Modeling and Analyzing Treatment Protocols for Pediatric Asthma Management Using the UPPAAL Timed Automata Framework

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ABSTRACT

Objectives

This research is centered around developing a foundational model for understanding and managing pediatric asthma, a common chronic condition in children globally. The aim is to build a preliminary model that allows us to simulate different aspects of pediatric asthma management, specifically observing and controlling symptoms. This model serves as a first step toward modeling this complex disease. The primary objective is to explore the relationships between asthma symptoms, medication protocols, and patient adherence, which are vital components of effective asthma treatment. Specifically, the study will model and compare the efficacy and costs of two treatment protocols, the Global Initiative for Asthma (GINA) treatment protocol, and the Medisch Spectrum Twente treatment protocol.

Methods

To achieve our objectives, we employed the UPPAAL timed automata framework, a computational tool designed to model and analyze complex systems. Our model comprises interconnected templates symbolizing various facets of asthma management, such as symptoms, adherence, medication regimens, environmental impacts, and outcomes. Utilizing UPPAAL for formal modeling, a novel application in pulmonology, we simulated a population of pediatric asthma patients by initiating simulations and queries based on various parameters.

Results

Our simulations revealed differences in the predicted number of mild flare-ups and costs between the Global Initiative for Asthma (GINA) and the Medische Spectrum Twente pediatric asthma treatment protocols. The latter protocol demonstrated fewer mild flare-ups and lower costs, indicating its potential for superior cost- effectiveness.

Conclusions

This study successfully developed a proof-of-concept model for analyzing pediatric asthma management protocols, providing the first formal simulation of treatment outcomes. Through the comparison of the Global Initiative for Asthma (GINA) and Medische Spectrum Twente protocols, the model's potential was showcased by highlighting their relative effectiveness and cost-efficiency. The research underscores the potential of computational modeling in chronic disease management, suggesting a future where treatment plans are increasingly data-driven and personalized. It lays the groundwork for advances in tailored treatment protocols based on individual patient characteristics.

Clinical Significance

The UPPAAL timed automata framework's utility in modeling and analyzing complex systems in healthcare is increasingly recognized [7]. By using this tool to compare the Global Initiative for Asthma (GINA) and the Medisch Spectrum Twente treatment protocols, this research opens up a dialogue about their efficacy, cost-effectiveness, and adaptability in real-world settings. These insights could eventually contribute to improving current treatment protocols and adherence strategies, which is of utmost importance, given the prevalence and impact of pediatric asthma globally.

Furthermore, the model generated in this research could potentially be extended and refined in future studies, serving as a foundation for more comprehensive models that incorporate additional factors, such as genetic predisposition, environmental triggers, socio-economic factors, and patient lifestyle. In this way, our research represents an important stepping stone in the quest for a more effective, personalized approach to pediatric asthma management.

KEYWORDS

timed automata, UPPAAL framework, model analysis, pediatric asthma

1 INTRODUCTION

Asthma is a widespread chronic respiratory ailment with a prevalence of 5-10% in children up to 12 years in the Netherlands [2] [6]. Managing this condition is often fraught with challenges, primarily due to the diverse factors that influence its severity and inconsistent patient adherence to treatment protocols.

This research constitutes a preliminary exploration into these issues, with a focus on the interplay among asthma symptoms, medication routines, and patient adherence.

The UPPAAL timed automata framework, an established tool within computer science for its efficacy in facilitating the communication of technical concepts to non-technical specialists from various disciplines, serves as our methodological choice for this exploratory endeavor. This represents one of its early applications within the realm of pulmonology, hinting at its potential utility in studying multifaceted health conditions.

Our strategy involves the formulation of a model using interlinked templates, each representing an integral facet of asthma management, including symptoms, medication regimens, patient adherence, environmental factors, and outcomes. Simulations of a pediatric asthma patient population are conducted, varying parameters to gain an elementary understanding of factors impacting disease progression.

Additionally, we've incorporated a visual representation to better understand the variation of asthma symptoms throughout different life stages:

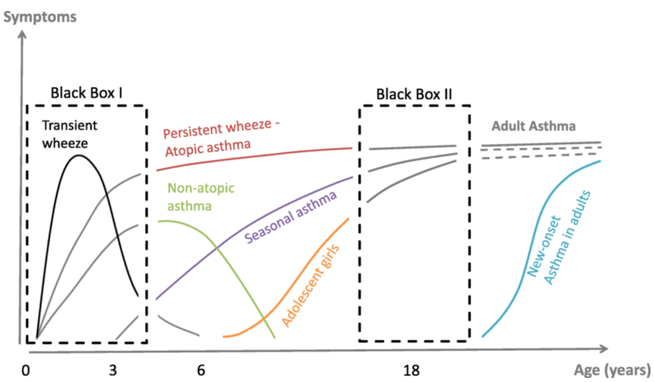

Figure 1: Wheeze and asthma phenotypes during childhood and adulthood. Adapted from [3].

