A Virtual Clinical Trial for Evaluation of Intelligent Monitoring of Exacerbation Level for COPD Patients

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Abstract. Chronic Obstructive Pulmonary Disease (COPD) is a progressive respiratory condition, ranking as the third leading cause of global morbidity and mortality. In this project, we simulate Real Clinical Trials using Virtual Clinical Trials (VCT) for COPD patients, offering possibilities not feasible in traditional trials, such as exploring treatment adherence levels and creating virtual cohorts with specific characteristics. We propose a cohort-based management strategy leveraging data analytics to identify patterns within the COPD patient population and advocate for employing a finite-state machine (FSM) approach to model COPD exacerbations. Further research and validation are crucial to refine and scale this integrated model.

Keywords: virtual clinical trial · Agent based modeling · Finite-state machine(FSM) · Self-management COPD patient.

1 Introduction

Simulating Real Clinical Trials via Virtual Clinical Trials (VCT) offers unique advantages unmatched by traditional trials. Once validated with real trial results, VCTs allow us to: 1. Explore scenarios and outcomes ethically restricted in real trials, such as varying patient adherence levels; 2. Create virtual cohorts with diverse characteristics, enhancing; intervention evaluation; 3. Control and manipulate environmental conditions for testing, including healthcare service occupancy rates and prevalent health conditions. Given these benefits, We

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are introducing a 'Virtual Clinical Trial' focusing on monitoring and follow-up to evaluate its impact on the care of COPD patients. COPD is projected to become the third leading cause of mortality by 2030 [1], imposing a significant global socioeconomic burden [2]. It is a persistent ailment initiated by factors like smoking or environmental pollutants, with manifestations including coughing, chest tightness, and breathlessness. Enhanced exacerbation management is crucial due to its correlation with decreased lung function and increased healthcare expenditures [3]. Traditional COPD management, reliant on clinic-based care, often overlooks the disease's dynamic nature. In response, we propose integrating virtual clinical trials with tailored self-management programs for COPD patients. This innovative model bridges clinical research and patient-centered care, empowering individuals to actively participate in their care and improve their well-being [4]. Additionally, cohort-based strategies leverage population-level insights to inform targeted interventions, employing data analytics to identify patterns within the COPD patient population. The synergy between self-management and cohort-based strategies aims to create a holistic COPD management framework [5]. Exacerbations occur due to various scenarios, requiring systematic modeling using finite-state machine (FSM) techniques to identify and predict exacerbation episodes accurately.

2 Methods

This section outlines the process, commencing with the FSM model for identifying exacerbation episodes from COPD patients' symptoms. Following this, it details the model of state patient care for extracting variables representing "stable" and "exacerbation" periods to generate training data for an algorithm based on robust features.

2.1 Finite-State Machine (FSM) for COPD Exacerbation

The Finite State Machine (FSM) is a valuable approach for understanding and categorizing different states of COPD exacerbations [6]. By representing patients' states and transitions based on symptoms and medication usage, it provides a structured framework for analyzing exacerbation events. In this model, patients can be in one of three states: normal, transitional, or exacerbation. Transitions between these states depend on inputs that encode changes in symptoms and medication usage. The inclusion of a transitional state accounts for instances where patients deviate from their normal state but do not meet the criteria for a full exacerbation. The inputs, representing medication usage and self-reported symptoms, allow for the dynamic characterization of patients' conditions. This enables healthcare professionals to track the progression of COPD and intervene appropriately based on the observed transitions. The definitions of exacerbation and symptom improvement provided by clinical experts offer clear criteria for categorizing events and determining when patients should transition between states. By aligning with clinical expertise and extensive literature review,

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this model enhances the accuracy and reliability of exacerbation identification. Overall, the FSM model provides a structured and pragmatic approach to understanding COPD exacerbations, addressing some of the challenges associated with existing definitions. Its incorporation of clinical input and clear criteria for state transitions makes it a valuable tool for both research and clinical practice in managing COPD.

