Outcome Prediction for Patients with Traumatic Brain Injury with Dynamic Features from Intracranial Pressure and Arterial Blood Pressure Signals: A Gaussian Process Approach

Marco A.F. Pimentel, Thomas Brennan, Li-wei Lehman, Nicolas Kon Kam King, Beng-Ti Ang, and Mengling Feng

Abstract Previous work has been demonstrated that tracking features describing the dynamic and time-varying patterns in brain monitoring signals provide additional predictive information beyond that derived from static features based on snapshot measurements. To achieve more accurate predictions of outcomes of patients with traumatic brain injury (TBI), we proposed a statistical framework to extract dynamic features from brain monitoring signals based on the framework of Gaussian processes (GPs). GPs provide an explicit probabilistic, nonparametric Bayesian approach to metric regression problems. This not only provides probabilistic predictions, but also gives the ability to cope with missing data and infer model parameters such as those that control the function's shape, noise level and dynamics of the signal. Through experimental evaluation, we have demonstrated that dynamic features extracted from GPs provide additional predictive information in addition to the features based on the pressure reactivity index (PRx). Significant improvements in patient outcome prediction were achieved by combining GP-based and PRx-based dynamic features. In particular, compared with the a baseline PRx-based model, the combined model achieved over 30 % improvement in prediction accuracy and sensitivity and over 20 % improvement in specificity and the area under the receiver operating characteristic curve.

Keywords Gaussian process • Intracranial pressure • Dynamic features and outcome prediction

M.A.F. Pimentel
Department of Engineering Science, Institute of Biomedical Engineering, University of Oxford, Oxford, UK

T. Brennan • L.-w. Lehman
Laboratory for Computational Physiology, Institute for Medical Engineering and Science, E25-505 Massachusetts Institute of Technology, 77 Massachusetts Ave, Cambridge, MA 02139, USA

N.K.K. King • B.-T. Ang
National Neuroscience Institute, Singapore, Singapore

M. Feng (✉)
Laboratory for Computational Physiology, Institute for Medical Engineering and Science, E25-505 Massachusetts Institute of Technology, 77 Massachusetts Ave, Cambridge, MA 02139, USA

Department of Data Analytics, A*STAR, Institute for Infocomm Research, Singapore, Singapore
e-mail: mfeng@mit.edu

Introduction

Background

Traumatic brain injury (TBI) is a serious health hazard worldwide [9, 26], not only because of the high incidence of death it causes (22 % of all TBI cases result in death), but also because of the large number of individuals who are left with some form of disability [14]. In Singapore, TBI is the number 1 killer of young male adults aged younger than 40, and it accounts for one-half of trauma-related deaths [19]. In Europe, around 1 million people suffer from TBI annually; in the United States, it is 1.5 million.

The recovery rate and long-term functional outcome of a patient with TBI are determined by the critical-care management of the patient [18]. In particular, the most crucial period is in the neurointensive care unit (NICU) immediately following the head injury [24, 28]. To prevent secondary insults to patients with TBI, continuous brain monitoring has become the gold standard in most NICUs around the globe [1, 25]. The contemporary multimodal brain monitoring in NICUs includes the monitoring of intracranial pressure (ICP), mean arterial pressure (MAP), brain tissue oxygenation (PbtO2), and brain temperature [27, 29].

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Problem

Predicting outcomes in patients with TBI has been a major research questions. Prediction methods have been proposed based on the values of ICP [7, 8, 20, 21], the variability of ICP [3, 4], the high-resolution morphologies in ICP [15, 16] and the combination of ICP and other physiological signals [3, 13]. We have learned that physiological signals contain complex dynamical structures that reveal the state of the underlying control and regulatory systems [6, 17]. Tracking the dynamic features that describe the time-variant dynamic changes and patterns in physiological signals can provide additional predictive information beyond that derived from static features based on snapshot measurements.