The graph depicts the progression of wheezing and asthma phenotypes from childhood into adulthood. The age (X-axis) and symptom manifestation (Y-axis) show that about 25–30% of children have at least one wheezing episode by age 3, indicating early clinical heterogeneity. Transient wheezing usually subsides by school age, and non-atopic asthma around age 8. Persistent atopic wheeze and seasonal triggers may extend into adulthood. The graph also shows an increase in new-onset asthma in adolescent girls, marking a sex-based shift. However, it is unclear if the distinctions seen in persistent childhood asthma phenotypes persist into adulthood.

The analysis encompasses a comparative study of the pediatric asthma protocol as delineated by the Global Initiative for Asthma (GINA) and the alternative Medisch Spectrum Twente treatment protocol. Their relative efficiencies in maintaining minimal flare frequencies and predicting medication needs based on individual, keeping minimal cost, and environmental parameters form the core of our investigation.

This research aims to be a first step in underscoring the potential benefits of considering these interactions when devising medical protocols for pediatric asthma management. However, it must be emphasized that this study is a nascent step, abstract in nature, and based on a series of assumptions. It merely offers proof of principle, and extensive further research is required to fully realize its potential.

2 RELATED WORK

Various studies have utilized formal methods and timed automata for modeling complex medical processes and systems. Schivo et al. [10] used timed automata to model the personalized treatment decisions in metastatic castration-resistant prostate cancer, demonstrating the technique's potential in evaluating the benefits of personalized treatment processes. Similarly, Wetselaar et al. [14] employed timed automata modeling using UPPAAL to evaluate tooth wear monitoring, addressing research questions and clarifying factors of influence in a multifactorial condition.

In the context of medical cyber-physical systems, Lee et al. [7] explored the challenges and research directions in this field, emphasizing the importance of safety, effectiveness, and interoperability. Parveen and Goveas [9] utilized timed automata to model and verify the resource allocation process in healthcare settings, demonstrating the efficient assignment of patients to available caregivers.

In the domain of pediatric asthma care, our MST treatment protocol will be primarily informed by the work of Van Der Kamp [5]. His research emphasized the use of eHealth strategies and smart home monitoring systems as methods to enhance the existing standard of care. Adibi et al. [1] developed a conceptual model of childhood asthma to inform asthma prevention policies, emphasizing the need for rigorous investigation before adopting widespread prevention strategies.

In this study, a medical expert in pediatric asthma was consulted to evaluate the UPPAAL model before analyzing it and answering the research questions. This collaborative approach helped in assessing the confidence of the model's scientific soundness and clinical relevance, building upon the existing literature and utilizing the potential of timed automata in healthcare applications.

3 METHODOLOGY

3.1 Overview of UPPAAL SMC

UPPAAL SMC (Statistical Model Checking) is a model checker for systems that are either too large or too complex for classical model-checking techniques. It utilizes a stochastic approach for verifying systems against specifications, expressed in terms of probabilistic weighted timed automata and logic.

UPPAAL SMC framework provides us with the capabilities of simulation and statistical model checking, which are particularly useful when considering uncertainty in the system's behavior. It provides an array of useful queries to express various aspects of the system's behavior, like probabilities, averages, comparisons, and optimization.

For our research, UPPAAL SMC allowed us to explore how multiple variables interact within a complex system. The advantages of using this system include its flexibility, as it allows us to easily alter variables and parameters, and its powerful simulation capabilities, which let us observe potential outcomes without needing a real-world testing environment.

3.2 Development of the Pediatric Asthma Treatment Model

The development of our pediatric asthma treatment model proceeded by first creating an abstract model of pediatric asthma within the UPPAAL SMC framework. The templates we designed were based on a thorough review of existing literature and treatment protocols, with specific attention paid to the relationship between patient adherence to medication regimens and asthma outcomes.

We then created models of two distinct treatment protocols: the Global Initiative for Asthma (GINA) and the Medisch Spectrum Twente. The former offers a general guideline for pediatric asthma treatment, whereas the latter is an adaptation considering individual patient differences such as hormone levels and household environments.

The Global Initiative for Asthma (GINA) is a key protocol in asthma management that our research seeks to evaluate. Established by the World Health Organization and the National Heart, Lung, and Blood Institute, GINA provides a standardized, stepwise approach to asthma treatment. The GINA protocol is designed to achieve and maintain control of asthma symptoms and to reduce the risk of exacerbations. The protocol is stratified into five steps, where each step represents increased treatment intensity. These steps range from as-needed reliever medication in Step 1, to high-dose inhaled corticosteroids plus another controller and/or oral corticosteroids in Step 5. The patient's step level is assessed periodically and adjusted based on their level of symptom control [8]. By providing a uniform approach to treatment, GINA aims to facilitate the delivery of high-quality asthma care across diverse healthcare settings worldwide.

