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A Cyber-Physical System Framework for Early Detection of Paroxysmal Diseases

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ABSTRACT Paroxysmal diseases of inpatients are globally recognized as one of the top challenges in medicine. Poor clinical outcomes are primarily caused by delayed recognition, especially due to diverse clinical diagnostic criteria with complex manifestations, irregular episodes, and already overloaded clinical activities. With the proliferation of measuring devices and increased computational capabilities, cyber-physical characterization plays an increasingly important role in many domains to provide enabling technologies. This paper presents a cyber-physical system (CPS) framework to assist physicians in making earlier diagnoses of paroxysmal sympathetic hyperactivity based on existing medical knowledge. We propose a configurable diagnostic knowledge model to characterize clinical criteria to reduce domain knowledge deficiency between physicians and computer scientists. We present a component-based medical CPS framework to employ the knowledge models and integrate medical devices. Our approach aims to relieve medical staff from the heavy burden of clinical activities and to provide timely decision support. We evaluate our approach on 128 real-world clinical cases. Compared with the state-of-the-art approach, the results demonstrate that we enable early detection in 11.02% more patients and detect the condition 16.57 hours earlier on average.

INDEX TERMS Cyber-physical system, early detection, knowledge model, paroxysmal disease.

I. INTRODUCTION

Diseases with paroxysmal features pose challenges for the current clinical circumstances. From the perspective of medical staff, who are continuously observing all kinds of devices and are checking patient for signs and symptoms, their job is stressful and error-prone [1]. Especially in an aging society, medical staff are overloaded. Due to long courses of treatment, these diseases consume a large portion of healthcare resources every year, worth millions of dollars [2].

PSH is one such disease, which causes episodes of increased activity of the sympathetic nervous system with complex clinical features. It requires 24-hour monitoring for a long time [31]. In the clinical environment, with monitoring of nutrition and early detection, morbidity will be reduced [4]. However, delayed recognition of PSH leads to poor outcomes, resulting in long-term disability and even death [5]. Cases reported in [6] show that only 7% of PSH patients achieved a moderate or good recovery. However, 45% had severe disability, and 30% exhibited a persistent vegetative state. Moreover, 18% of patients died.

To achieve better outcomes, physicians are trying their best to make a diagnosis as early as possible. However, from discussions with physicians,[1] we know that underdiagnoses and misdiagnoses are extremely common. The reasons are as follows:

- Physicians usually propose criteria sets according to their clinical experience. For example, Lv *et al.* [7] present a criteria set as *Simultaneous occurrence of 5 or more of the following features: (1) heart rate > 120 beats/min, (2) respiratory rate > 30 breaths/min, (3) temperature > 38.5 °C, (4) blood pressure > 160 mmHg), (5) increased muscle tone, (6) posturing, and (7) excessive sweating at least 1 daily paroxysm that occurs for at least 3 days.* However, individual differences harm the universally accepted diagnostic standard.
- Syndromes with sophisticated manifestations to which many diseases have similar appearances are extremely hard to take into consideration in a clinical environment.

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- The paroxysmal clinical features require several symptoms to be recurrent and episodic to make a diagnosis. Unfortunately, medical staff are already overloaded at hospitals. It is impractical to perform frequent clinical monitoring activities manually.

Therefore, all these limitations hamper the awareness of a diagnosis, and it is not easy for medical staff to make an early detection.

With the proliferation of diverse measuring devices and the increase in computational capabilities, CPS is playing an increasingly important role in many domains [8], [9]. Recently, some researchers have applied automation technology to solving medical problems [10], [11]. In this paper, we propose a CPS framework to detect PSH early based on existing medical knowledge. Efforts to improve medical aspects are beyond the scope of this paper.

We propose a configurable diagnostic knowledge model to describe diverse clinical criteria sets uniformly. Because some signs and symptoms cannot be monitored automatically, such as sweating or posturing, we allow for the physicians to easily customize the alert constraint on performing manual checks in the configuration file, which is also suitable for individual differences. For multiple criteria sets, we provide an algorithm to compute the patient conditions of compositional models.

We present a component-based CPS framework, which is extended from our previous case study [12], to integrate knowledge models and medical devices. In our framework, a model generator is implemented to parse the configuration file of the formalized models provided by physicians and to construct the compositional diagnostic models. Medical device adapters designed for an integrated clinical environment (ICE) [13] will sample patient vital signs. With the real-time patient data parsed and computed by the monitoring detector, our system displays patient data on the monitor screen and sends the results to physicians. This will relieve medical staff from the heavy burden of manual monitoring of activities and will provide timely decision support. We evaluate our approach on 128 real-world medical cases. With the knowledge models constructed from two widely-used criteria sets in natural language descriptions, we use our system prototype to assist the diagnostic procedure.

In summary, our work contributes the following:

- We propose a configurable knowledge model to describe diverse clinical criteria uniformly for paroxysmal disease, which reduces physicians' memory load, narrows the domain knowledge deficiency between physicians and computer scientists, and augments the detection capacity.
- We present a component-based CPS framework to integrate the knowledge model and medical devices for early detection of paroxysmal diseases. We employ PSH as an example and implement an early detection system to guide the use of our methodology.
- We evaluate our method on 128 real-world medical cases. Compared to the state-of-the-art, our approach is able to early detect 11.02% more patients with nearly the same false positive rate (2.52% compared to 0.96%). For the confirmed cases, detection occurred 16.57 hours earlier on average.