2.2 Model of state patient care

The patient care process is modeled using an FSM, depicted in Figure 1. The

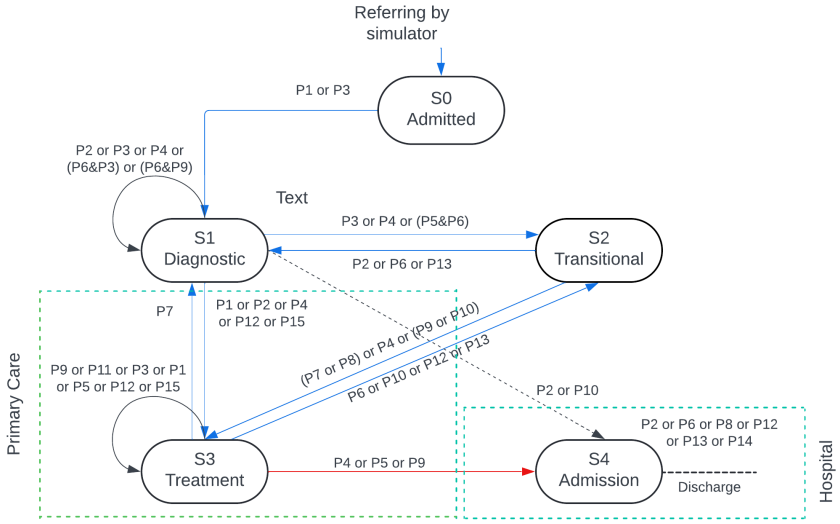

Fig. 1. A finite state machine (FSM) models a patient treatment process, where events and the state transitions they initiate are depicted as labels.

initial state begins with the patient's admission (S0) to a medical ward. Subsequently, the physician examines the patient to gather diagnostic information (S1) and plan further transitions (S2). This diagnostic phase may involve single or multiple examinations and tests. Based on the assessment, a treatment plan is prescribed (S3) in primary care. The patient undergoes comprehensive examination and evaluation, leading to either discharge or hospitalization based on their condition. Throughout treatment, additional examinations may necessitate therapy adjustments or repeat diagnostics. Upon satisfactory conclusion of therapy, the patient is discharged (S4) from the ward. This example identifies five

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Table 1. Defined activities and events within the patient treatment process.

State at:	Process event (outcome)	Activated
S0, S1, S2	P1: Confirms the declared symptoms; P2:Without problem; P3: New symptom emerge; P4: Medical test required	E1: Physical examination in Primary care
S1, S2, S3	P4: Medical test required; P5: Positive result; P6: Negative result	E2: Medical laboratory test in primary care
S1, S2, S3	P7: Diagnosed confirm and treatment assigned; P8: Diagnosed not confirm and patient discharge; P4: Medical test required	E3: Case assessment in primary care
S2, S3, S4	P3: New symptom emerge; P9: Symptom Increasing; P10: Symptoms decreasing; P11: Side effect emerged; P12: Stable situation; P13: End of therapy	E4: Therapy in hospital
S3, S4	P2: without problem; P14: End of recovery therapy; P15: New medical or personal evidence received	E5: Evidence received

states: Q=(S0, S1, S2, S3, S4), and outlines eight process activities triggering state transitions from admission to discharge states (S0 to S4). The details are presented in Table 1.
In our formal framework, an activity denoted as E is characterized by the pair $< S, PE >$ where:

$$S \subseteq Q \tag{1}$$

• Signifies the set of states from which this activity can be invoked (though not necessarily required).

$$PE \subseteq \sum \tag{2}$$

• PE subset of sigma represents the set of events resulting from the activity's execution, with the potential to initiate a state transition. For each activity E, the state transitions that may occur upon its completion can be determined as follows:

$$\delta A : S * PE = P(S) \tag{3}$$

Consider activity E2 (Medical laboratory test) with states S: S1, S2, S3 and events E: P5, P6, P4. Certain events, like P10 - condition improved, can be contextual and independent of specific activities. To predict exacerbation episodes, it's vital to identify intervals of stable to unstable conditions and deterioration trends preceding exacerbations. The FSM portrays states like mild, moderate, severe, and very severe exacerbation, linked by transitions reflecting health condition shifts. The table-set complements the FSM, detailing parameters like respiratory rate, blood pressure, and BMI influencing state transitions (Table 2). This organized overview enhances understanding of COPD patient health progression during a flu episode.

