An Integrated Medical CPS for Early Detection of Paroxysmal Sympathetic Hyperactivity

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***Abstract*—Paroxysmal sympathetic hyperactivity (PSH) is an important clinical problem of severe traumatic brain injury (TBI) which incurs approximately 90% of all TBI-related costs. However, current detection approach is hampered by no consensus clinical diagnostic criteria, paroxysmal episode feature with complex manifestations, and already overloaded clinical activities. These limitations cause delayed recognitions which result in poor clinical outcomes. In this paper, we design an integrated Medical Cyber-Physical System (Medical CPS) for early detection of paroxysmal sympathetic hyperactivity patients. First, a formal model is proposed to describe clinical diagnostic criteria. With the formalized models employed, we implement an early detector and integrate it with revised medical device adapters into Medical CPS. Our system will monitor patient conditions automatically and continuously to relieve medical staff from the heavy burden of clinical activities and provide timely decision supports. Evaluations on 107 clinical cases extracted from medical publications demonstrate the effectiveness and the efficiency of our integrated system.**

***Index Terms*—Paroxysmal Sympathetic Hyperactivity; Medical Cyber-Physical System; Early Detection**

I. Introduction

Paroxysmal sympathetic hyperactivity (PSH) is a syndrome manifested with: simultaneously increased heart rate, respiratory rate, blood pressure, body temperature and other clinical features, such as severe sweating, posturing, etc. It is primarily caused by traumatic brain injury (TBI). Every year, TBI affects millions of Americans, in which up to 33% severe patients have been reported with PSH [7], [13]. Delayed recognition of PSH may increase morbidity, resulting in long-term disability, even death[1]. This situation causes approximately 90% of all TBI-related costs which is worth millions of dollars [10].

To detect PSH, physicians have devoted great efforts to propose a number of diverse criteria sets according to clinical experience [21], [22]. However, through the discussions with physicians, underdiagnoses and misdiagnoses are particularly common in current clinical diagnosis and treatment. First, no universally accepted clinical diagnostic criteria exist because of the limited evidence of pathophysiology and the evolution of PSH definition. Thus, many physicians learn a little background on it. Second, PSH is a syndrome with complex manifestations to which a lot of conditions have similar appearances. Third, the paroxysmal clinical feature requires symptoms to be recurrent and episodic to make a diagnosis. Unfortunately, medical staff are already overloaded at hospitals, and it is impractical to perform frequent clinical monitoring activities.

In this paper, we design an integrated Medical Cyber-Physical System (Medical CPS) for early detection of PSH based on the existing medical knowledge. Efforts to improve medical aspects are out of the scope of this paper. First, we propose a formal model to describe diverse clinical criteria sets uniformly. Physicians can utilize multiple well-known clinical diagnostic criteria sets with a weight vector to monitor a patient. It can reduce physicians' memory load and augment the detection capacity. We implement an early detector in terms of the formal models and integrate it with medical device adapters which are revised on Integrated Clinical Environment [1] into a medical CPS to observe patient vital signs automatically and continuously, which reduces medical staff burden and provides timely decision supports. In our system, we accumulate patient data and usages of clinical criteria in a format which can be used by data science research. To the best of our knowledge, this is the first study on applying Medical CPS to perform early detection of PSH. We evaluate our approach on 97 real-world clinical cases extracted from medical publications on PSH and 10 cases from overlap syndromes which have similar clinical features. Compared to the current approach, our work is able to early detect 17.5% more PSH patients with almost the same false positive rate (3.12%).

This paper is organized as follows. Related work is introduced in Section II. Section III presents a formal diagnostic criteria model to describe diverse clinical criteria and presents our integrated Medical Cyber-Physical System based on the models. Evaluation on real world clinical cases is given in Section IV and we conclude the paper in Section V.

II. Related work

Background of PSH Paroxysmal sympathetic hyperactivity is a syndrome where transient nervous system activity

[1]Cases reported in [21] showed that only 7% of PSH patients achieved a moderate or good recovery, however, 45% with severe disability, 30% with persistent vegetative state and 18% with death.