The rest of this paper is organized as follows. In Section II, we introduce related work. Section III presents our configurable diagnostic knowledge model to describe diverse criteria and our component-based CPS framework for early detection of paroxysmal diseases based on the models. We evaluate our work against real-world clinical cases, and the results are shown in Section IV. We conclude the paper in Section V.

II. RELATED WORK

A. DETECTION OF PAROXYSMAL SYMPATHETIC HYPERACTIVITY

PSH is an important clinical problem that has been studied for more than sixty years. Since the first diagnostic criteria were presented in 1993 [34], many criteria sets have been proposed, such as [14] or modified [15] to help physicians make diagnoses. There is strong agreement on simultaneous and paroxysmal features, each of which contribute equally to the diagnosis process. However, there are some inconsistencies: *(1) Duration*, two weeks is reported in [16], which is the longest of all the criteria published. Three days is reported in [7]. *(2) Occurrence*, such as 38.5°C of body temperature in [7], 39°C in [16] and undefined in [15], respectively. Through a systematic literature review, it was found that the duration of each episode is on average 30 minutes, and frequency is on average 3-8 times/day [15].

To provide a consensus on the definition and diagnostic criteria of PSH, Baguley *et al.* [17] proposed a tool called the PSH-Assessment Measure (PSH-AM), which consists of two components: a diagnosis likelihood tool addressing the probability and a clinical feature scale assessing the severity. These components were used to estimate the diagnostic likelihood of PSH. However, the only case study to use PSH-AM is published in [18]. In this case study, four patients were confirmed. PSH-AM remains a conceptual workflow without a fully automatic system. The authors envisaged that PSH-AM would be completed daily by medical staff at a standardized time to check patients manually.

Therefore, the lack of a well-established set of criteria and manual checking activities hamper the awareness of PSH and result in underdiagnoses and misdiagnoses. This is especially true in facilities that are overloaded with clinical activities and exhibit underreporting of adverse clinical events in a handwritten format [1].

B. MEDICAL CYBER-PHYSICAL SYSTEM

With the proliferation of diverse measuring devices, many researchers have been paying more attention to Medical CPS for providing continuous high-quality care [10], [11]. They are especially focusing on anomaly behavior detection in the clinical environment.

Jiang *et al.* [19] applied a runtime verification technique for medical decision support systems to ensure complex temporal properties in medical guidelines. With medical practice scenarios described in a domain-specific language called DRTV, event sequences and runtime property verifying automata can be generated to rigorously verify the properties automatically. To deal with epilepsy, a paroxysm feature was used, Kjaer *et al.* [20], which utilized a portable electroencephalogram(EEG) to identify the paroxysms of absence seizures in long-term monitoring based on patient-specific modeling. Clinically satisfactory performance with a positive predictive value showed that portable EEG recorders are a promising tool for patients and physicians dealing with absence epilepsy. Voros *et al.* [21] presented a CPS system architecture for multi-parametric monitoring and analysis of patients with epilepsy, using different hardware and software modules of systems with defined interfaces. To balance the high security and high accessibility for the implantable medical devices (IMDs), Zheng *et al.* [22] presented an electrocardiogram (ECG)-based data encryption (EDE) scheme. Protected by the EDE, IMDs could not be accessed by adversaries; however, medical personnel can have access to them by measuring real-time ECG data in emergencies. Ivanov *et al.* [23], proposed a predictive monitor to detect sharp decreases in the arterial blood oxygen content (CaO2) caused by a pulmonary shunt in infants. Based on the model characterized by unknown patient specific parameters, they first applied a parameter-invariant technique in Medical CPS. To control the outbreak of mosquito-borne diseases (MBDS) at an early stage, Sood *et al.* [24] proposed a novel system based on Internet of Things (IoT) sensors, cloud computing and fog computing to distinguish, classify and monitor users infected with MBDs.

In contrast to the approaches mentioned in [20], [23] and [24], our work focuses on a more complicated syndrome, PSH, for which some features require manual checks. This poses a great challenge to interactions with physicians. Patients with PSH usually have a traumatic brain injury and have to be hospitalized, implying that the sensors used in [24] are hard to use in our work. Similar to epilepsy [20], [21] with a paroxysm feature, PSH requires symptoms to be recurrent and episodic to make a diagnosis. However, there are no existing pathophysiologic models or medical guidelines to apply runtime verification techniques. Therefore, we propose a different strategy by employing a configurable diagnostic knowledge model and involving physicians to customize the knowledge models and the constraints to perform manual checks in a Medical CPS approach with a portable tablet.

III. APPROACH

In this section, we present a CPS approach for early detection of PSH. We introduce our configurable diagnostic knowledge model first. Then, the component-based CPS framework is presented.

A. CONFIGURABLE DIAGNOSTIC KNOWLEDGE MODEL

As discussed in Section II-A, the clinical criteria consist of a group of clinical features with thresholds to confirm an episode. The duration and frequency of the episodes are used to confirm a diagnosis. However, there may be differences between criteria sets, mainly in *duration* and *occurrence*. In the following section, we introduce our configurable diagnostic knowledge model.

We use the criteria from Lv *et al.* [7] to illustrate the definition, construction and semantic structure of our model, where PSH is defined as follows: *Simultaneous occurrence of 5 or more of the following features: (1) heart rate > 120 beats/min, (2) respiratory rate > 30 breaths/min, (3) temperature > 38.5 °C, (4) blood pressure > 160 mmHg), (5) increased muscle tone, (6) posturing, and (7) excessive sweating, and at least 1 daily paroxysm that occurs for at least 3 days.*

To aid understanding, we provide a visualization of our model in the format of an extended automata [25] in Figure 1. The $s_{i,j}$ represents the j-the episode in the i-th day defined in Definition 3, and the expressions on the arrows are the guards that control the states defined in Definition 4.