The Medische Spectrum Twente (MST) Protocol is another key distinctive method of asthma management that is central to our study. The MST protocol, named after the Dutch hospital where it was developed, provides a comprehensive and responsive approach to asthma treatment. Unlike traditional protocols which prescribe a fixed treatment regimen, the MST Protocol adjusts the medication type and dosage in response to changes in the patient's condition. This dynamic treatment plan is developed using a combination of home-based measurements using eHealth, including lung function tests, exercise provocation, adherence monitoring, and patient-reported symptoms. By closely tailoring the treatment to the patient's current state, the MST protocol aims to minimize the frequency and severity of asthma flares while keeping the overall treatment cost low [5]. The choice to employ the MST protocol in this study is rooted in its adaptability, making it a fitting protocol for our modeling approach which seeks to evaluate the outcomes of different treatment strategies in dynamic and diverse patient populations.

These models enabled us to simulate and evaluate both protocols in a controlled and customizable environment. Simulations were run with various parameter settings to represent a diverse population of pediatric asthma patients. This approach allowed us to assess the costs and efficiency of both treatment protocols, and their effectiveness under various conditions and scenarios.

In each template, we defined a set of variables to represent key attributes or factors, such as the severity and frequency of asthma flares, and dynamic factors like allergen and air quality indexes. Once the model was built, we observed relationships between variables, and assessed the effectiveness of the GINA protocol and the modified Medisch Spectrum Twente protocol, particularly focusing on their effectiveness at maintaining a low frequency of flares and prescribing the required medication. This methodology provided us with a comprehensive and flexible tool for analyzing pediatric asthma treatment protocols and their effectiveness under various conditions and scenarios.

3.3 Assumptions

This study is underpinned by a set of assumptions that facilitated the development and implementation of the UPPAAL Statistical Model Checker (SMC) for pediatric asthma management. It is crucial to bear in mind these assumptions while interpreting the results and discussing the potential implications of this research.

3.3.1 Framework Validity. The principal assumption in this study is that the UPPAAL SMC, a model-checking tool for systems, is a suitable and effective framework for modeling complex medical processes like pediatric asthma management. Given that this tool was originally developed for system verification, its use in a medical context is innovative but also speculative. Therefore, the validity of the framework in providing a realistic representation of the medical domain is a foundational assumption.

3.3.2 Data Reliability. The validation of the model was carried out using data extracted from both established literature and insights provided by medical professionals. Certain data points were readily available in the existing literature [8] [12] [1]. In instances where the literature did not provide the required information, educated assumptions were made. These assumptions were then informally validated through discussions with medical experts.

3.3.3 Model Simplification. To manage the complexity of asthma and its management protocols, the model necessitates several simplifications. It assumes a homogeneous patient population with standard responses to treatments and neglects individual patient characteristics such as age, genetics, and other specific factors that could influence the disease progression and treatment effectiveness. This simplification aids model construction and interpretation but might limit the model's predictive capacity on individual patient outcomes.

3.3.4 Treatment Protocol Adherence. Another critical assumption is that the prescribed treatment protocols (GINA and Medische Spectrum Twente) are strictly adhered to by healthcare professionals and that pediatric patients follow the prescribed treatments with a standardized degree of adherence. In reality, adherence rates can vary widely, influenced by a multitude of factors like a patient's understanding of the condition, perceived effectiveness of treatment, socio-economic status, and many others [4].

3.3.5 Non-inclusion of External Factors. This model does not consider external factors like environmental variables, lifestyle changes, and co-morbid conditions that could potentially influence the disease progression and treatment outcomes. The exclusion of these factors is an explicit simplification to make the model manageable and interpretable [12].

Each of these assumptions presents a simplification of the complex real-world scenario of pediatric asthma management. While they facilitate the model's development and the execution of the study, these assumptions could also introduce a certain degree of bias in the results and limit the model's external validity and generalizability. Future research can focus on relaxing some of these assumptions to create a more comprehensive and nuanced model.

3.4 Collaboration with Medical Experts

Our collaboration with medical professionals from Medische Spectrum Twente played a pivotal role in this research. We established several meetings at MST Hospital, presenting our progress and assumptions for scrutiny and discussion.

Initial interactions were not without challenges, predominantly due to the apparent divergence between our simplified pediatric asthma model and the intricate real-world medical treatment protocols. The medical experts found our model to be making several assumptions that might not hold in the complex, dynamic medical context.

Moreover, there was a fundamental difference in our categorization of patients. While the experts' perspective leaned towards a classification based on asthma control levels—controlled, partly controlled, uncontrolled, following the GINA guidelines—we approached the categorization based on the patient's immediate asthma burden, separating them into intermittent asthma, mild asthma, moderate asthma, and severe asthma.

However, these initial misunderstandings served as catalysts for critical discussions and refining the model. The expertise of these medical professionals played a crucial role in maintaining the relevance and applicability of our research despite its inherent assumptions. As such, this collaboration emerged as a critical element in the successful execution of our study.