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occurs manifested with simultaneously increased heart rate, respiratory rate, blood pressure, body temperature and other clinical features, such as severe sweating, posturing and so on. To detect PSH, physicians have proposed many clinical diagnostic criteria sets [21]. Through the systematic literature review, there is a strong agreement on simultaneous and paroxysmal feature. However, some inconsistencies are illustrated as below. *Episode duration and frequency:* In [4], episodes need to persist for more than two weeks, but more than 1 daily episode for at least 3 days in [19]. *Clinical feature composition and severity:* Some features like heart rate, sweating are commonly used, but some vary between criteria sets, like pupillary dilation and muscle tone. However, severity for the same feature may be distinct, like 38.5°C of body temperature in [19] , 39°C in [4] and undefined in [12], respectively.

PSH Detection: Currently, detection of PSH is by manual checks by diagnostic criteria presented in literature or modified according to clinical experience [9]. To our best knowledge, the only "tool" applied to detection of PSH is PSH-AM, which is composed of two components: Diagnosis Likelihood Tool addressing the probability and Clinical Feature Scale assessing the severity to estimate the diagnostic likelihood of PSH [22]. In contrast to our work, it is not a runnable tool and the authors envisage that PSH-AM would be completed daily by medical staff at a standardized time.

Medical CPS: With the proliferation of measuring devices, researchers have been paying attention to Medical CPS to provide continuous high-quality care for patients [17]. One of the main applications focuses on anomaly detection [6], [15], [16]. In contrast to these existing approaches, there are no existing pathophysiologic models or medical guidelines to apply runtime verification technique like [15], [16] and not enough data with accurate event annotations to train data-driven models like [6]. Therefore, we propose a different strategy, involving physicians to customize the formal models and the constraints to perform manual checks for early detection of PSH.

III. Approach

In this section, we present our approach for early detection of PSH. First, we introduce our formal models. Then, the integrated Medical CPS is described.

A. Formal Diagnostic Criteria Model

In this subsection, we introduce the formal diagnostic criteria model to describe the current widely used clinical criteria sets.

a) Model Formalization: As discussed in Section II, clinical criteria consist of a group of clinical features with thresholds to confirm an episode, and duration and frequency of the episodes to confirm a diagnosis. However, each of them may differ between criteria sets. Therefore, we propose a formal diagnostic criteria model to describe them uniformly. Our formal model is specified as an extended automata and the definition is a tuple $\mathcal{M} = \langle S, s_0, s_f, E, C, G, T\rangle$, where:

- S is a set of states: $S = \{s_{1,1}, s_{1,2}, \ldots, s_{i,j}\} \cup \{s_0, s_f\}$, where $s_{i,j}$ is a state corresponding to the episode condition of a patient, indicating the occurrence of the j-th episode in the i-th day.
- s_0 is the initial state where a model starts, also labeled as $s_{0,0}$.
- s_f is the final state where a model reaches indicating PSH confirmed, also labeld as $s_{max,0}$.
- E is a set of events: $E = \{e_1, e_2, \ldots, e_n\}$, where e_i is an event to trigger a transition. In each event, there is a set of vital signs of a patient labeled as $e.vs$ with a timestamp of these vital signs labeled as $e.tt$.
- C is a tuple of criteria variables: $C = \langle d, F, \xi\rangle$, where d is the least episode duration to make a diagnosis; F is an array of frequencies, where f_i is the least episode frequency of the i-th day; ξ is a predicate to describe the occurrence of an episode under a given event.
- G is a set of guards: $G = \{g_{(s_0,s_{1,1})}, \ldots, g_{(s_{d,f},s_f)}\}$, where $g_{(s_{i,j},s_{m,n})}$ is a Boolen expression defined in Equation 1 on an event e to guard the transition between two states labeled as $s_{i,j}$ and $s_{m,n}$. A guard is composed of three predicates referring to episode occurrence constraint as $C.\xi$, episode frequency constraint as fre and episode duration constraint dur, respectively. We set $g_{(s_0,s_{1,1})}$ as $True$ to initialize our model.
- T is a set of transitions: $T = \{t_1, t_2, \ldots, t_n\}$, where t_i is the transition between two states triggered by an event e and guarded by a guard g, as $t_i \in S \times E \times G \times S$.