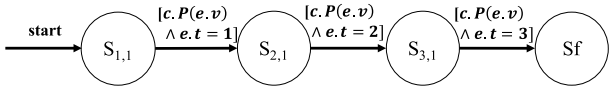

FIGURE 1. A simplified visualization of the diagnostic knowledge model. Guards are presented in square brackets, and transitions with contradiction guard are eliminated.

1) MODEL DEFINITION AND CONSTRUCTION

Definition 1: An event $\mathbf{e} = < v, t >$ consists of a set of vital signs of a patient labeled as $e.v$ and a timestamp of these signs sampled as $e.t$. We label a series of events as $\mathbf{E}$.

In clinical monitoring activities, medical staff write down patient conditions after manual checking or use of medical devices. We can parse these signals into a structured format as follows:

$$e = \{e.v[hr : 120, rr : 30, sweating : 1, \dots], \\ e.t[2018 : 1 : 25 : 23 : 30]\}$$

indicating that at 23:30 of 2018-1-25, the patient's heart rate was 120 beats/min, breath was 30 resp/min, the patient was sweating, etc.

Definition 2: The diagnostic criteria are defined as a tuple $\mathbf{c} = <$ d, Fre, Pre$>$, where d is the shortest duration of episodes, *Fre* is a d-length vector of frequencies for each day and *Pre* is a predicate to record the occurrence of an episode under a given event.

With the natural language description defined above, we can construct the criteria tuple

$$c =< 3, [1, 1, 1], Pre >, \tag{1}$$

where *Pre* is whether a simultaneous occurrence of 5 or more of the features. For the first two parts of c, this means that

at least 1 daily paroxysm that occurs for at least 3 days. The *c.Pre* parameter is used to check whether the episode occurs under a given *e*.

Definition 3: A state **s** is a description of the status of a patient, which is labeled as $s_{i,j}$ indicating the occurrence of the *j*-th episode in the *i*-th day. We label a set of states as **S**. s_f is used as the final state that a diagnosis is confirmed.

From the diagnostic criteria c in Equation (1), we can automatically generate the S as

$$S = \{s_{1,1}, s_{2,1}, s_{3,1}\} \cup \{s_f\} \tag{2}$$

where $s_{1,1}, s_{2,1}, s_{3,1}$ for the each paroxysm for three days and s_f for the final state to confirm the patient.

Definition 4: A guard $g_{(s_{i,j},s_{m,n})}$ is a Boolean expression that guards the transition between two states, where $s_{i,j}$ presents the j-th episode in i-th day and $s_{m,n}$ presents the n-th episode in m-th day. More precisely, we formalize the guard in Equation (3), where the episode occurrence constraint is as follows: *c.Pre*, episode frequency constraint as *freq* and episode duration constraint *dur*, respectively. We label a set of guards as **G**.

$$g_{(s_{i,j},s_{m,n})}(e) = c.Pre(e.v) \wedge freq_{(s_{i,j},s_{m,n})}(e) \wedge dur_{(s_{i,j},s_{m,n})}(e) \tag{3}$$

A guard is defined on an event e to guard the transition between two states. As shown in Equation (3), it contains three parts, where *c.Pre* is defined in Definition 2, the constraint on episode frequency is defined in Equation (4), and the constraint on episode duration is defined in Equation (5).

$$freq_{(s_{i,j},s_{m,n})}(e) = \begin{cases} True, & \text{if } p_1 \text{ or } p_2 \text{ or } p_3 \\ False, & otherwise. \end{cases} \tag{4}$$

$$dur_{(s_{i,j},s_{m,n})}(e) = \begin{cases} True, & \text{if } p_1 \text{ or } p_4 \text{ or } p_5 \\ False, & otherwise. \end{cases} \tag{5}$$

From the diagnostic criteria, duration and occurrence are two primary differences between diverse criteria sets. Therefore, we use the *freq* and *dur* constraints to model the criteria in a uniform format. In Equation (4) and (5), $p1$ is defined as

$$p_1 = (i \text{ is } c.d) \wedge (j \text{ is } c.f_d) \tag{6}$$

indicates the constrain on the transition to the final state. p_2 and p_4 cooperate to control the transitions between states in the same day,

$$p_2 = (i \text{ is } m) \wedge (j \text{ is } n-1) \tag{7}$$

$$p_4 = (i \text{ is } e.t) \wedge (j \text{ is } n-1) \wedge (m \text{ is } e.t) \tag{8}$$

and p_3 and p_5 cooperate to constrain the transitions between two continuous days.

$$p_3 = (i \text{ is } m-1) \wedge (j \text{ is } c.f_i) \wedge (n \text{ is } 1) \tag{9}$$

$$p_5 = (i \text{ is } e.t) \wedge (j \text{ is } c.f_i) \wedge (m \text{ is } i+1) \wedge (n \text{ is } 1) \tag{10}$$

Definition 5: A transition **t** is the connection order between two states triggered by an event **e** and guarded by a guard **g**, where $t \in S \times E \times G \times S$. We label a set of transitions as T.

Definition 6: A configurable diagnostic knowledge model is a tuple $m = \langle S, c, G, T \rangle$ that uniformly presents the different clinical criteria sets and monitors the patient condition under a series of events E.