4 MODEL SPECIFICATION

4.1 State Variables and Parameters

The goal of our model is to simplify the real-world complexity of pediatric asthma management into a clear and computationally manageable structure. We recognize the difficulty of accurately modeling asthma, a complex medical condition, hence we decided to build a statistical model that can handle essential variables.

We've based our model on the Global Initiative for Asthma (GINA) guidelines which define four asthma states - intermittent, mild, moderate, and severe. Usually, these states are identified during outpatient visits to indicate a patient's chronic asthma severity. However, in our model, we use these states as temporary markers to demonstrate the impact of asthma on a patient at a specific time.

We see these states as changeable, allowing a patient's asthma condition to fluctuate over time. This makes sense given the nature of asthma, and it's particularly important for children and adolescents who experience significant hormonal changes and growth spurts. We hope this model will help improve our understanding of pediatric asthma management, despite its simplicity and the inherent complexity of the condition.

- The **global_clock** serves as a reference to the time scale in months.
- The variable flares counts the number of asthma flare-ups, while **p** represents the current state of the patient's asthma on a scale from 1 to 4, 1 being mild asthma and 4 being severe asthma.
- The **eff** variable for medication effectiveness, an abstract combination of compliance and inhaler technique.
- The **hospitalize** broadcast channel is used to signal to the system that the patient has been hospitalized, hence the environment and therefore, treatment changes.
- The **check** broadcast channel is used to signal to the system that the patient needs to be checked by a doctor, hence the environment changes.

4.2 Defining Transitions and Probabilities

Probabilities for certain variables and outcomes within our model were derived from consultations with a medical expert specializing in pediatric asthma. This collaboration helped in obtaining a more realistic and clinically-informed perspective, thereby increasing the relevance and potential applicability of our model. The medical expert's contributions have been instrumental in shaping the model and their expert insights have significantly enhanced the validity of our research.

As asthma is a multifaceted condition, its progression and control are influenced by a myriad of factors, however, in our research, we focus on statistical probabilities. We utilize several functions to estimate the probabilities related to pediatric asthma, considering variables such as a patient's medication adherence and current asthma state.

- **light()** This function computes the probability of a light flare-up or exacerbation, dependent on the patient's current asthma state *(p)*.
- **no_flare()** This function calculates the probability of no flare-up occurring, also dependent on the patient's current asthma state *(p)*.
- **up()** This function calculates the probability of the asthma state worsening (*p* increases). If the current state is worse than what the medication can handle, the probability increases with decreasing medication effectiveness. If the current state is not worse, the increase in probability is more moderate but still dependent on the medication's effectiveness. This suggests that a lack of effective medication can lead to a deterioration in the asthma state.
- **down()** This function estimates the likelihood of an improvement in the patient's asthma state. It suggests that a reduction in the severity of the asthma state *(p)* is possible when the medication type *(m)* is suited to the current state and the medication effectiveness *(eff)* is at its maximum.

4.3 UPPAAL SMC Model of the Treatment Protocols

The UPPAAL SMC model consists of eight interconnected templates: **Env**, **Flare**, **Patient**, **G_Treatment**, **MST_Treatment**, **MST_FlareReset**, **G_Check**, and **MST_Check**.

- The **Env** template models the assumption that the effectiveness of medication *(eff)* decays over time.
- The **Flare** template represents light and severe flares.
- The **G_Treatment** template is used to simulate the treatment dynamics of pediatric asthma based on the Global Initiative for Asthma (GINA) guidelines, which involves managing asthma in sequential steps. [8].
- The **MST_Treatment** template is used to model the MST treatment protocol based on the measured *(p)* state.

- The **MST_FlareReset** template is used to adapt the flare counter to the MST_Treatment protocol, such that the comparison with G_Treatment is still valid.
- The **G_Check** template models routine checks and measurements that are carried out to assess the patient's health status. This check is carried out every 6 months or if the patient is in the hospital.
- The **MST_Check** template models routine checks and measurements that are carried out to assess the patient's health status. This check is done monthly or if the patient is in the hospital and does not necessarily need the presence of the patient [5].
- Lastly, the **Patient** template represents the patient's current health state and personal factors that could affect asthma management.

Each template contains local declarations, states, and transitions that represent the dynamics of each component of the asthma management system. The templates interact via synchronization on shared channels, and their behavior depends on the state of the global variables and parameters. Given the complexity and multifactorial nature of asthma, it is very difficult to incorporate everything into our UPPAAL SMC. However, the model is designed with multiple interconnected templates that allow for an abstract representation of the asthma management process. Each template encapsulates an abstraction of a particular component of the process, ranging from medication effectiveness to treatment regimens and patient factors. All the technical details can be found on Figshare [11]. The model attempts to simulate the interactions and dependencies among these components, thereby offering insights into the potential outcomes of different scenarios. By manipulating various variables and parameters, we can explore different management strategies and identify which ones yield the best outcomes in terms of reducing the severity and frequency of asthma flares, as well as maintaining a low cost.

