changes are filtered via the model predictions and the filtered changes are incrementally added into the baseline nICP. Results of the two methods on the clinical training dataset are within clinically acceptable accuracy for appropriate values of the configuration parameters. Tests on the head-up tilt experiments further indicate that both methods are able to track the drop in ICP due to head-up tilts. We also showed that the SaT approach performed better than the PDA scheme in tracking longitudinal variations on our synthetic dataset. We then analyzed the SaT method’s sensitivity to CBFV signal noise and to change in the tGMM distribution’s mode. These analyses indicate that noise in the CBFV signals does not significantly impact estimation results of the SaT approach. Changes in \( \mu_1 \), the tGMM distribution’s mode, also do not significantly impact the estimation RMSE.

In the SaT approach, we use a time-invariant, single-state model to describe inter-
estimation-window ICP changes. An encouraging aspect of this model is that it produced accurate results not only on stable, nearly-constant ICPs (clinical training dataset) but it also performed well on ICPs with significant temporal changes (head-up tilt and synthetic datasets) with unchanged model-parameters \((\gamma_m = 0.8, \sigma_c^2 = 49 \text{ mmHg}^2)\). That is, it achieved a bias of 0.6 mmHg and an RMSE of 5.5 mmHg on the unmodified clinical dataset; with the same parameters, it then achieved a bias of -2.4 mmHg, and an RMSE of 6.8 mmHg while tracking ICPs exceeding 25 mmHg in the synthetic dataset. We applied the SaT method to the complete clinical dataset. The estimation results are presented in the next chapter.
Table 4.6: Results corresponding to Table 3.7 for the SaT approach.

<table>
<thead>
<tr>
<th>Noise variance (cm$^2$/s$^2$)</th>
<th>Bias</th>
<th>SDE</th>
<th>RMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>0.6</td>
<td>5.5</td>
<td>5.5</td>
</tr>
<tr>
<td>1</td>
<td>[-0.1, 1.5]</td>
<td>[5.5, 6.0]</td>
<td>[5.5, 6.2]</td>
</tr>
<tr>
<td>25</td>
<td>[-0.2, 1.0]</td>
<td>[5.2, 5.5]</td>
<td>[5.3, 5.6]</td>
</tr>
<tr>
<td>100</td>
<td>[-1.4, 1.1]</td>
<td>[5.2, 6.5]</td>
<td>[5.2, 6.7]</td>
</tr>
</tbody>
</table>

Figure 4-10: nICP estimation results obtained by varying the mode, $\mu_1$, of the tGMM prior distribution for the SaT approach. Results with the IR (blue) and second-order exponential likelihood models (red) are shown.
Chapter 5

Results on clinical test-sets

Thus far in our development we had blinded ourselves to data from the remaining ten patients of our thirteen-patient clinical database. In this chapter we present the nICP estimation results on the ensemble clinical data with the SaT method of Chapter 4. We briefly review the SaT method before presenting the estimation results. A discussion follows in Chapter 6 where we also present our concluding remarks.

5.1 Estimation method summary

The SaT method is based on the pseudo-Bayesian approach of Chapter 3. In the pseudo-Bayesian approach, we create a likelihood distribution, \( L(I, d) \), by transforming the residual-error norms, \( \zeta^{I,d} \) for a range of ICPs and time offsets. We explored three such transformations and concluded that the second-order exponential likelihood model of Equation 3.17a was most appropriate among these three. The likelihood distribution generated via the second-order exponential model is marginalized across the time offsets, which results in a likelihood distribution only across the ICPs. This distribution is then multiplied by a prior distribution, and the resulting posterior distribution’s mode is taken as the nICP estimate.