The execution semantics of our diagnostic knowledge model are similar to the state-space model [26], [27], where we treat the input signals at each time point like a state and find the final error model based on the data. In this paper, we can consider it as a labeled transition system [28], which can be visualized easily. The model begins at the initial state *Start* to monitor patients under a series of events recording vital signs lasting criteria-duration days. When one state transitions to another, this indicates that an episode has occurred, and parts of the episode duration and frequency constraints are satisfied. Finally, if the model arrives at the final state, a diagnosis is confirmed because all of the constraints are satisfied. As visualized in Figure 1, the diagnostic knowledge model of criteria in [7] starts from state $s_{1,1}$ to wait for the first episode of the first day. Given a set of events in which each event e contains patient signs v with a timestamp t, our model transits between states guarded by the guard listed in square brackets generated from the equations defined above. If the guard between $s_{1,1}$ and $s_{2,1}$ is satisfied on an event e, the model transits to $s_{2,1}$, implying that one episode happens in the first day. The model then waits for the first episode of the second day. Finally, if the model arrives at s_f , the patient is confirmed.

2) MODEL COMPOSITION

Because of insufficient pathophysiology knowledge, it is difficult to create a consensus clinical criteria. Through discussions with physicians, one alternative approach has been developed, which utilizes multiple clinical criteria.

Definition 7: A compound model is defined as a tuple $\mathbb{M} =< M, W, \tau >$, where M is a set of configurable diagnostic knowledge models constructed from a set of criteria sets C, W is the weight vector for M provided by physicians and τ is a result threshold used to make the final diagnosis.

In Figure 2, we visualize an example of our compound model, where $\mathbb{M}$ is composed of three single models with

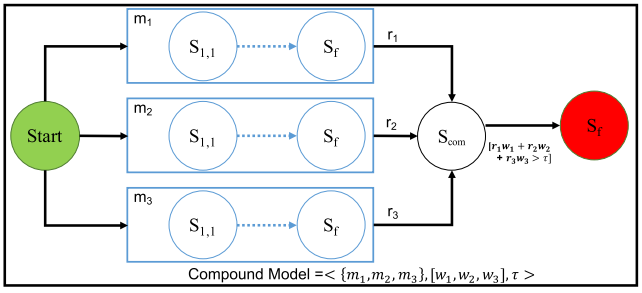

FIGURE 2. Visualization of compound model consisting of three single models.

a weight vector $W = [w_1, w_2, w_3]$ and τ, indicating that the combination of the three models crosses the pre-defined threshold τ. This means that a diagnosis is confirmed.

ALGORITHM 1: Diagnostic Computation of Compositional Model

input : Event set E, clinical criteria sets C, weight vector W and result threshold τ
output: Diagnosis Result d

```
𝕄 ← ConstructModel(C, W, τ);
score ← InitScore();
for m ∈ 𝕄.M do
    r ← CheckEvent(m, E);
    score ← UpdateScore(score, r, 𝕄.W);
end
d ← JudgeResult(score, 𝕄.τ);
```

ALGORITHM 2: Diagnostic Computation of Single Model

input : Event set E, clinical criteria model m
output: Single model diagnosis result r

```
while E′ ← ExtractEvents(E, m.c.d) do
    current ← InitCurrent ();
    for e ∈ E′ do
        current ← Transit(e, m) ;
        if current is m.s_f then
            return 1;
        else
            continue ;
        end
    end
end
return 0;
```

In Algorithm 1 , we present our diagnostic computation of compound models. The inputs are a series of events E in which each event e records patient signs $e.v$ with a timestamp $e.t$, a set of clinical criteria C with the weight vector W and a confirmed threshold τ. The result is the final diagnosis. First, we construct diagnostic knowledge models $\mathbb{M}$ according to Definition 7 by function *ConstructModel*. Second, a variable *score* is initialized to record the combination result. For each model, we will compute the diagnostic result with a series of given events by function *CheckEvent* and combine the single model result with *score* according to the weight vector $\mathbb{M}.W$.

The concrete computational steps are illustrated in Algorithm 2, which is explained in Section III-A.1. Finally, we make the diagnosis according to the threshold $\mathbb{M}.\tau$ by function *JudgeResult*.

Suppose that the compound model consists of $|m|$ single models and the size of Event is $|e|$. According to Algorithm 2, for $e \in E'$, the time complexity of the checking process is $O(1)$. The *ExtractEvents* will divide the events into groups according to the shortest episode duration defined in Definition 2, indicating that there are at most $|e|$ groups, and each group has $|e|$ elements. Therefore, the time complexity of Algorithm 2 is $O(|e|^2)$. For the computation of the compositional model, we conclude that the time complexity of Algorithm 1 is $O(|m||e|^2)$. The longest criteria duration is two weeks in [16], and the duration of each episode is 30 minutes on average, indicating that the input event at most has fourteen days with a finite sample for each day. Additionally, through a literature review and discussions with the physicians, it was determined that the number of models are usually fewer than five. Because the only differences between models are in the duration and occurrence, as discussed in Section II, and because five different models can be sufficient, the computation of a compound model can finish in finite time.

B. COMPONENT-BASED CYBER-PHYSICAL SYSTEM FRAMEWORK

In this section, we present our component-based CPS framework for early detection of paroxysmal diseases. First, we present an overview of our system and the interactions between the components: Revised ICE Device Adapter, Model Generator, Monitoring Detector and Display Module. After that, we describe the workflow of our framework and the applications of our framework for PSH.

1) SYSTEM COMPONENTS AND INTERACTIONS

As illustrated in Figure 3, our system consists of four main components: a Revised ICE Device Adapter, a Model Generator, a Monitoring Detector and a Display Module.