$$g_{(s_{i,j},s_{m,n})}(e) = C.\xi(e.vs) \wedge fre_{(s_{i,j},s_{m,n})}(e) \wedge dur_{(s_{i,j},s_{m,n})}(e) \quad (1)$$

$$fre_{(s_{i,j},s_{m,n})}(e) = \begin{cases} True \text{ , if } P_1 \vee P_2 \vee P_3 \ ^{2} \\ False, otherwise. \end{cases} \quad (2)$$

$$dur_{(s_{i,j},s_{m,n})}(e) = \begin{cases} True \text{ , if } P_1 \vee P_4 \vee P_5 \ ^{3} \\ False, otherwise. \end{cases} \quad (3)$$

$$\begin{cases} P_1 = (i == C.d) \vee (j == C.f_d) \\ \qquad \vee (m == max) \vee (n == 0), \ ^{4} \\ P_2 = (i == m) \vee (j == n-1), \\ P_3 = (i == m-1) \vee (j == C.f_i) \vee (n == 1), \\ P_4 = (i == e.tt) \vee (j == n-1) \vee (m == e.tt), \\ P_5 = (i == e.tt) \vee (j == C.f_i) \\ \qquad \vee (m == i+1) \vee (n == 1). \end{cases} \quad (4)$$

In our formal model, criteria variables tuple C is configured by a physician to describe the medical constraints to make diagnoses. Thus, when the pathophysiology develops, our model can easily be extended by modifying the predicate ξ. And other elements can be generated and computed from C automatically. We label the initial state s_0 as $s_{0,0}$ and the

[2] P are predicates on i, j, m, n defined in Equation 4

[3] P are predicates on i, j, m, n defined in Equation 4

[4] max is used to label the s_f state. In practice, we assign $max = C.d+1$

final state s_f as $s_{max,0}$ for a unified equation to calculate the guards. In Equation 4, P_1 constrains the transition to the final state s_f. P_2 and P_4 cooperate to constrain the transitions between states in the same day, and P_3 and P_5 for the transitions between two continuous days. We will describe the semantics for these predicates in the *Model Semantics* part.

b) Model Semantics: The execution semantics of our formal diagnostic criteria model can be considered as a labelled transition system [23]. The model starts from the initial state to monitor a patient under a series of events recording the patient vital signs lasting criteria-duration days. When a state transits to another, it implies that an episode occurs and parts of episode duration and frequency constraints are satisfied to make a diagnosis. Finally, if the model reaches the final state, a diagnosis is confirmed because all the constraints are satisfied.

For the lack of pathophysiology knowledge, it is hard to create a consensus clinical criteria. One alternative approach is utilizing multiple clinical criteria sets with a weight vector. We present our diagnostic computation of combined models in Algorithm 1. The inputs are a series of events $\mathbb{E}$ in which each event e records patient signs (vs) with a timestamp (tt), a set of clinical criteria $\mathbb{C}$ with the weight vector $\mathbb{V}$ and a confirmed threshold τ. The result is computed by function $computation$ in statements 1-10. First, formal diagnostic criteria models is generated by $construct$ in statement 2 as discussed in *Model Construction* part. A variable $score$ is initialized to combine the each criteria diagnostic result in statement 3. For each formal model, we compute the diagnostic result under the given events by function $check$ in statement 5 and update the $score$ according to the weight vector by function $updateScore$ in statement 6. As different clinical criteria may propose its specific episode duration, a subset of events will be extracted to meet the time constraint by $Extract$ in statement 12. Then, the model and events are used in function $check$ illustrated in statements 11-22 to make a diagnosis based on the model semantics. After all the clinical criteria sets have been computed, we make the final diagnosis result according to the relationship between $score$ and τ by function $judge$ in statement 8.

Algorithm 1 Diagnostic computation of combination model

Input: Event set $\mathbb{E}$, clinical criteria sets $\mathbb{C}$, weight vector $\mathbb{V}$ and result threshold τ
Output: Diagnosis $\mathfrak{D}$

```
1:  function computation()
2:      M ← construct(ℂ)
3:      score ← initScore()
4:      for m ∈ M do
5:          r_tem ← check(m, 𝔼)
6:          score ← updateScore(𝕍, r_tem)
7:      end for
8:      𝔇 ← judge(score, τ)
9:      return 𝔇
10: end function
11: function check(m, 𝔼)
12:     for E ← Extract(𝔼, m → d) do
13:         current ← initCurrent()
14:         for e ∈ E do
15:             current ← transit(e)
16:             if current is m → s_f then
17:                 return True
18:             end if
19:         end for
20:     end for
21:     return False
22: end function
```

B. Integrated Medical CPS

In this subsection, we will present an integrated Medical CPS for early detection of PSH. The following part describes the work-flow of the detector and the implementation of our system.