The SaT approach introduces a two-step estimation procedure based on the pseudo-Bayesian approach. First, a seed ICP is established by applying the unmodified pseudo-Bayesian estimation method using a tGMM prior distribution. Next, we use
Table 5.1: Parameter values for the SaT method.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimation window</td>
<td>20 cardiac cycles</td>
</tr>
<tr>
<td>$I_s$</td>
<td>$-10.0 \text{ mmHg}$</td>
</tr>
<tr>
<td>$\Delta I$</td>
<td>$1.0 \text{ mmHg}$</td>
</tr>
<tr>
<td>$\mu_1, \sigma_1$</td>
<td>$13.6, 10.0 \text{ (mmHg)}$</td>
</tr>
<tr>
<td>$\mu_2, \sigma_2$</td>
<td>$50.0, 20.0 \text{ (mmHg)}$</td>
</tr>
<tr>
<td>$w_1, w_2$</td>
<td>$0.8, 0.2$</td>
</tr>
<tr>
<td>Likelihood distribution</td>
<td>Exponential model ($p = 2$) (Marginalization)</td>
</tr>
<tr>
<td>Point estimator</td>
<td>Mode</td>
</tr>
<tr>
<td>$M_{Seed}$</td>
<td>5</td>
</tr>
<tr>
<td>$\gamma_m$</td>
<td>0.8</td>
</tr>
<tr>
<td>$\sigma_e^2$</td>
<td>$49.0 \text{ mmHg}^2$</td>
</tr>
</tbody>
</table>

a single-state auto-regressive model of inter-estimation-window ICP changes and combine the resulting model predictions with nICP changes observed with a uniform prior distribution. Doing so helps increase the range of transiently varying ICPs that our model can capture (see Section 4.5). The parameter choices for the SaT approach are further summarized in Table 5.1.

## 5.2 Results on BCH database

We computed nICP estimates on the ensemble clinical database. This database comprises data from thirteen patients as was summarized in Tables 2.1 and 2.3. Seven hours of data (1,778 estimation windows from 122 data records) were analyzed, and our method achieved an estimation bias of 0.3 mmHg and an RMSE of 5.2 mmHg. A Bland-Altman analysis of the ensemble data is illustrated in Figure 5-1. The per-patient and per-record estimation statistics are plotted in Figure 5-2. Also, Figure 5-3 illustrates the fraction of nICP estimates at or below a certain RMSE on a per-patient, per-record, and per-estimation-window basis. This figure illustrates that 80% of all our nICP estimates were within ±6 mmHg of the reference EVD measurements.
5.3 Manually excluding noisy records

The results presented above are very encouraging as the bias and RMSE are within clinically acceptable accuracy. We found three recordings, however, where the input data were noisy, and had not been rejected by the initial data pre-screening stages. There were two recordings where the ABP signal indicated possible catheter clogging. An example of this is plotted in Figure 5-4. It may be seen here that the SaT approach (rightly) recorded an increase in ICP. Moreover, one recording had a noisy ICP as shown in Figure 5-5. We recomputed the estimation results by excluding all three of these recordings and our method achieved a bias of 0.3 mmHg and an RMSE of 4.8 mmHg.

5.4 Effect of hydrostatic offset correction

In the estimation results presented thus far, we accounted for height differences between the rABP and ICP pressure transducers. We recomputed our nICP estimates (for all records) without accounting for these height differences and obtained an estimation bias of 2.5 mmHg, and an RMSE of 5.9 mmHg. Figure 5-6 shows a histogram of the hydrostatic pressures that were subtracted from the rABP signals prior to nICP estimation. This distribution has a mean of 9.8 mmHg. Our estimation bias, on the
contrary, changed by 2.2 mmHg when we did not account for the hydrostatic offset. This indicates that while our estimation method is sensitive to hydrostatic offset removal, the effect might not be as pronounced due to the presence of the tGMM prior distribution in the seed-acquisition stage.