Modern hospitals are equipped with a number of advanced medical devices for specific purposes. Some are designed to automatically observe patient vital signs by using sensors, and they display the data on built-in screens. Heart rate and respiratory rate, for example, are monitored and displayed on the device screen. However, few of these devices are able to provide specific diagnostic analysis functions.

a: REVISED ICE DEVICE ADAPTER

To widely utilize these devices, a medical device adapter was revised on ICE to extract patient vital signs from different medical devices. Therefore, we can combine different signs to customize the monitoring activities for different individuals. However, some clinical features, such as sweating and posturing, cannot be monitored automatically. To overcome these difficulties, we invite physicians to customize the manual check alert thresholds with other necessary system properties like data sampling frequencies.

b: MODEL GENERATOR

is designed to parse the configurations and to generate diagnostic knowledge models as defined in Section III-A. We have provided a user-friendly graphical tool to help physicians to create the model and system properties by clicking buttons and filling in numbers. The generated model is used

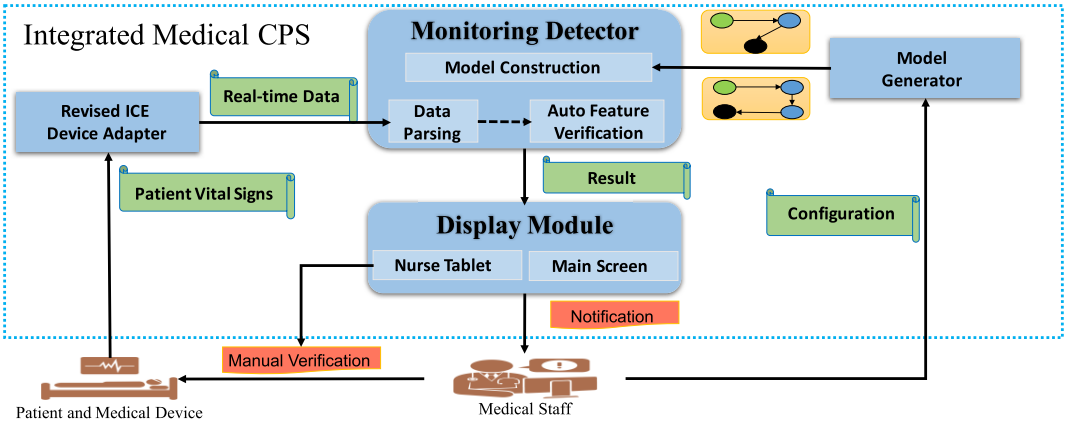

FIGURE 3. Components and interactions of our integrated Medical CPS for early detection of PSH.

as an input to the monitoring detector. Another benefit of parsing a configuration is to minimize the impact of changes to the PSH definition.

c: MONITORING DETECTOR

is designed to observe patients with the formalized models employed from the model generator. When real-time data are sampled from the Revised ICE Device Adapter, the monitor detector will read the data and start the analysis process according to the algorithm illustrated in Section III-A.2. All of the results and patients data will be stored on the hard disk.

d: DISPLAY MODULE

We provide two types of display strategy: Main-Screen and Nurse-Tablet. The main screen will display the patient conditions in real time, while the revised ICE device adapter samples the patient data. When abnormal conditions are detected, the monitoring detector will alert the physicians for a further manual check, in which the tablets will be used.

With all the components integrated, our Medical CPS will sample real-time patient data to relieve medical staff from the heavy burden of repeated monitoring activities and to provide timely decision support. With the model parsed from configurations, we try our best to minimize the impact of changes to the PSH definition.

2) MONITORING DETECTOR WORKFLOW

The Monitoring Detector is the kernel component in our system. It uses the formalized models and monitors patient condition to provide decision support for physicians. We present the workflow details below. The data parsing step processes patient vital signs. When the predefined sampling period arrives, the Monitoring Detector will read patient data from the Revised ICE Device Adapter and preprocess all of the data. It checks data rationality, fills in empty values, interprets data and performs additional steps. All of the processed data are sent to the next step and stored for further use.

The auto feature verification step uses the diagnostic knowledge models generated from clinical criteria to perform early detection. Even though medical devices can monitor some quantitative clinical signs like blood pressure and heart rate successfully, some qualitative signs are not available to automated systems, like sweating or posturing. Therefore, with the data from the first step, we automatically verify the patient condition to decide whether there is a need for further manual verification. If the patient is safe, the system jumps to the result display step because of the simultaneity feature; with this feature, all signs and symptoms occur simultaneously to confirm an episode, which is described in Section II. If the patient needs further clinical tests, the medical staff will be alerted. In the manual verification step, medical staff will use tablets to check the patient's condition, using a checklist automatically generated from the diagnostic criteria by our system. With all of the vital signs ready, we encapsulate them with historical data as events to compute the diagnostic results. The results are sent to the next step.

The result display step displays all of the processed data and analysis results. In our system, we update the patient vital signs in the main screen rapidly. It is critical that Medical CPS should not mislead the medical staff. In particular, the reasons for no anomaly are that the patient is in good condition or the system has failed. Therefore, we display the runtime system state to overcome this limitation. For the computation result, the Monitoring Detector will send it to the Display Module. Physicians can use the tablet to do further manual checks along with analysis procedures in an easy-to-follow format to provide timely decision support. All of the results will be saved for review and further use.

3) FRAMEWORK APPLICATIONS

We have implemented our system in the Java platform, which can be deployed on any Java-capable computers. Currently, a medical device adapter based on the revised Integrated Clinical Environment specific to Phillips IntelliVue MP70 is designed to continually read patient vital signs as shown

FIGURE 4. Deployment of network environment and medical devices.