4.3.1 Asthma Flare. This UPPAAL SMC template named "Flare" models the occurrence and severity of asthma flares, considering their effect on the cost variable. The template includes a clock named *hc* to measure the time for effectiveness checks after hospitalization. Two functions *light()* and *no_flare()* define probabilities of different events based on a patient's current state *(p)*. There are five distinct locations in this model, representing different stages of asthma flare and treatment:

NoFlare: This state represents the patient's normal condition where no asthma flare has occurred. The exponential rate label of 8*p determines the rate at which transitions from this state occur per month, where p is a representation of the patient's condition. The '8' in '8*p' represents the frequency of possible flares, and this frequency is related to the patient's state *(p)* [13].

Light: This state signifies the occurrence of a mild asthma flare. It's marked as urgent to prioritize immediate transitions once the patient enters this state.

Serious: This state represents a serious asthma flare, also marked as urgent.

Hospital: The patient enters this state after a serious asthma flare, requiring hospitalization. This state also includes an invariant label *hc<=1*, ensuring that the patient leaves this state after 1 month.

If the patient experiences a serious flare (Serious state), they are transitioned to the Hospital state, and the hospitalization cost is added to the cost variable.

After experiencing a light or serious flare, the patient eventually transitions back to the NoFlare state.

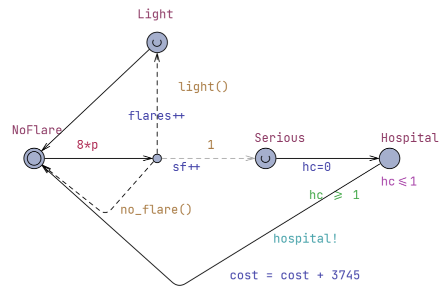

Figure 2: Flare Model

4.3.2 Patient. The UPPAAL SMC model outlined above describes a "Patient" template, which is used to represent the condition of a patient with asthma in a simulation. This model captures the dynamics of a patient's asthma condition over time, as well as their adherence to treatment protocols. The patient's condition and adherence level can influence the severity of their asthma, which is categorized into four states: Intermittent, Mild, Moderate, and Severe.

Firstly, the model defines several clocks such as *pc* (patient clock in months, with *pc=0* indicating the patient is 6 years old), and *tp1* through *tp4*, which measure the time spent in each asthma severity state.

The template then describes several locations representing the asthma severity states: Intermittent, Mild, Moderate, and Severe. In each location, the model maintains invariants that ensure the patient can only stay in one state at a time.

The branchpoints and transitions in the model represent the changes in the patient's condition and adherence level over time. These transitions occur based on various factors, such as the time elapsed since the last state change *(pc>=1)* and the current adherence level. The probability of these transitions is determined by the functions *down()* and *up()*, reflecting the dynamic nature of the patient's condition.

Each transition is labeled with an assignment that modifies the patient's state *(p)* or adherence level *(adh)*, and a probability that determines how likely this transition is to occur. The model also has initial urgent locations and an init transition which sets the initial conditions of the simulation.

This model, while a simplification of real-world dynamics, captures important aspects of pediatric asthma management. It provides a basis for simulating different treatment protocols and understanding how patient adherence and treatment efficacy might impact the progression of the disease.

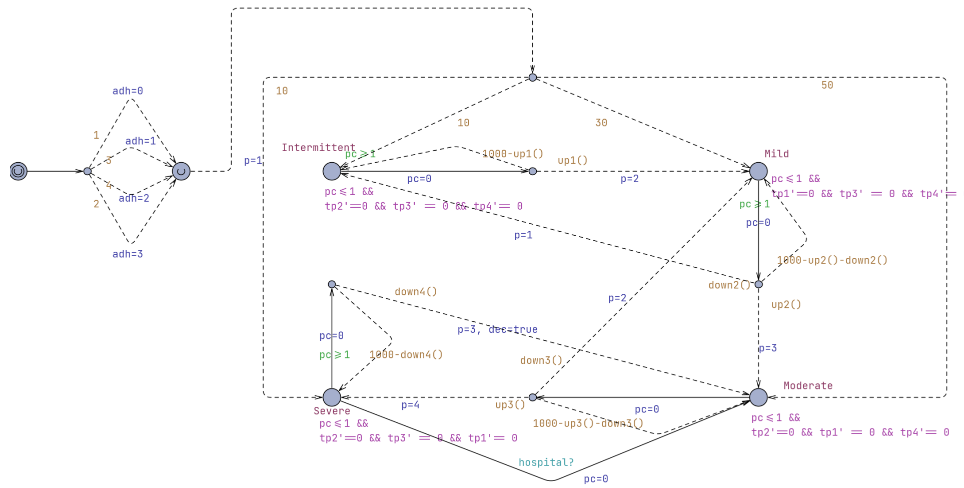

Figure 3: Patient Model

4.3.3 G_Treatment. At the core of this template are multiple states, namely Step1, Step2, Step3, and Step4, corresponding to the GINA guidelines. The transitions between these steps are governed by the number of asthma flares and the time elapsed since the last treatment adjustment (tracked by the *tc* clock). The *tc* clock resets every time a treatment change occurs, reflecting the dynamic nature of asthma management.