5.5 Summary

We computed the nICP estimation results on our testing data with the SaT method and achieved an estimation bias of 0.3 mmHg and an RMSE of 5.2 mmHg in a total of 1778 estimation windows across a thirteen-patient cohort. Importantly, this cohort comprised pediatric patients with a diverse set of pathologies that include TBI, hydrocephalus, and intraventricular hemorrhage. It is encouraging, therefore, to note
that our method achieved an RMSE of nearly 5 mmHg—manually excluding noisy data resulted in an RMSE of 4.8 mmHg—that is less than the RMSEs of 5.7 mmHg and 7.8 mmHg achieved by Fanelli et al. and Kashif et al.,$^{1}$ respectively. The latter also averaged the nICP estimates obtained from simultaneously recorded left and right MCA CBFVs, and reported that this averaging resulted in a reduced RMSE of 6.1 mmHg. While our dataset did not have such bilateral CBFV recordings, averaging nICP estimates in this manner can further improve our estimation accuracy.

A comparison between our method’s performance on the ensemble data both with

---

$^{1}$A word of caution here is that our data had less ICP variability than that of Kashif et al.
and without the training data was not possible because these data were extracted differently – training data were manually extracted, while the testing data were extracted via an automated software routine. It is worthwhile to note, however, that our proposed SaT method achieved an estimation bias of 0.6 mmHg and an RMSE of 5.5 mmHg in the training data – values larger than those achieved on the testing data. A potential reason for this is that the testing data comprise consistently noise-free data segments that lend to better estimation performance.

We further discuss these results and the inherent limitations of the present work in the next chapter where we also outline avenues for future exploration.
Chapter 6

Discussion and next steps

In this chapter, we discuss our results, analyze the limitations of the present work, and present avenues for future exploration.

6.1 Discussion

The nICP estimation results presented in the previous chapter have an ensemble RMSE of 5.2 mmHg on data that include dubious records. Manually excluding these recordings results in an even smaller RMSE on our thirteen-patient cohort. Of these thirteen patients, we originally unblinded ourselves to data from only three patients and developed our methods using only these data. We then tested the proposed SaT method on the entire dataset in a blinded fashion, that is, we did not alter any configuration parameter. The resulting estimation RMSE of 5.2 mmHg relative to EVDs approaches the 3.5 mmHg RMSE of invasive Codman intraparenchymal ICP transducers as reported in [27], which is highly encouraging.

Importantly, we achieved our nICP estimation results without suppressing the mean ABP and CBFV levels by high/band-pass filtering, and instead achieved estimation robustness through the use of a prior distribution. We attempted to keep this prior distribution as generic as possible. To this end, we used \( \sigma_1 = 10 \) mmHg, whereas the standard deviation in the 46 training windows that we used to generate our prior distribution was less than 3 mmHg. Likewise, we modeled the likelihood of low ver-
sus high ICPs in a 4:1 ratio by assigning appropriate weights to the tGMM prior distribution components. The likelihood of encountering high ICPs in our dataset, however, is negligible. In addition, we attempted as much as was possible to develop a method that is least dependent on prior information, which prompted selecting the second-order exponential likelihood model along with selecting the mode estimator of the posterior distribution as the final nICP estimate (the mode is least dependent on the ICP scan range). This objective also provided impetus for developing the PDA and SaT approaches. Furthermore, the empirical sensitivity analyses in Chapters 3 and 4 provide valuable evidence with regards to our method’s dependence on prior information. These analyses indicate that while the estimation bias may vary linearly (with a slope less than unity) with the prior distribution’s mode, \( \mu_1 \), the estimation RMSE, that is considered a more important measure of estimation accuracy than bias, remains largely invariant to such changes.

As was shown in Chapter 4, the proposed SaT method successfully tracked transient ICP trends. That it performs accurately on our clinical data with the same configuration parameters is therefore highly encouraging. The SaT nICP estimation accuracy suffered in two recordings in which the ABP signals showed signs of catheter clogging. This can be addressed in the future by introducing checks on the physiologic plausibility of input signals. Tracking can then be disabled for the duration of such data windows.

The estimation framework proposed in this thesis addresses several of the challenges outlined earlier in Section 2.4. Specifically, our method proposes scanning over a range of plausible time offsets between ABP and CBFV signals instead of using one fixed offset. Moreover, we proposed combining model-based and probabilistic reasoning for nICP estimation, which partially addresses the challenges posed by using the radial ABP as a surrogate for the cerebral ABP and the uncertainty introduced by improper CBFV measurements. Furthermore, we proposed using a simple, linear description of inter-estimation-window ICP dynamics, and we combined this description with the observed nICP changes to propose a method that is relatively independent of prior distributions and that can track a wider range of transiently varying ICPs than
that of the original, pseudo-Bayesian scheme. These contributions address some of the shortcomings of the Kashif approach outlined in Section 2.4 and may be summarized as follows.