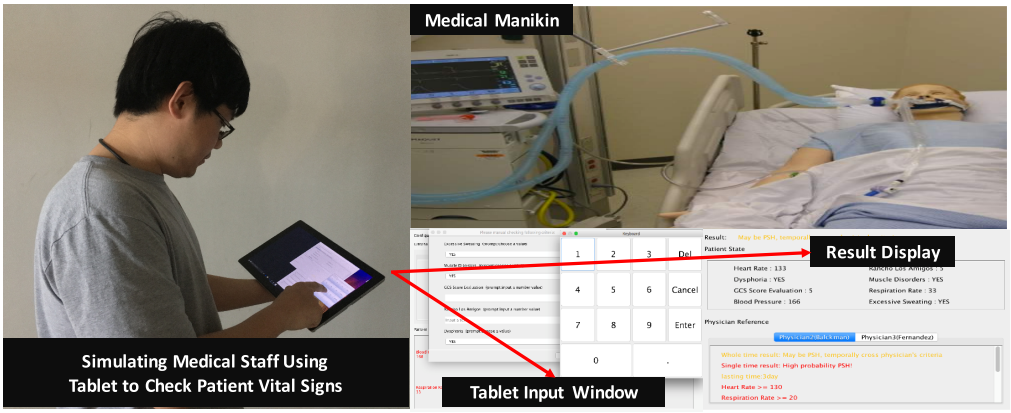

FIGURE 5. Simulation of medical staff using a tablet to check a patient's vital signs.

in Figure 4. A tablet shown in Figure 5 is built into our system for manual feature verification and medical requirements. Tablets are easy to clean and portable. We have conducted simulations on a Microsoft Surface Pro with physicians, and the usage is gaining wide acceptance. We built a graphical tool for physicians to generate clinical criteria by clicking buttons, and all the diagnostic criteria generated by our system are stored in a readable file format.[2] Our system decreases the dependency on individual components and can be easily extended for other diseases, especially when the definition of PSH is well established. Furthermore, all the raw data and computational results are stored for further research use.

IV. EVALUATION

In this section, we describe the results of evaluating the performance of our approach by using patient data extracted from medical publications. First, we describe the experimental setup, including test case composition, system deployment in a lab environment for simulation and the method of evaluation. Finally, the results and discussions are presented.

[2]For more details, refer to this website: http://publish.illinois.edu/mdpnp-architecture/advanced-situation-awareness/

A. EXPERIMENTAL SETUP

Test Cases. We used patient data extracted from medical publications with the help of physicians to evaluate our approach. Publications were recommended by physicians or identified through searches of the online database PubMed [40] by use of the following keywords: paroxysmal sympathetic hyperactivity, case studies, and criteria. For those references with only statistical distributions and episode descriptions, we automatically generated data that satisfied the constraints. The most widely used values from the references were used as default values for quantitative features described in natural language. Those values were 120 beats/min, 160 mmHg, 30 breaths/min, and 38.5 °C for increased heart rate, blood pressure, respiratory rate, and body temperature or other terms with the similar meaning, respectively. Qualitative clinical features that were not mentioned in the case description were treated without those symptoms.

Because the duration of each episode of PSH is on average 30 minutes, as described in Section II-A, we sampled patients' data with a time-window of 30 minutes. The input for evaluation are these sampled data. Furthermore, we collected patient data from day three and day six to compare effectiveness and efficiency, respectively. Hence, we ensured

TABLE 1. Evaluation results in lab environment.

Publication	Cases			PSH Monitor								Manual							
	PSH	N-PSH	Total	TP		TN		FP		FN		TP		TN		FP		FN	
				3d	6d	3d	6d	3d	6d	3d	6d	3d	6d	3d	6d	3d	6d	3d	6d
Lee [30]	2	0	2	2	2	0	0	0	0	0	0	2	2	0	0	0	0	0	0
Hughes [31]	44	0	44	43	44	0	0	0	0	1	0	39	42	0	0	0	0	5	2
Baguley [32]	15	0	15	15	15	0	0	0	0	0	0	13	15	0	0	0	0	2	0
Blackman [14]	20	0	20	19	20	0	0	0	0	1	0	18	20	0	0	0	0	2	0
Deepika [33]	4	0	4	4	4	0	0	0	0	0	0	4	4	0	0	0	0	0	0
Lv [7]	6	0	6	6	6	0	0	0	0	0	0	5	6	0	0	0	0	1	0
Baguley [34]	6	0	6	6	6	0	0	0	0	0	0	4	6	0	0	0	0	2	0
F-Ortega [15]	18	0	18	18	18	0	0	0	0	0	0	15	16	0	0	0	0	3	2
Akcil [36]	1	0	1	1	1	0	0	0	0	0	0	1	1	0	0	0	0	0	0
Goddeau [37]	1	0	1	1	1	0	0	0	0	0	0	1	1	0	0	0	0	0	0
Nazif [38]	1	0	1	1	1	0	0	0	0	0	0	1	1	0	0	0	0	0	0
Umbriaco [39]	0	5	5	0	0	4	4	1	1	0	0	0	0	4	4	1	1	0	0
Martin [40]	0	5	5	0	0	3	3	2	2	0	0	0	0	5	5	0	0	0	0
Total	118	10	128	116	118	7	7	3	3	2	0	103	114	9	9	1	1	15	4

PSH Monitor represents our approach and Manual represents the current medical approach. PSH represents confirmed patients, and N-PSH represents those confirmed as having other diseases. TP is true positive (PSH cases detected as PSH). TN is true negative (N-PSH cases detected as N-PSH). FP is N-PSH cases misdiagnosed as PSH, and FN is PSH cases not diagnosed. Data in the 3d and 6d columns are the patient data on days 3 and 6, respectively.

that there were more than 2 episodes per day for 6 days to meet the episode duration thresholds in the criteria sets. The composition of patient data is presented in the first four columns of Table 1, which consists of 118 PSH cases labeled as PSH and 10 non-PSH cases labeled as N-PSH. The clinical features overlapped for false alarm testing. For non-PSH cases, we randomly generated cases based on the clinical features described in the publications. All of the cases were confirmed by the physicians (All of the data can be obtained by emailing the authors for academic purposes only.).