Each step of the GINA protocol carries distinct costs, determined by monthly averages extracted from realistic data, as supplied by a medical expert and substantiated by resources from the Dutch Healthcare Authority (NZA)[1] and the Dutch Pharmacotherapeutic Compass[2]. These costs, considering the flare frequency associated with each stage, are aggregated cumulatively to the 'cost' variable. Specifically, costs account for medication expenses related to each step and potential hospitalizations due to severe asthma flares, along with the regular costs of doctor consultations.

The transition conditions between the steps, described by the 'guard' labels, are based on both the number of flares and the *tc* value. If the conditions are met, the template executes a*t()* function which alters the treatment step *('m')*, resets the *tc* clock, recalculates the cost *('v')*, and adds it to the total *cost*. This function provides an abstract representation of a treatment adjustment in response to the patient's condition.

This template, thus, provides a simplified but valuable abstraction of the dynamic and responsive nature of pediatric asthma treatment, incorporating both the clinical *(flares, treatment step)* and economic *(cost)* aspects.

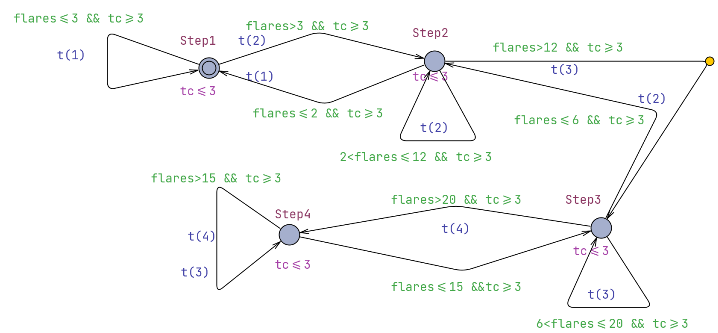

Figure 4: G_Treatment Model

4.3.4 MST_Treatment. This model consists of two primary states. The first state, associated with a time-invariant condition *tc<=1*, reflects that it waits one month. Upon the completion of this month, the model transitions to a *branchpoint* and adds a monthly cost of 50 to the total cost, denoting a constant monthly expense for treatment management. Here we measure the *p* state of the patient using eHealth [5] with two alternate paths available. One path leads to the 'Check' state with a probability of *2* (reflecting a 2% chance). In this case, the model doesn't make any changes to the treatment step. On the other path, taken with a 98% chance, the model establishes the current treatment level *('m')* based on the patient's condition *('p')* before proceeding to the 'Check' state. This simulates the precision of the *p* measurement using eHealth devices.

Once in the 'Check' state, the model awaits for the *tc* clock to reach 1 month. Upon this, the model performs a synchronization using *check!* calling the **MST_Check** template, and the *t()* function is executed. This function resets the *tc* clock, calculates the cost for the treatment level for the next month, and adds it to the total cost.

In essence, this template represents a monthly review of the patient's condition and adjustment of the treatment regimen. It

[1] https://zorgproducten.nza.nl/ZorgproductViewer.aspx#
[2] https://www.farmacotherapeutischkompas.nl/

incorporates probabilistic transitions to reflect the inherent uncertainties in patient response and the decision-making process of clinicians.

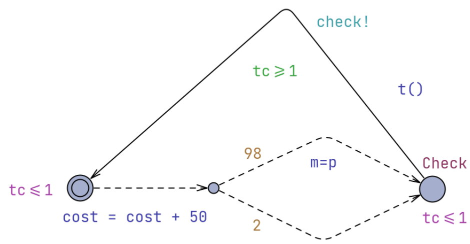

Figure 5: MST_Treatment model

5 RESULTS

The visual representations shown in Figure 6 and Figure 7 serve to illustrate the simulation of an asthma patient's treatment regimen. This patient, commencing at six years of age, is followed for 144 months, ensuring a robust longitudinal view. For both protocols, the patient's adherence level *(adh)* is set to 1 and the patient begins with *p* state of 1, indicating relatively low adherence to treatment and intermittent asthma. The depicted lines represent three variables - the medication treatment *(m)*, medication efficiency *(eff)*, and the patient's state *(p)*.

In Figure 6, the patient's management is undertaken using the Global Initiative for Asthma (GINA) treatment protocol. It is observed that the medication efficiency *(eff)* exhibits a degree of fluctuation. This variability arises from the patient's low adherence to the medication regimen.