The pressure reactivity index (PRx) [13] is one of the most commonly used dynamic features. PRx is a continuous index that quantifies cerebrovascular reactivity and approximates global cerebral autoregulatory reserve by observing the response to slow spontaneous changes in MAP [3], i.e., PRx captures the continuous interactions between MAP and ICP. PRx ranges between 1 and −1. A PRx value close to 0 indicates preserved autoregulation, whereas a PRx value close to 1 indicates impaired autoregulation. Abnormal PRx values were found to be associated with poor outcome for patients with TBI [3]. However, PRx suffers from some limitations. First, PRx requires regular and continuous sampling of the signals. In reality, however, missing values are commonly observed in real brain monitoring signals (as shown in Fig. 1). Second, as PRx is defined based on Pearson's correlation, it is very sensitive to noise and outliers in signals. Similar limitations are also observed in most of the previously proposed dynamic features.

Contributions

To address the limitations of PRx and other proposed dynamic features, we propose a probabilistic framework to extract dynamic features from brain monitoring signals based on the concept of a Gaussian process (GP). GP has been a popular probabilistic model for time series [23] and continuous sensor data modeling [5]. The GP model is able to summarize the dynamic patterns and structures in time-series signals into a small set of hyperparameters. Unlike other dynamic feature extraction methods, the GP model not only provides probabilistic predictions (i.e., each data point is estimated as a distribution rather than as a fixed point), but also gives the ability to infer model parameters such as those that control the function shape, noise level, and dynamics of the signal. This makes GP robust against noise and outliers, and it also allows us to calculate a confidence interval to quantify the statistical uncertainty of the underlying estimation. Moreover, the GP model does not require evenly sampled data, which makes it an ideal choice for brain monitoring signals with missing values. Through experimental evaluation, we have demonstrated that dynamic features extracted based on GP provide additional predictive information in addition to PRx. Significant improvements in patient outcome prediction were achieved by combining GP-based and PRx-based dynamic features.