Simulation Environment: As presented in Figure 4, our system was deployed in a lab environment to simulate a real-world monitoring scene. In our evaluation, we chose two of the most widely used methods published in [7] and [15] with the weight vector [1, 1] to construct the compound model. We set the result threshold τ at 1, indicating that a patient was confirmed when any of the criteria sets was satisfied. We visualized the compound model in Figure 6. To the best of our knowledge, there is no existing automated tool for detecting PSH. The current clinical approach is based on checking patient signs and symptoms manually. Therefore, we invited volunteers with medical experience to simulate physicians in a hospital to check patient data and make diagnoses. First, we presented the two sets of criteria and ensured that all the volunteers had understood them. Then, we sent the data to the volunteers at fixed time intervals and asked them to make a diagnosis, which is similar to the clinical activities performed in a hospital. We recorded the first time a confirmed PSH diagnosis was produced.

Method: The input of evaluation is the patient data sampled in *Test Cases*, and the output is the result of the diagnoses. First, we define the following:

- TP represents true positives, indicating that a PSH case was detected as PSH

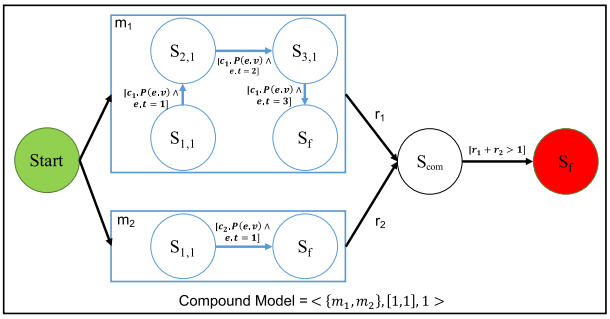

FIGURE 6. A visualization of the compound model for evaluation.

- TN represents true negatives, indicating that a non-PSH case was detected as non-PSH
- FP represents false positives, indicating that a non-PSH case was detected as PSH implying a misdiagnosis
- FN represents false negatives, indicating that a PSH case was detected as non-PSH, implying underdiagnosis

The results are evaluated based on two characteristics: precision and recall. Precision is the ratio of correctly detected patients to the number of patients classified as PSH:

$$Precision = \frac{TP}{TP + FP} \tag{11}$$

Low precision implies that an approach treats a large proportion of non-PSH patient as PSH, resulting in misdiagnosis. Recall is the ratio of correctly detected PSH patients to the total number of PSH patients in the input:

$$Recall = \frac{TP}{TP + FN} \tag{12}$$

Approaches with low recall cannot detect PSH cases well, resulting in underdiagnosis.

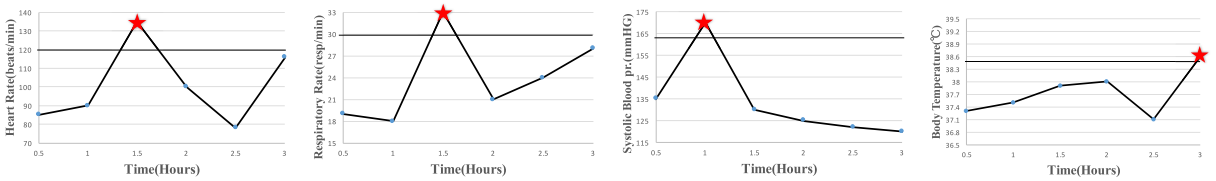

FIGURE 7. Patient vital signs for the first three hours in a case from [29], which was missed by manual checking but detected by our system. Red stars indicate outlier points above the criteria. Gradations on the *X* axis indicate 30 min intervals. The patient showed sweating and posturing during the first and the second hour. (a) Heart Rate. (b) Respiratory Rate. (c) Blood Pressure. (d) Body Temperature.

B. RESULTS

All the experiment results are described in Table 1. We display the results of our work in columns 5-12, and the average results of the current approach are shown in columns 13-20, where 3 d stands for the day 3 results, and 6 d stands for the day six results. TP, TN, FP, and FN have been discussed in the *Method* part in Section IV-A.

TABLE 2. Statistical summary of detection results.

Label	PSH Monitor(%)		Manual(%)	
	3 d	6 d	3 d	6 d
Precision	97.48	97.52	99.04	99.13
Recall	98.31	100	87.29	96.61

a: EFFECTIVENESS

To compare our work and the current approach, we use precision defined in Equation (11) and recall defined in Equation (12) to compare the effectiveness. These parameters focus on how many correct diagnoses an approach can achieve. The results are shown in Table 2.

Precision is the ratio of correctly detected PSH patients to the number of patients classified as PSH. As shown in Table 1, TP is 116 and 118 and FP is 3 on day 3 and day 6, respectively. Therefore, the precision of our result is $116/(116 + 3) = 97.48\%$. Compared to $103/(103 + 1) = 99.04$ % for manual checking on day 3, our approach performs almost the same in terms of the correctness. Thus, we will not burden medical staff with more false alarms than the current approach. In addition, both of the approaches performed well enough on days 3 and 6; they had precision greater than 95%.