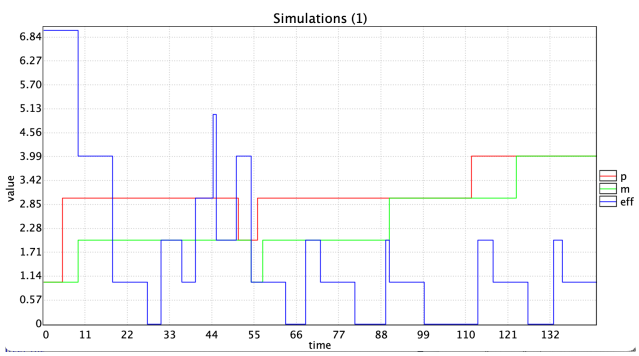

Figure 6: G_Treatment result

On the other hand, Figure 7 illustrates a simulation using the Medische Spectrum Twente treatment protocol. When contrasting Figure 6 with Figure 7, it can be observed that the medication treatment *(m)* aligns more closely with the patient's state *(p)*, demonstrating a more accurate matching of the medication regimen to the patient's condition. Another discernible difference is in the medication efficiency *(eff)*, which dips very low in Figure 6, compared to Figure 7.

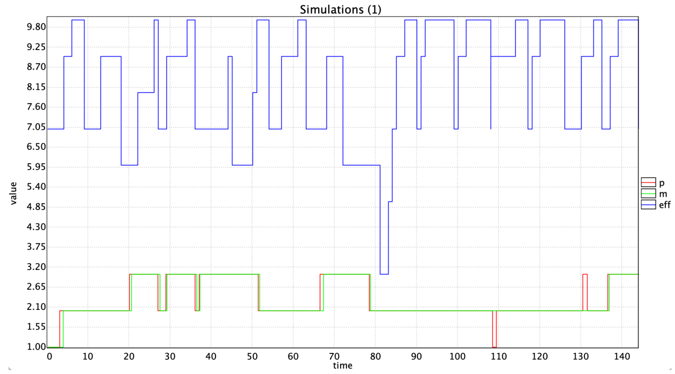

Figure 7: MST_Treatment result

The comparison of these simulations provides insightful findings regarding the dynamic response and effectiveness of these two treatment protocols under conditions of low patient adherence.

In the subsequent set of findings, we conducted simulations for a thousand patients (representing our population) over a time frame of 144 months. Results obtained from the application of the GINA treatment protocol demonstrated the following outcomes: the predicted count of mild flare-ups was 67.178, with a 95% confidence interval of ±2.536; the anticipated number of severe flare-ups was 6.114, with a 95% confidence interval of ±0.193. The estimated cost associated with this protocol was 34151.4, with a 95% confidence interval of ±794.5.

On the other hand, the application of the Medische Spectrum Twente treatment protocol produced different outcomes: the expected count of mild flare-ups was 24.826, with a 95% confidence interval of ±1.812; the predicted number of severe flare-ups was 5.048, with a 95% confidence interval of ±0.166. The estimated cost related to this protocol was 30282.53, with a 95% confidence interval of ±675.2.

Protocol	Mild Flare-ups (95% CI)	Severe Flare-ups (95% CI)	Cost in € (95% CI)
GINA	67 (±3)	6.1 (±0.2)	34000 (±800)
Medische Spectrum Twente	25 (±2)	5.1 (±0.2)	30000 (±700)

Table 1: Comparison of Predicted Outcomes for GINA and Medische Spectrum Twente Treatment Protocols

Our study reveals considerable differences between the two treatment protocols regarding the forecasted number of mild flare-ups and expected costs. Despite this, due to certain assumptions, the projected 80% reduction of severe flare-ups (hospitalizations), as suggested in this paper [5], was not fully corroborated by our findings.

6 FUTURE WORK

The research undertaken in this paper marks an important milestone toward the formal modeling of pediatric asthma and the exploration of its treatment protocols. However, it is only the first step in a much larger journey. The potential of the approach introduced here can be vastly extended to produce more comprehensive and sophisticated models, ultimately contributing to the optimization of pediatric asthma management strategies.

The subsequent phase of research should aim to expand the scope of the model by incorporating additional aspects of asthma treatment and management. This might include, but not be limited to, environmental factors, genetic predispositions, lifestyle variables such as sleep patterns [15], and mental health considerations. This expanded model could offer a more holistic view of asthma management, relax our initial assumptions, and integrate medical treatments with factors related to patients' everyday lives.

In addition, a compelling next step should work towards creating a personalized, patient-centered model. Considering the individual differences among patients in terms of their symptoms, responsiveness to medication, adherence to treatment, and other personal factors could lead to a truly individualized treatment protocol. This would be a major leap towards personalized medicine in pediatric asthma treatment, potentially transforming how we manage this chronic condition.