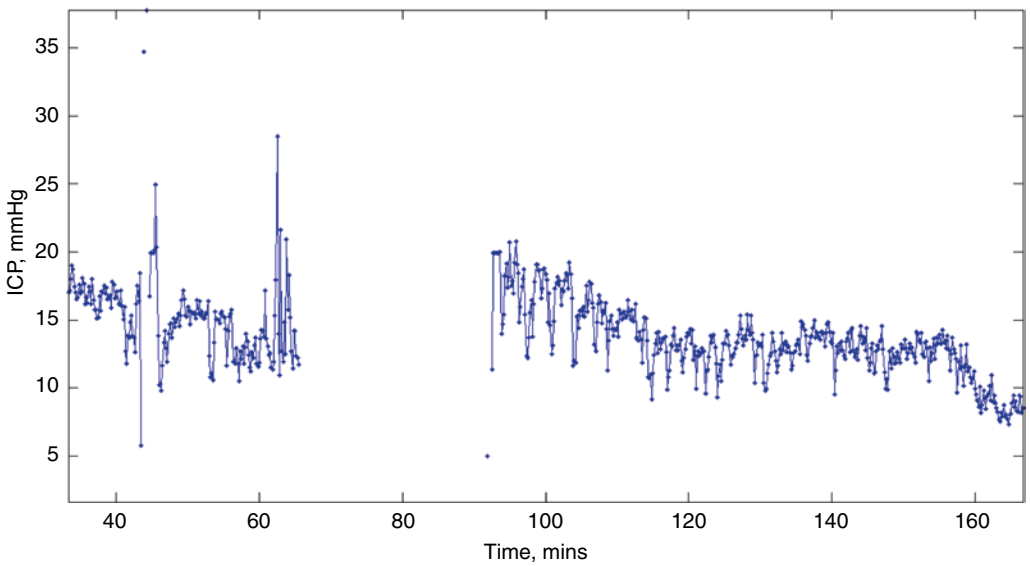

Fig. 1 An example of intracranial pressure (*ICP*) signal with missing values

Materials and Methods

Patients and Monitoring

This analytical study was conducted using the monitoring data of TBI patients who were admitted to the neurocritical care unit of a tertiary hospital between January 2009 and December 2010. Thirty-five patients who underwent invasive monitoring of ICP and MAP for more than 24 consecutive hours were selected for the study. After informed consent was obtained, intraparenchymal probes were inserted based on the preoperative CT findings. ICP was continuously monitored using a fiber-optic intraparenchymal gauge (Codman and Shurtleff, Taynham, MA, USA). MAP was measured through an arterial line from the radial artery using a standard pressure monitoring kit (Biosensors International Pte. Ltd., Hillegom, Netherlands). The continuously monitored physiological readings were sampled and recorded every 10 s using ICM+ software [12]. As can been seen in Fig. 1, because both the signals were recorded from the actual clinical environment, the signals were inevitably contaminated by artifacts and missing values. All patients underwent multimodality monitoring with continuous recording of clinical data on a Hewlett-Packard Carevue System.

Patients were managed based on a protocol incorporating the guidelines for the management of severe TBI [3]. The ICP of patients was optimized based on an incremental regimen to maintain ICP <20 mmHg and CPP > 60 mmHg. First-tier ICP control treatment included elevation of the bed to 30°, sedation with propofol (2–10 mg/kg/h), and adequate analgesia (intravenous morphine 1–5 mg/h). Boluses of 20 % mannitol (2 mg/kg up to a plasma osmolarity of 320 mosmoI/L) were administered, if there was a sudden increase in ICP. Second-tier measures then included paralysis, cooling of the core body temperature to 36 °C and institution of a barbiturate coma, which is achieved with intravenous thiopentone 250 mg boluses of over 10–20 min (up to a total dose of 500–1,000 mg), with a maintenance dose of 125–500 mg/h titrated to ICP control or to maintain burst suppression on electroencephalography (EEG). Surgical decompression was also used, when ICP could not be controlled with second-tier measures.

Patient Outcome

On discharge from the NICU, patients were divided into five groups based on their outcome. Among the 35 patients, 13 (36 %) were *dead*, 7 (20 %) were in a *vegetative state*, 5 (14 %) suffered from *severe disability*, 3 (9 %) suffered from *mild disability*, and 7 (20 %) achieved *good recovery*. For this study, we grouped the patients into two categories. The 20 patients who were dead or in a vegetative state were grouped together as *non-survivors (with a vegetative state)*, and the 15 patients who suffered severe or mild disabilities or who achieved good recovery were grouped together as the *survivors*. As a result, we had a quite a balanced breakdown of 56 and 44 % of patients respectively.

Extraction of Dynamic Features from ICP and MAP Signals: A Gaussian Process Approach

We propose a method that uses the GP framework [22] to extract dynamic features from ICP and MAP signals. These features were used to improve the outcome prediction of TBI patients.

An Introduction to Gaussian Processes

The GP framework is a nonparametric Bayesian regression tool that has been used in several machine-learning problems [22]. Compared with other regression techniques, such as support vector regression, GP-based models have the advantage that prior knowledge of the functional behavior (such as periodicity or smoothness) can easily be integrated. In this section, we provide a brief introduction to GP models.

Let $D = \{(X_i, Y_i) | i = 1,\ldots,n\}$ be our data set of observations composed of input–output pairs, with $X_i, Y_i \in \mathbb{R}$. We consider the regression model $y = f(x) + \varepsilon$, which expresses a dependent variable y in terms of an independent variable x, via a latent function, and a noise term. The function can be interpreted as being a probability distribution over functions, such that

$$f(x) \sim GP\left(m(x;\theta_M), k(x,x';\theta_K)\right) \tag{1}$$

where $m(x;\theta_M)$ is the mean function of the distribution, which has hyperparameters θ_M, and $k(x,x';\theta_K)$ is a covariance function, which has hyperparameters θ_k and describes the coupling between two values (X and X') of the independent variable as a function of the (kernel) distance between them (the hyperparameters' terms will be omitted in the following equations for simplicity). The nature of the GP is such that, conditional on observed data, predictions can be made about the function values y_* at any "test" input location x_* by computing the posterior density $p(y_* | x_*, D)$, which is Gaussian,

$$p(y_* | x_*, x, y) \sim N\left(y_*, var[y_*]\right) \tag{2}$$

where the mean and variance are given as:

$$y_* = m(x_*) + k(x_*, x) k(x, x)^{-1} \left(y - m(x)\right) \tag{3}$$

$$var\left(y_*\right) = k\left(x_*,x_*\right) - k\left(x_*,x\right)k\left(x,x\right)^{-1}k\left(x_*,x\right)^T \quad (4)$$