- We proposed incorporating model-based nICP estimation within a Bayesian framework. Our description bypasses the need for applying conventional computationally intensive Bayesian system identification techniques by considering a discrete set of possible ICP and time offset pairs.

- In addition, we proposed using a simple, linear model of inter-estimation-window ICP dynamics for tracking nICP longitudinally, potentially across a wide range of ICPs.

- Our proposed framework computed nICP estimates with negligible ensemble bias and with an RMSE of 5.2 mmHg – values that are well within clinically acceptable error bounds – in data from a pediatric population not limited to TBI patients.

- Our method achieves its estimation accuracy without suppressing mean ABP and CBFV levels.

- We demonstrated that our method successfully tracked ICP changes in subjects undergoing head-up tilt experiments using noninvasively measured arterial blood pressure. This therefore suggests that our method might pave the way towards truly noninvasive ICP monitoring via noninvasive ABP and CBFV measurements.

Future work in this direction can focus on overcoming the existing limitations of our work. A fundamental limitation, for instance, is that the ICPs in our clinical database do not vary greatly. While we have attempted, with the aid of tilt-table experiments and with the synthetic data of Chapter 4, to investigate our method's behavior in ICP ranges outside that of our present clinical database, it remains desirable to test this method on data with greater ICP variation. This is difficult, however,
since modern neuro-critical care guidelines dictate that any ICP excursions (for example beyond 22 mmHg) should be lowered aggressively. It is therefore difficult to collect data with abnormally high ICPs. A further limitation of our present work is that we estimate the mean ICP levels only, and a possible future course of exploration might be to noninvasively estimate ICP pulsatility as well. Furthermore, as was shown in the previous chapter, our testing data included three recordings where the ICP/rABP quality was unreliable. Thus, work can be done in refining our present noise-free data selection procedure. These and other possible avenues for further work are presented in the next section.

6.2 Future work

Possible future work may focus on testing our proposed method on a larger dataset comprising subjects with more diverse pathologies, age and gender. Moreover, on the data collection and preprocessing front, the following aspects may be further explored:

- Checks of physiological plausibility may be developed and integrated into our preprocessing chain. The existing signal quality assessment protocol should be expanded to include ICP signal quality in addition to the CBFV and ABP signal quality.

- The present signal quality assessment routine should be tailored to generate real-time signal quality assessments. This would enable translation of our method to the bedside.

- Statistical signal processing techniques may be employed to remove CBFV signal artifacts. For example, ABP signals may be set as input to adaptive filters that use the corresponding CBFV as a reference. The adaptive filter would then attempt to transform the ABP into the CBFV waveform, and in doing so, will reduce any CBFV signal artifacts that are not simultaneously present in the ABP.
• At present, we used device-generated CBFV signals. Alternative CBFV estimation algorithms such as those proposed in [48, 49] may also be used for generating CBFV signals from raw received Doppler ultrasound data.

• Work may be done to improve CBFV signal quality at the TCD device level. Accelerometers may be attached to the TCD probes, and the measured accelerations may be used to cancel motion artifacts in the CBFV signals. Such ideas have been proposed previously for improving photo-plethysmogram recordings, for instance in [50].

• A wearable phased-array TCD device has been proposed in [51], where the authors use electronic ultrasound beam-steering to potentially reduce motion-artifacts in the recorded CBFVs. This avenue may be developed and explored further for nICP estimation.