Alternatively, future work could focus on harnessing machine learning and artificial intelligence to evolve and optimize the model dynamically. By continuously learning from new data, the model could adapt and refine its predictions and recommendations over time, making it a living tool that grows in accuracy and sophistication.

It is important to acknowledge that these suggestions are ambitious. However, the goal is not merely to extend the existing work but to truly advance our understanding and management of pediatric asthma. The pathways outlined here are intended to inspire new research directions that build upon the initial steps taken in this study. Each step taken, however big or small, brings us closer to the ultimate goal of improving the lives of children with asthma.

7 CONCLUSION

The primary objective of this research, as laid out in the introduction, was to advance a proof-of-concept model that allows us to analyze and compare various protocols for pediatric asthma management. We aimed to develop this model as a stepping-stone toward future exploration of asthma management strategies. I am pleased to affirm that we have successfully delivered on this objective.

Our work contributes the first formal model for simulating the outcomes of pediatric asthma treatment protocols. This innovative model, despite being a simplified representation of the complex nature of asthma, has provided us with a unique lens to observe the dynamic interactions between treatment protocols, medication adherence, and patient outcomes.

By applying this model, we made a comparative analysis of two distinctive treatment protocols: the Global Initiative for Asthma (GINA) and the Medische Spectrum Twente. This comparison has not only proven the feasibility and utility of our model but also shed light on the potential differences in the effectiveness and cost-efficiency of these protocols.

This study signifies the importance and potential of computational modeling in chronic disease management. Even though our model focuses on pediatric asthma, the methodology, and framework can inspire researchers in other domains to use formal modeling for exploring disease management strategies.

Looking forward, this initial research points towards a future where treatment plans are increasingly data-driven and personalized. As we refine our models and incorporate more variables, we move closer to an era where treatment protocols can be customized based on individual patient characteristics and responses. Our work lays the foundation for such advancements, promising a brighter future for children with asthma and those tasked with managing this chronic condition.

In addition, as our models become increasingly precise in predicting patient outcomes, how do we balance the mathematical determinism of these advanced tools with the intrinsic unpredictability and subjectivity of human health experiences? The exploration of this question is crucial as we further harness technology for personalized healthcare, and it underpins the ethical dilemmas we must address in future advancements of probabilistic medical models.

7.1 Disclaimer

While this research on pediatric asthma management provides a formal model using the UPPAAL timed automata framework, it is intended strictly for academic discussion and protocol examination. It should not be used to guide medical treatment or clinical decision-making. Although this model was developed with expert advice and is based on established literature, it is primarily a "toy model". Its purpose is to demonstrate the potential of the approach and it is not designed for direct application in medical practice. The model's future usage that might influence protocol decisions would require extensive validation and a comprehensive understanding of its constraints. All assumptions, methodologies, and procedures utilized in the study have been transparently outlined to maintain research integrity and allow for responsible replication or further development by other researchers.

8 ACKNOWLEDGMENTS

This work has benefitted greatly from the guidance and expertise of several individuals.

I am thankful to my supervisor, Dr. Ir. Rom Langerak, for his guidance throughout this research. His feedback and encouragement were invaluable to the progress and quality of this work.

I also extend my thanks to the medical team at Medisch Spectrum Twente. Special thanks to dr. M.R. van der Kamp and drs. P.B. Keijzer, the technical physicians, and dr. B.J. Thio, the pulmonary pediatrician, for their time and the expertise they brought into this research. Their input on asthma treatment procedures and costs greatly improved the accuracy and relevance of this study.

To all, your support has been instrumental in the completion of this research.

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kortademigheid. Hieronder valt ook het gebruik van inhalatiecorticosteroïden. Bij de meeste kinderen gaan de klachten binnen een tot twee jaar over. Ongeveer 5% van de kinderen blijft klachten houden en heeft die nog op 12-jarige leeftijd. Meer jongens dan meisjes hebben astmasymptomen en kinderen van ouders met astma of allergie hebben een sterk verhoogd risico. Kinderen met astmasymptomen hebben vaak ook een allergie, eczeem of neusklachten. Dit blijkt uit het zogenoemde PIAMA-onderzoek, waarin kinderen zijn gevolgd vanaf hun geboorte tot de leeftijd van 12 jaar. PIAMA is een lopend onderzoek dat wordt uitgevoerd door het RIVM, de Universiteit van Utrecht, het UMC Groningen, het Erasmus MC in Rotterdam en Sanquin Research in Amsterdam. Psychisch even gezond. Desondanks zijn kinderen met astmasymptomen psychisch even gezond als kinderen zonder astmasymptomen. Zij zijn ook even tevreden over hun vriendschappen, hun uiterlijk, hun prestaties op school en bij gym en hun vrijetijdsbesteding. Op school presteren zij net zo goed als andere kinderen. Bovendien zijn ze even vaak lid van een sportclub, hoewel 30% van de kinderen met astmasymptomen medicijnen gebruikt bij het sporten. (2011). http://hdl.handle.net/10029/259345.

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