The mean and covariance functions, $m(x_*)$ and $k(x_*,x)$, encode our prior knowledge regarding the structure and functional behavior of the time series that we wish to model. There is a large class of mean and covariance functions (as shown in Rasmussen and Williams [22]). In this study, although it did not fully describe the true phenomenon, we assumed, for the simplicity of discussion, that our observations of ICP and MAP were (independently) obtained from an underlying linear decay with an unknown additive constant. Our mean function is hence described by

$$m\left(x\right) = \theta_a + \theta_b.x, \theta_M = \left\{\theta_a, \theta_b\right\} \quad (5)$$

where θ_a and θ_b are the hyperparameters of the mean function. Intuitively, a corresponds to the additive constant (i.e., the overall mean of the signal), and b corresponds to the overall trend of the signal (see Fig. 1). For the covariance function, the most frequently used is the squared-exponential covariance function:

$$k\left(x,x'\right) = {\theta_d}^2 \exp\left(-\frac{\left(x-x'\right)^2}{2{\theta_c}^2}\right), \theta_K = \left\{\theta_c, \theta_d\right\} \quad (6)$$

where θ_c is the length-scale parameter that determines the typical timescale on which the function varies (i.e., it corresponds to how smooth the function is), and θ_d is the amplitude that determines the typical amplitude of deviation from the mean (i.e., it is associated with the variance of the signal).

Dynamic Feature Extraction With Gaussian Process

The framework described is traditionally used in regression problems, in which the underlying latent function (and confidence level) of the data is obtained. In this work, we use the GP framework not only to perform regression on each one of the signals (ICP and MAP signals), but also to extract the corresponding hyperparameters of the GP models that are fitted to the data and use them as features in classification tasks.

One of the main advantages of the probabilistic GP framework is the ability to choose the hyperparameters and covariances directly from the training data used for regression. In our study, the selection of the priors for the hyperparameters of $m()$ and $k()$ has been performed using a grid-search optimizer by minimizing the negative log marginal likelihood with regard to the hyperparameters and noise level. The optimized hyperparameters of the mean and covariance functions contain information about the behavior of the physiological signals (such as the overall trend and variability of the data), and can then be used for classification tasks (see Fig. 2).

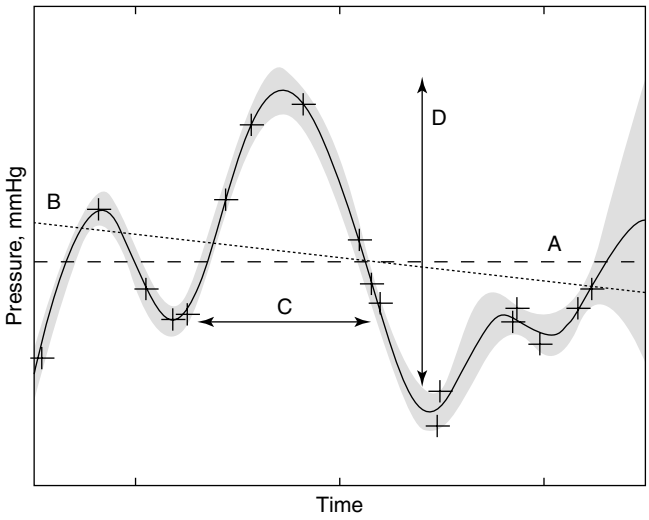

Fig. 2 Dynamic feature extraction based on the Gaussian process (*GP*) model. A GP regression model is fitted to the data points (+), where the *solid line* refers to the fitted mean function and the 95 % confidence region is highlighted as *shaded area*. Dynamic features *A* and *B* correspond to the constant and trend values of the mean function, and dynamic features *C* and *D* correspond to the length-scale (measure of roughness/smoothness) and magnitude (measure of variability) parameters of the covariance function