a) System Structure and Interactions: As illustrated in Figure 1, our system consists of three main components: revised ICE device adapter, model generator and monitoring detector. Modern hospitals have been equipped with a number of advanced medical devices to automatically observe patient vital signs by sensors and display the data on device monitors. However, few of these devices provide specific diagnostic analysis functionality. In order to comprehensively utilize these devices, a medical devise adapter is revised on Integrated Clinical Environment(ICE) to extract patient vital signs from different medical devices. Because some clinical features like sweating and posturing cannot be monitored automatically, we allow physicians to customize the manual check alert constraints with other necessary system properties like data sampling frequencies in configuration files. Then, model generator will automatically parse the configurations into the formal diagnostic criteria models defined in Section III-A to minimize the impact from PSH definition evolution. With the formalized models employed, we implement an early monitoring detector. With all the components integrated, our Medical CPS will sample the real-time patient data to relieve medical staff from the heavy burden of monitoring activities and provide timely decision supports.

b) Implementation: As described above, we implement our system in Java platform which can be deployed on any java-capable computers. Currently, we design a medical device adapter based on the revised Integrated Clinical Environment for Phillips IntelliVue MP70 to continually get patient vital signs. We also implement a GUI tool for physicians to generate clinical criteria and all the diagnostic criteria generated by our system are stored in a readable file format. The raw data and computation results are stored for further use.

IV. Evaluation

In this section, we evaluate the performance of our approach by patient data extracted from medical publications.

A. Experimental Setup

In our evaluation, we choose two of the most widely used ones [12], [19] and set weight vector $\mathbb{V}$ as $[1, 1]$ and result

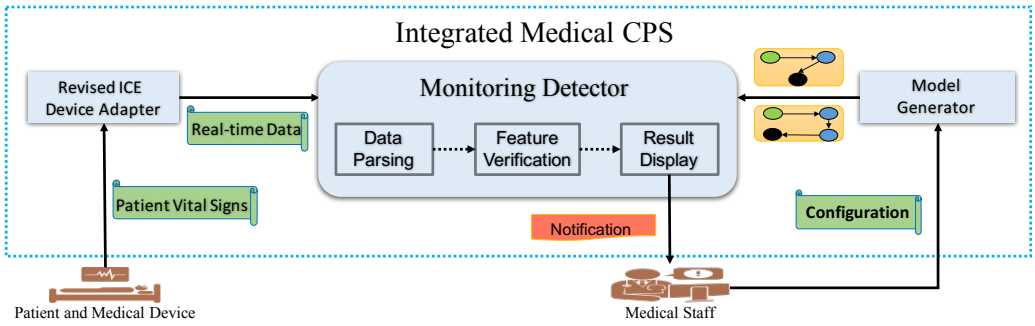

Fig. 1: Components and interactions of our integrated Medical CPS for early detection of PSH

threshold τ as 1 to perform the detection as described in Algorithm 1, indicating that a patient is conformed if any of the criteria sets is satisfied. We use patient data extracted from medical publications illustrated in Table I to evaluate our approach. References are recommended by physicians. For references without concrete patient signs and symptoms, but with statistics distributions and episode descriptions, we automatically generate data satisfied the constraints. We ensure that there are more than 3 episodes in each day for 3 days to meet the episode duration thresholds in the criteria sets. The composition of patient data is presented in Table I which consists of 97 PSH cases and 10 non-PSH cases with clinical features overlapped for false alarm testing.

Our system samples patient data every 30 minutes, because the duration of each episode is on average 30 minutes which is reported in [8]. To our best knowledge, there is no runnable tool to detect PSH up to now. Therefore, we invite volunteers with medical experience to manually check patient data every hour[5] using the same criteria sets to verify the effectiveness and efficiency of our system.

B. Results

All the experiment results are presented in Table I. The first two columns are patient data composition. In the third and fourth columns, we illustrate the results of our work and the average results of the current approach performed by volunteers, respectively. We discuss the the results as follows,

a) Effectiveness: In order to compare our work and current approach, we use *Precision* and *Recall* to compare the effectiveness. *Precision* is a ratio between correctly detected PSH patients and the number of patients assigned as PSH. As illustrated in Table I, for this evaluation cases set, our precision is 93/96 (96.88%) compared to 76/78 (97.44%) for manually checking. Therefore, in terms of the correctness, our approach performs almost the same as manually checking Namely, we will not burden medical staff with too many alarms than the current approach. *Recall* is a ratio between correctly detected PSH patients and the number of PSH patients in our case set. With 97 cases as PSH patients, we successfully detect 93 of them with a recall as 95.88%, which is better than manually checking with 76/97 (78.35%). Namely, in terms of the detection ability, our approach performs better than the current approach. In the medical domain, human safety is the first factor. With a reasonable false alarm rate, a higher recall indicates a better solution.