• We have used invasively measured rABP recordings for estimating ICPs in our clinical dataset. Our estimation results on data from tilt-table experiments where the ABP data were recorded via noninvasive monitors, however, suggest that the proposed framework might be able to generate accurate nICP results with noninvasive ABP monitors too. Thus, future work can explore the feasibility of using such noninvasive ABP monitors for nICP estimation in clinical settings. To this end, we have recently proposed a method [52] to reduce differences between radial and noninvasive ABP recordings. The method of [52] can potentially be integrated into our nICP estimation framework to yield fully noninvasive ICP monitoring.

We employed the two-element Kashif model in our method, and found that this model, in combination with a prior belief, generated nICP estimates with clinically acceptable accuracy. Thus as a next step,

• Work may focus on harnessing information in the estimated model resistance and compliance both for monitoring a subject’s cerebral autoregulation status, and for assessing nICP estimation confidence on a window-by-window basis.
• Negative compliance estimates, for instance, may be indicative of poorer estimation performance. Estimation windows with negative compliance estimates, therefore, should be analyzed in greater detail.

Furthermore, avenues for refinement of the SaT method include:

• Exploring time-varying linear models of cerebral autoregulatory dynamics. Our present method employs a single-state ICP-change-prediction model with a fixed parameter value. This parameter value can be switched in realtime to better describe patients' hemodynamic statuses and this can lead to improved stability and tracking speed. The resulting method, however, would require robust schemes to switch between appropriate parameter values.

• Higher-order models such as the ones proposed in [38, 39] may be integrated within the Bayesian framework. Estimating parameters of such higher-order models might require constrained optimization schemes in order to counter non-uniqueness problems.

• We showed that the SaT approach can be susceptible to drifts in cases, for instance, where the radial ABP shows evidence of clogging. Periodic recalibration stages may be interleaved in the SaT method to guard against such situations. This can potentially be achieved, for example, by using both PDA and SaT methods in parallel, and correcting the estimates of one method by analyzing the other method’s estimates.

• Our method generates a probability distribution of ICPs for each estimation window. Estimation confidence metrics that are derived from these distributions may be further developed and explored.

Continuous noninvasive ICP monitoring can benefit a large number of patients. The nICP estimation framework proposed in this thesis hopefully paves the way towards developing a reliable, continuous, realtime, accurate, and fully noninvasive ICP monitoring device that can improve the state of neuro-critical care across the world.
Appendix A

Review of Kalman filtering

This appendix relates to our ICP tracking approach in Chapter 4 and reviews the Kalman filter which is a framework for tracking the state, $\theta[m]$, of a (possibly time-varying) linear, discrete-time dynamical system over time. Here, $\theta[m] \in \mathbb{R}^k$, and $m$ is the discrete-time sampling index. Following the development in Speyer and Chung [53], we assume that the system of interest is described by two models. The first is of the form

$$\theta[m + 1] = \Gamma_m \theta[m] + \Psi_m v[m]$$  \hfill (A.1)

Here, $\{v[m] \in \mathbb{R}^k, m = 1, 2, \ldots\}$ is a zero-mean, IID Gaussian noise sequence with covariance $V_m \in \mathbb{R}^{k \times k}$. Also, $\Psi_m \in \mathbb{R}^{k \times k}$ and $\Gamma_m \in \mathbb{R}^{k \times k}$ are state-space and noise-mixture descriptions, respectively. The second model is called the measurement model, and is of the form

$$z[m] = H_m \theta[m] + u[m]$$  \hfill (A.2)

where $H_m \in \mathbb{R}^{l \times k}$, and $z[m] \in \mathbb{R}^l$ is a measured output corrupted by another zero-mean, IID Gaussian measurement noise sequence $\{u[m] \in \mathbb{R}^l, m = 1, 2, \ldots\}$ with covariance $U_m \in \mathbb{R}^{l \times l}$.

The state-estimation task is to estimate for each $m$, an a posteriori probability distribution, $p(\theta[m] \mid Z_m)$, of $\theta[m]$ conditioned on $Z_m = \{z[1], \ldots, z[m]\}$. Here $Z_m$ is the observed output sequence up to $m$. The state estimation can be done through an iterative process where the a posteriori distribution at $m - 1$, $p(\theta[m - 1] \mid Z_{m-1})$,
is first used to obtain \( p(\theta[m] \mid Z_{m-1}) \), the prediction of \( \theta[m] \) using only the outputs up to \( m - 1 \). In the next step, this prediction is updated by incorporating \( z[m] \), the actual observed output at \( m \).