Experimental Evaluation

In this study, we used the first 24 h of 10-s mean ICP and MAP signals from the study cohort. Both mean ICP and MAP signals were preprocessed using a 3-sigma filter to remove noise and artifactual data [11]. PRx was used as the baseline to demonstrate the value of the additional information that can be captured with the dynamic features extracted based on the GP model. How the additional information can help to better predict TBI patients' outcome was experimentally evaluated. PRx was calculated as a moving (Pearson's) correlation coefficient between the MAP and ICP signals averaged over 10 s with a 5-min moving time window (i.e., 30 consecutive ICP and MAP data points) [13]. Additionally, we used the probabilistic GP framework described in the previous section to model both ICP and MAP signals and obtain the optimized features from the corresponding mean and covariance functions. We evaluated the ability of these dynamic features to provide additional information for discriminating TBI patient outcomes.

To assess the performance of the proposed approach, three different outcome prediction models were built: the *PRx-based model*, the *GP-based model*, and the *combined model*. The features used in the *PRx-based model* included the mean and variance of PRx, the proportion of time that the PRx value is above the critical threshold of 0.2 and 0.35 as defined in [13], and the 25th, 50th, and 75th percentile values of mean ICP and MAP signals. The *GP-based model* used

the hyperparameters of the mean and covariance functions of the trained GP as the predictive features. As illustrated in Fig. 2, the hyperparameters of the GP model characterized the dynamic variations of ICP and MAP signals. The *combined model* merged the features from both the *PRx-based* and the *GP-based model*. Logistic regression classification was used to predict patients' recovery outcomes using a "leave-one-out" approach, and the performance of the different models was assessed using the predictor's accuracy, sensitivity and specificity, and the area under the receiver operating characteristic curve (AUROC).

Results and Discussion

Experimental Results

Figure 3a, b shows a 2-h window of the ICP and MAP signals for one sample patient and the regression results of the estimated GP model. We can see that the GP model provided a good estimation of the underlying trends of the ICP and MAP signals. Moreover, the GP model was able to estimate the underlying signals even in the presence of missing values (e.g., between minute 65 and 95 in Fig. 3). On the other hand, we observed that, limited by its definition, PRx cannot be calculated for the period of missing values (Fig. 3c).

Table 1 compares the performance of the *PRx-based model*, the *GP-based model*, and the *combined model*. The performance of the three models was evaluated based on their *accuracy*, *sensitivity*, *specificity*, and *AUROC*. As previously mentioned, patients in the study were divided into the *non-survivors* (including vegetative state) and *survivors*. We arbitrarily define the *non-survivors* (including the vegetative state) group as the *positive* class and the *survivors* group as the *negative* class for performance evaluation. The *accuracy* is then defined as $(TP+TN)/(TP+TN+FP+FN)$, the *sensitivity* is defined as $TP/(TP+FN)$, and *specificity* is $TN/(TN+FP)$, where TP means true positive, TN true negative, FP false positive, and FN false positive.

We observed that, compared with the PRx-based model, the GP-based model achieved 22 % improvement in *accuracy*, 28 % improvement in *sensitivity*, 4 % improvement in specificity, and 11 % improvement in *AUROC*. When we