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3 Proof of Concept

In this project, data processing revolves around time-specific captured information, managing baseline data, and environmental variables. The raw data is grouped into categories, each indicating specific situations through numeric and string variables [7]. Table 2 presents a sample of ten virtual patients from the cohort, each identified by a unique ID number for easy data access. Patient characteristics include gender, where women may have a higher predisposition to COPD. Body Mass Index (BMI) plays a crucial role, with a lower BMI potentially increasing COPD risk. COPD is influenced by factors like smoking status, categorized into current smokers, ex-smokers, and never-smokers. The mMRC scale assesses dyspnea, while respiratory rate, heart rate, and sputum are evaluated based on various criteria. Oxygen saturation (SpO2) is categorized into four groups, and FEV1 measures lung function [8].

Table 2. Defined 10 sample datasets for COPD patients in the cohort

ID	Age	Sex	BMI	mMRC	Smoke	RR	HR	Spo2	Sputum	EFV1
1	47	Male	$21 < BMI < 25$	0	3	13	Higher	%97	Normal	80-above
2	60	Female	$< 21kg/m2$	3	1	18	Higher	%95	Purulent	30-49
3	55	Female	$30 > BMI < 35$	4	1	24	Normal	%89	Purulent	29 or less
4	78	Male	$25 > BMI < 30$	1	2	15	Higher	%98	Normal	50-79
5	71	Male	$30 > BMI < 35$	4	1	22	Lower	%88	Purulent	29-less
6	82	Female	$> 35kg/m2$	3	1	20	Lower	%94	Purulent	30-49
7	79	Male	$21 < BMI < 25$	2	1	18	Higher	%95	Normal	50-79
8	69	Female	$21 < BMI < 25$	0	3	13	Higher	%96	Normal	80-above
9	45	Male	$21 < BMI < 25$	1	2	15	Higher	%97	Normal	50-79
10	88	Male	$< 21kg/m2$	3	1	21	Lower	%93	Purulent	30-49

3.1 Specify the outcome variable

The study aims to create a fuzzy logic-driven medical decision system for diagnosing COPD using symptoms and test results. Employing fuzzy sets to quantify symptoms and results, it seeks to provide precise COPD severity measures and guide treatment.

Fuzzy logic-based medical decision framework involves: 1. Formulate fuzzy rules for COPD diagnosis: A. IF high respiratory rate OR high heart rate OR low oxygen saturation OR exposure to occupational dust and chemicals AND current smoker, THEN severe/very severe COPD; B. IF normal respiratory rate OR high heart rate OR purulent sputum OR exposure to home and office environment AND current ex-smoker, THEN moderate COPD; C. IF young age OR normal respiratory rate OR normal body temperature OR current never-smoker, THEN mild COPD [9]; 2. Specify fuzzy logic operations: A. AND: minimum operator; B. OR: maximum operator; C. NOT: complement operator; 3. Assess input

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variables using fuzzy sets and logic operations; 4. Combine fuzzy output values with the weighted average aggregation method; 5. Transform fuzzy output value into definite value using the centroid defuzzification method; 6. Present diagnostic outcome based on determined crisp output value; 7. Validate and assess the system using the dataset of confirmed COPD patients, comparing diagnostic accuracy to conventional methods.

3.2 Performance

The dataset includes 10 virtual patients as a sample for developing a comprehensive model. Table 2 presents a subset of these patients. The fuzzy logic algorithm was implemented by loading the dataset into a data frame. The algorithm's time complexity is:

$$O(n^2) \tag{4}$$

With a dataset size of 10 entries and 10 input variables, the time complexity is $O(10^2 * 10) = O(1000)$. The execution time was 0.47 ms. Overall, the fuzzy logic algorithm showed low memory usage, no redundancy, and reasonable execution speed for this dataset size. The output classifies patients into four categories: control, direct assessment, modifying medicine, and hospital referral (Table 3). Figures 2 and 3 illustrate the characteristics of these classes. This study quan-