For the system description in Equations A.1 and A.2, it can be shown [53] that\(^1\)

\[
\begin{align*}
p(\theta[m] \mid Z_{m-1}) &= \mathcal{N}(\hat{\theta}_{m|m-1}, \hat{P}_{m|m-1}) \\
p(\theta[m] \mid Z_m) &= \mathcal{N}(\hat{\theta}_{m|m}, \hat{P}_{m|m})
\end{align*}
\]

where \( \mathcal{N}(\theta, P) \) is the multivariate Gaussian distribution with mean \( \theta \) and covariance \( P \), and

\[
\begin{align*}
\hat{\theta}_{m|m-1} &= \Gamma_{m-1}\hat{\theta}_{m-1|m-1} \\
\hat{P}_{m|m-1} &= \Gamma_{m-1}\hat{P}_{m-1|m-1}\Gamma_{m-1}^\top + \Psi_{m-1}V_{m-1}\Psi_{m-1}^\top \\
\hat{P}_{m|m} &= (\hat{P}_{m|m-1}^{-1} + H_m^\top U_m^{-1}H_m)^{-1} \\
\hat{\theta}_{m|m} &= \hat{\theta}_{m|m-1} + \hat{P}_{m|m}H_m^\top U_m^{-1}(z[m] - H_m\hat{\theta}_{m|m-1})
\end{align*}
\]

where these equations are solved for \( m > 0 \) by using an initial prior belief about the state at \( m = 0 \), \( p(\theta[0]) = \mathcal{N}(\hat{\theta}_0, P_0) \). The Equations in A.5 are collectively called the Kalman filter equations, and this framework is attractive because normal distributions are completely characterized by their means and covariances that can in turn be computed by relatively simple matrix computations.

Finally we note that the Kalman filter attains a simpler and more intuitive form [53] for a single-state system \((k = 1)\) of the form

\[
\begin{align*}
\theta[m + 1] &= \gamma_m\theta[m] + \psi_m v[m] \\
z[m] &= h_m\theta[m] + u[m]
\end{align*}
\]

where \( \theta[m] \), \( \gamma_m \), \( h_m \) and \( \psi_m \) are scalars, and \( v[m] \) and \( u[m] \) are IID, zero-mean Gauss-

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\(^1\)The Kalman filter can be shown to be an optimal minimum-variance estimator for linear state-space systems even if \( v[m] \) and \( u[m] \) are IID but non-Gaussian. The interested reader is referred to Chapter 4 of Speyer and Chung [53] for a proof.
Gaussian random sequences with variance $\sigma_{v[m]}^2$ and $\sigma_{u[m]}^2$, respectively. In this case, for $h_m = 1$,

$$\tilde{\theta}_{m|m-1} = \gamma_{m-1} \tilde{\theta}_{m-1|m-1}$$

$$\sigma_{m|m-1}^2 = \gamma_{m-1} \sigma_{m-1|m-1}^2 + \psi_{m-1}^2 \sigma_{v[m]}^2$$

$$x = \frac{\sigma_{m|m-1}^2}{\sigma_{m|m-1}^2 + \sigma_{u[m]}^2}$$

$$\sigma_{m|m}^2 = x \sigma_{u[m]}^2$$

$$\tilde{\theta}_{m|m} = (1 - x) \tilde{\theta}_{m|m-1} + x z[m]$$

(A.8)

Here, the posterior mean, $\tilde{\theta}_{m|m}$, can be interpreted as the fusion of two estimates, one derived from the model, and the other based on the observed output. The relative importance ascribed to each of the two estimates is based on the inverse of the variance of that estimate. In our SaT approach of Chapter 4, we draw inspiration from this idea in merging predicted inter-estimation-window changes with noninvasively observed changes in the ICP.
Bibliography