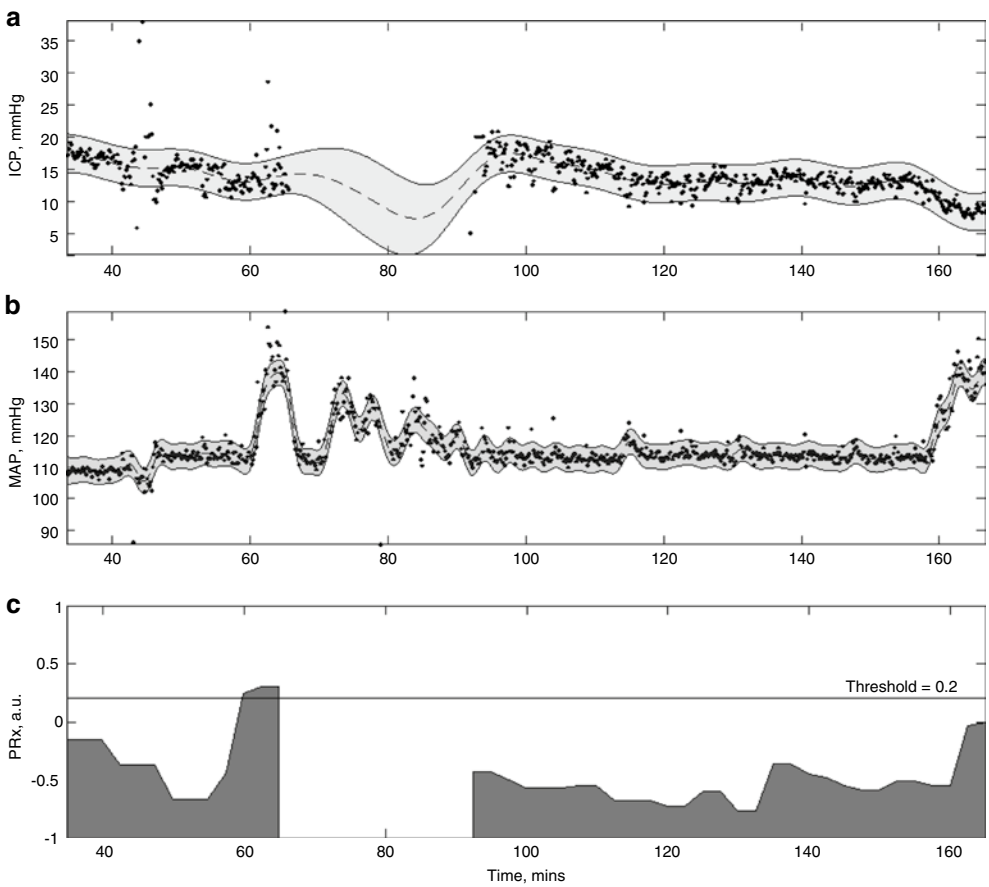

Fig. 3 (**a**, **b**) Fitted GP regression model on ICP and mean arterial pressure (*MAP*), where the *dashed lines* indicate the fitted mean functions and the 95 % confidence regions are highlighted as the shaded areas. (**c**) Calculated pressure reactivity index (*PRx*) for the corresponding ICP and MAP signals

Table 1 Comparison of the prediction performance of the pressure reactivity index (PRx)-based, Gaussian process (GP)-based, and combined models

Model	Accuracy	Sensitivity	Specificity	AUROC
PRx-based	0.57	0.6	0.53	0.63
GP-based	0.7 (↑22 %)	0.77 (↑28 %)	0.55 (↑4 %)	0.7 (↑11 %)
Combined	0.74 (↑30 %)	0.83 (↑33 %)	0.65 (↑22 %)	0.76 (↑21 %)

The performance improvement achieved by the GP-based and combined models in contrast to the PRx-based model is also presented
AUROC area under the receiver operating characteristic

combine features from both the PRx-based and GP-based models, we achieved further improvements in accuracy (30 % improvement), sensitivity (33 % improvement), and AUROC (21 % improvement), and we improved the specificity significantly from 0.53 to 0.65 (equivalent to a 22 % increase). These results indicate that features from the GP model that describe the dynamics of the ICP and MAP signals offer predictive information on patients' outcomes.