Table 3. Defined 10 sample datasets for COPD patients in the cohort

ID	Age	Sex	Smoke	RR	HR	Spo2	Sputum	Categories
1	47	Male	3	13	Higher	%97	Normal	**Control**
2	60	Female	1	18	Higher	%95	Purulent	**Ref-Primary care**
3	55	Female	1	24	Normal	%89	Purulent	**Ref-Hospital**
4	78	Male	2	15	Higher	%98	Normal	**D-Assessment or M-Medicine**
5	71	Male	1	22	Lower	%88	Purulent	**Ref-Hospital**
6	82	Female	1	20	Lower	%94	Purulent	**Ref-Hospital**
7	79	Male	1	18	Higher	%95	Normal	**D-Assessment or M-Medicine**
8	69	Female	3	13	Higher	%96	Normal	**Control**
9	45	Male	2	15	Higher	%97	Normal	**D-Assessment or M-Medicine**
10	88	Male	1	21	Lower	%93	Purulent	**Ref-Primary care**

tifies the predictive efficacy of three key physiological parameters (Age, SpO2, and RR) and emphasizes their reliability in home monitoring with the mMRC scale. Incorporating the mMRC scale in future remote monitoring studies is advisable due to challenges in logging symptom-worsening episodes among COPD patients. Allowing patients to self-report with the mMRC scale at home provides real-time insight, aiding timely intervention. Figure 2 illustrates the output of the simulator, with two patients categorized into the Not-monitored (control) group and eight patients in the monitored group. Within the monitored group, three

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patients are identified by the simulator for hospital referral based on their variables. Simultaneously, three patients are placed into the direct assessment and

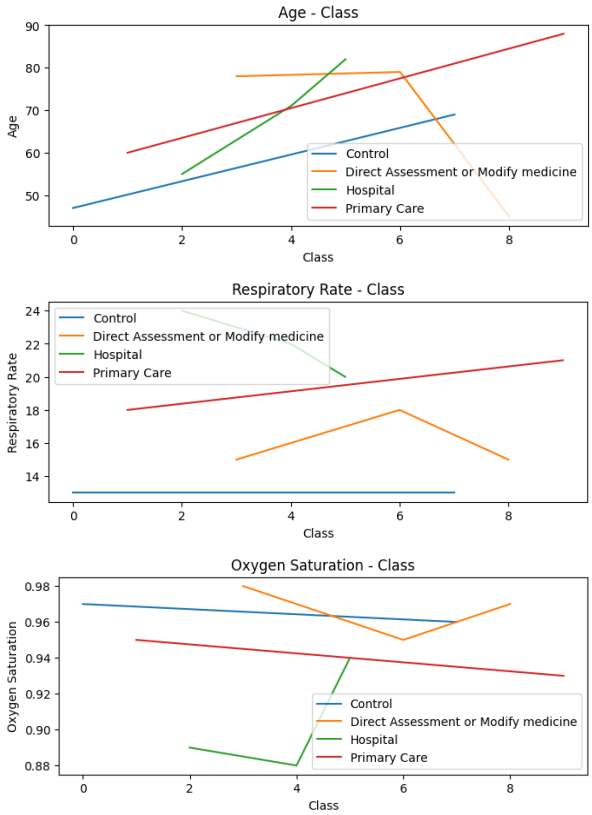

Fig. 2. The outcome of age, respiratory rate, and oxygen saturation was comprehensively assessed within the monitored group, highlighting the rates of each variable

modification group, managed by a doctor or authorized personnel. Additionally, two patients are referred to primary care. Furthermore, Figure 2 demonstrates the combination of patients in both groups, showcasing the variables of each class for the specific patient groups.

4 Conclusion

Previous research hasn't proposed FSM or similar models for COPD cohort identification, continuous patient monitoring, and addressing external variables like pollution and daily activity on vital signs. Our findings shed light on vital sign distribution during stable and exacerbation periods, based on data from 10

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COPD patients. This method can deepen our understanding of symptom deterioration and medication impact. Future research will involve using real patient data. We'll evaluate the system's diagnostic accuracy, comparing it to conventional methods. If the system proves effective, there's potential for clinical testing to improve COPD diagnosis precision and efficiency

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