b) Efficiency: With the same diagnostic criteria, current detection approach underdiagnosed 17 cases (17.53%) in all PSH cases than us, which indicates that our approach can perform better in terms of early detection of PSH. In an effort to understand the primary reason, we illustrate the patient data for the first 3 hours in a case from [18]. We note that heart rate (HR), respiration rate (RR) and blood pressure (BP) crossed the threshold at 1.5 hours and 1 hour, respectively. However, it is unreasonable for medical staff to observe every patient every 30 minutes. Thus, the volunteers missed the syndromes, precisely high HR and RR, resulting in an underdiagnosis. We successfully detected this episode because our system combined the data in the near 30 minutes. From another perspective, we calculate the average detection time of true positive groups respectively. The result shows that manual checks have an average 4.5 hours delay than our system. Along with the paroxysm and complex clinical features, we believe the real world situation is worse. Additionally, during the manual checks process, a volunteer mixed up two criteria sets resulting in under-recognition of a case. Therefore, our approach provides a benefit of steady performance and detects anomalies earlier.

c) False Alarms: In all the cases, we have 3 false positives and 4 false negatives. After reviewing the cases manually, we note that for all the false positives, they have crossed the PSH criteria, but belong to other diseases. Therefore, the reason for false positives is there are many overlapped clinical features between PSH and Sepsis, resulting in misdiagnoses. It is the future work of us to provide a relevant analysis component to show the possibilities faced with the same clinical features. For the 4 false negatives, we note that all of them are lack of enough vital signs to meet the criteria, which are important to do the computation. These cases are also missed by manual checks. To detect these cases, we can decrease the thresholds of each vital signs. However, it will disturb physicians with many *false positives*. In the future, we

[5]After the discussions with physicians, we learn that the most frequent manual checking routine in their department is 1 hour. Therefore, we manually check patient data every hour in our evaluation.

TABLE I: Detection results on cases from medical publications

Publication	Cases			PSHMonitor				Manually			
	PSH	N-PSH	Total	TP	TN	FP	FN	TP	TN	FP	FN
Lee [18]	2	0	2	2	0	0	0	1	0	0	1
Hughes [14]	44	0	44	44	0	0	0	37	0	0	7
Baguley [3]	15	0	15	14	0	0	1	13	0	0	2
Blackman [5]	20	0	20	20	0	0	0	16	0	0	4
Deepika [9]	4	0	4	3	0	0	1	1	0	0	3
Lv [19]	6	0	6	6	0	0	0	4	0	0	2
Baguley [2]	6	0	6	4	0	0	2	4	0	0	2
Umbriaco [24]	0	5	5	0	4	1	0	0	4	1	0
Martin [20]	0	5	5	0	3	2	0	0	4	1	0
Summary	97	10	107	93	7	3	4	76	8	2	21

PSH is for patient confirmed as PSH and N-PSH is used for other cases like *Sepsis* and *Malignant hyperthermia*. TP is true positive for PSH cases detected as PSH. TN is true negative for N-PSH cases detected as N-PSH. FP is N-PSH cases misdiagnosed as PSH and FN is PSH cases underdiagnosed .

will carry out more experiments to balance this issue.

V. Conclusion

In this paper, we presented an integrated Medical Cyber-Physical System for early detection of paroxysmal sympathetic hyperactivity. We proposed a formal diagnostic criteria model to describe diverse widely used clinical criteria. With the models employed, we implemented an early detector and integrated it into a Medical CPS to monitor patient vital signs and help physicians make diagnoses. The evaluation on cases from medical publications shows the effectiveness and the efficiency of our approach. In the future, we will evaluate on real-world patient data in hospitals to strengthen our work.

Acknowledgment

The authors thank Andrew Ou, Jiangxiang Liu and Xiaoyu Song for the discussions and help in this work. This work is supported in part by NSF CNS 1329886, NSF CNS 1545002, ONR N00014-14-1-0717, NSFC 91218302, NSFC 61527812, National Science and Technology Major Project(No.2016ZX01038101), MIIT IT funds (Research and application of TCN key technologies) of China, and The National Key Technology R&D Program (No. 2015BAG14B01-02).

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