Strengths and Limitations of GP

Through theoretical and experimental investigations, we observed the following strengths of the GP model. Distinct from PRx or other dynamic feature extraction methods, the GP model estimates each data point of a signal as a distribution rather than as a fixed point. As a result, in addition to the point (mean) estimation, GP is able to provide a 95 % confidence interval that statistically quantifies the underlying uncertainties of the estimation. This also makes the GP model extremely robust against noise, artifacts, and outliers that are frequently present in the signals. Moreover, the GP model does not require a regular sampling rate from the underlying time-series signal (i.e., it may be applied to time series that are unevenly sampled). This makes the GP model a good choice for brain monitoring signals with gaps of missing values. As shown in Fig. 3a, when a segment of data is missing, the GP model was able to provide a probabilistic estimation of the missing values with a mean expected value and the associated uncertainty of the estimation (the 95 % confidence interval region). In addition, the hyperparameters of the GP model are interpretable features that describe dynamic structures and patterns of the underlying signal. For example, in our study, the slope parameter of the mean function captures the low-frequency long-term trends in the ICP and MAP signals; the length–scale parameter of the covariance function describes the "roughness" of the signals; the magnitude parameter of the covariance function measures the variability of the signals. Based on the hyperparameters of GP, the types of dynamic structures or patterns in the brain monitoring signals that are most predictive for the outcomes of TBI patients can be investigated. This is one of the future research directions we plan to pursue when more patient data have been collected.

The application of the GP model can be limited by its assumption of a Gaussian likelihood function for each data point. This assumption may not be true in some cases for the brain monitoring signals. Let us take the ICP signal as an example. Depending on the patient's physiological and recovery status, the distribution of ICP values may not follow a symmetrical distribution like the Gaussian. It may have a heavier tail on one side than on the other. In this case, to accommodate the heavier tail, the GP model produces a wider confidence interval region, indicating a higher level of estimation uncertainty. The GP model is also limited by the relatively high computational complexity required to infer its hyperparameters. The worst case computational complexity for the hyperparameter estimation is $O(N^3)$, where N is the number of data points in the signal. Therefore, as the number of data points, N, grows, effective parallel processing methods are required for GP model inference [2, 10]

Conclusion

To achieve a more accurate prediction of the outcomes of TBI patients, we proposed to use the probabilistic Gaussian process framework to extract dynamic features from the brain monitoring signals. Compared with PRx and other dynamic features, the GP model has a number of advantages that were described throughout the paper. Through experimental evaluation, we have demonstrated that features related to the dynamics of the physiological signals may be easily extracted from GP models and provide additional predictive information in addition to PRx-based features. Significant improvements in patient outcome prediction were achieved by combining GP-based and PRx-based dynamic features. Both our theoretical and experimental studies suggested that the GP framework has great potential as a probabilistic model to summarize dynamic features from brain monitoring signals for more accurate TBI patient outcome prediction.

Future work will involve assessing the utility of the proposed approach after including other physiological variables,

and extending the Gaussian process framework to include the dependency of the variables and track the coupling of ICP and MAP during the recovery of the patient in the NICU.

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Conflict of Interest Statement We declare that we have no conflicts of interest.