Recall is the ratio of correctly detected PSH patients to the number of PSH patients in our case set. With 118 cases classified as PSH patients, we successfully detected 116 of them in the first three days and all of them in six days. Thus, the recall was $116/(116+2) = 98.31$ % and 100 %, which is better than the results of manually checking, which resulted in recall of $103/(103 + 15) = 87.29$ % and $114/(114 + 4) = 96.61$ %. In terms of the detection capability, our approach performs better than the current approach because we detect 11.02% more potential PSH patients at an earlier time.

Human safety is the most important factor in the medical domain. With a reasonable false alarm rate, we achieve higher recall, indicating a better solution.

b: EFFICIENCY

In this part, we compare the efficiencies and focus on how much earlier an approach can make a correct diagnosis.

With the same diagnostic criteria, manually checking underdiagnosed 13 more cases than our method out of all the PSH cases in the first three days, which shows that our approach can perform better in terms of the early detection of PSH, by 11.02 %.

In Figure 7, we show the patient data for the first 3 hours in a case from [29] to illustrate the efficiency of our approach. Because the duration of each episode of PSH is on average 30 minutes, as described in Section II-A, we sampled patients' data with a time window of 30 minutes. Therefore, the increased heart rate, respiration rate and blood pressure can be captured at 1.5 hours and 1 hour, respectively, in our system. An alert is produced to notify the nurses for further manual checking, and we successfully detected this episode within 1 hour to 1.5 hours. However, it is unreasonable for medical staff to observe patients all the time. Thus, most of the volunteers missed the syndromes either at 1 hour or 1.5 hours, resulting in underdiagnosis.

From another perspective, we grouped the confirmed timestamps of all PSH cases as shown in Table 3. The results show that manual checks have an average of 16.57 hours' delay relative to our system. We believe that the real-world situation is worse when paroxysm and complex clinical

TABLE 3. Distribution of confirmed timestamps of PSH cases.

Time Window (hours)	PSH Monitor	Manual
0-24	106	73
25-48	0	19
49-72	10	10
73-96	2	9
97-120	0	2
121-144	0	3
144+	0	2
Total	118	118
Average Time Delay	0	16.57 hours
Max. Time Delay	0	96.5 hours

features are considered. Additionally, during the process of manual checking, a volunteer mixed up two criteria sets, resulting in under-recognition. Hence, our approach provides the benefit of steady performance.

c: FALSE ALARM

Out of all cases, we had 3 false positives and 2 false negatives in the first three days. Reviewing the cases manually, we notice that for all the false positives, they met the PSH criteria. For example, the patient in [38] was confirmed as having sepsis with BT 39.2 °C, HR 190, RR 35, posturing and poor response to interactions. However, these symptoms are sufficient for diagnosis of PSH. Therefore, the main reason for false positives is that there are many overlapping clinical features between PSH and sepsis. In future work, we will seek to provide a relevant analysis to distinguish conditions with the same clinical features. For the 2 false negatives, they were detected on the fourth day. To detect these cases early, we can decrease the thresholds of each of the vital signs. However, this will disturb physicians with too many false positives. In the future, we will carry out more experiments to balance this issue.

C. DISCUSSIONS

1) LIMITATION

In our evaluation, we used real-world cases extracted from medical publications. However, some of them lacked concrete data values and were described in human natural language. With the default values generated based on statistics, we filled in these cases and sampled from every 30 minute period to make a diagnosis. All of these processes may affect the evaluation results. Currently, we are working with physicians to deploy our system in hospitals for further evaluation.

2) LESSONS

During discussions and sessions with physicians, we learned many lessons.

- Medical CPS is desired. Medical devices have been equipped in hospitals to provide information that improves health care. However, physicians say they need more intelligent tools to help them make better decisions with reasonable amounts of disturbances.
- False alarms are difficult. According to our experience, the most efficient solution is to provide easy access to the thresholds and invite physicians to define the thresholds.
- Simple is better. Computer technologies are unfamiliar to medical staff. Therefore, we need to develop applications with user-friendly interfaces. Moreover, an extensible structure is needed to cope with the volatile clinical requirements, such as changes in the definitions of diseases.

V. CONCLUSION

CPS has attracted increased attention recently. With the proliferation of diverse measuring devices and increases in computational capabilities, researchers are successfully applying automation of CPS to diverse domains. In this paper, we propose a CPS framework for the early detection of long-term monitoring diseases. A configurable diagnostic knowledge model is presented to describe long-term monitoring disease criteria in a uniform way. Using this model, we illustrate the details of each component of the medical CPS. Our approach aims to relieve medical staff of some of their clinical activities and provide timely decision support. In the future, we will evaluate real-world patient data from hospitals to strengthen our work and apply our system to more diseases. Our work also sheds light on the great demand for the deep convergence of automation technologies, biomedical engineering, and health informatics under the rapid development of health engineering for the prediction and prevention of disease and the development of precise and personalized medicine.

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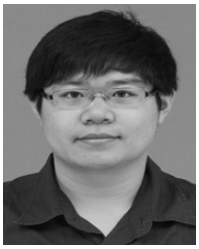

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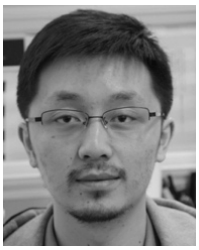

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