References

1. Abad N, Druzgalski C (2009) Medical and engineering support and needs in neurological intensive care units. In: Proceedings of the PAHCE'09, Mexico City, Mexico, pp 157–159
2. Arindam C, Prasanth BN, Andy JK (2002) A data parallel approach for large-scale Gaussian process modeling. Proceeding of SDM
3. Balestreri M, Czosnyka M, Steiner LA, Hiler M, Schmidt EA, Matta B, Menon D, Hutchinson P, Pickard JD (2005) Association between outcome, cerebral pressure reactivity and slow ICP waves following head injury. Acta Neurochir Suppl 95:25–28
4. Catherine JK, Robert LB, Pamela HM (2008) Intracranial pressure variability and long-term outcome following traumatic brain injury. Acta Neurochir Suppl 102:105–108
5. Clifton L, Clifton DA, Pimentel MA, Watkinson PJ, Tarassenko L (2013) Gaussian processes for personalized e-health monitoring with wearable sensors. IEEE Trans Biomed Eng 60(1):193–197
6. Costa M, Goldberger AL, Peng CK (2002) Multiscale entropy analysis of complex physiologic time series. Phys Rev Lett 89:68–102
7. Czosnyka M, Pickard JD (2004) Monitoring and interpretation of intracranial pressure. J Neurol Neurosurg Psychiatry 75:813–821
8. Czosnyka M, Hutchinson PJ, Balestreri M, Hiler M, Smielewski P, Pickard JD (2006) Monitoring and interpretation of intracranial pressure after head injury. Acta Neurochir Suppl 96(4):121–125
9. Dutton R, McCunn M (2003) Traumatic brain injury. Curr Opin Crit Care 9(6):503–509
10. Edward S, Zoubin G (2005) Sparse Gaussian processes using pseudo-inputs. NIPS
11. Feng M, Loy LY, Zhang F, Guan CT et al.(2011) Artifact removal for intracranial pressure monitoring Signals. In: A Robust Solution with Signal Decomposition. Proceedings of 33rd international conference of the IEEE Engineering in Medicine and Biology Society (EMBC)
12. Guendling K, Smielewski P, Czosnyka M, Lewis P, Nortje J, Timofeev I, Hutchinson PJ, Pickard JD (2006) Use of ICM+ software for on-line analysis of intracranial and arterial pressures in head-injured patients. Acta Neurochir Suppl 96(4):108–113
13. Hlatky R, Valadka AB, Robertson CS (2005) Intracranial pressure response to induced hypertension: role of dynamic pressure autoregulation. Neurosurgery 57:9117–9123
14. http://www.slavicabiochem.com/traumaticBrainInjury.html
15. Hu X, Xu P, Scalzo F, Vespa P, Bergsneider M (2009) Morphological clustering and analysis of continuous intracranial pressure. IEEE Transactions on Biomedical Engineering 56(3):696–705
16. Hu X, Asgari XP, Vespa P, Bergsneider M (2010) Forecasting ICP elevation based on prescient changes of intracranial pressure waveform morphology. IEEE Transactions on Biomedical Engineering 57(5):1070–1078
17. Ivanov PC, Amaral LA, Goldberger AL, Havlin S, Rosenblum MG, Struzik ZR, Stanley HE (1999) Multifractality in human heartbeat dynamics. Nature 399:461–465
18. Jones P, Andrews P, Midgley S, Anderson S, Piper I, Tocher J, Housley A, Corrie J, Slattery J, Dearden N (1994) Measuring the burden of secondary insults in head-injured patients during intensive care. J Neurosurg Anesthesiol 6(1):4–14
19. Lee KK, Seow WT, Ng I (2006) Demographical profiles of adult severe traumatic brain injury patients: implications for healthcare planning. Singapore Med J 47(1):31–36
20. Marmarou A, Anderson JRL, Ward JD, Choi SC, Young HF, Eisenberg HM, Foulkes MA, Marshall LF, Jane JA (1991) Impact of ICP instability and hypotension on outcome in patients with severe heal trauma. J Neurosurg 75:59–66
21. Marmarou A (2000) Increased intracranial pressure in head injury and influence of blood volume. J Neurotrauma 9:327–333
22. Rasmussen E, Williams CKI (2006) Gaussian processes for machine learning. MIT Press, ISBN 0-262-18253, US
23. Roberts S, Osborne M, Ebden M, Reece S, Gibson N, Aigrain S (2012) Gaussian processes for time-series modelling. Philosophical Transactions of the Royal Society (Part A), 371(1984): online
24. Robertson C, Valadka A, Hannay H, Contant C, Gopinath S, Cormio M, Uzura M, Grossman R (1999) Prevention of secondary ischemic insults after severe head injury. Crit Care Med 27(10):2086–2095
25. Ross N, Eynon CA (2005) Intracranial pressure monitoring. Curr Anaesth Crit Care 16(4):255–261
26. Signorini D, Andrews P, Jones P, Wardlaw J, Miller J (1999) Predicting survival using simple clinical variables: a case study in traumatic brain injury. J Neurol Neurosurg Psychiatry 66(1):20–25
27. Swiercz M, Mariak Z, Krejza J, Lewko J, Szydlik P (2000) Intracranial pressure processing with artificial neural networks: prediction of ICP trends. Acta Neurochir 142(4):531–542
28. Wald S, Shackford S (1993) The effect of secondary insults on mortality and long-term disability after severe head injury in a rural region without a trauma system. J Trauma 34(3):377–382
29. Wright W (2007) Multimodal monitoring in the ICU: when could it be useful? J Neurol Sci 261(1–2):10–15