EpiSpec: A Formal Specification Language for Parameterized Agent-Based Models against Epidemiological Ground Truth

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***Abstract*—Building complex computational models of the spread of epidemics is a problem that has seen renewed interest in recent years. Such models are being used for understanding real-time disease evolution prediction and are also proving useful in the prevention, monitoring and control of contagious diseases. There is a pressing need to ensure reliability of epidemiological models since they are widely used in safety-critical applications. In this paper, we present a new spatio-temporal specification language, *EpiSpec*, for describing detailed properties of agent-based computational epidemiological models. We describe the formal syntax of EpiSpec and demonstrate its use by describing various spatio-temporal properties related to disease evolution, and propose the use of statistical model checking as an algorithmic technique for verification and validation of large computational epidemiological models.**

I. Introduction

The construction of detailed computational models for studying the spatio-temporal evolution of epidemics has gained sustained attention over several decades [19]. Models used for analyzing the spread of epidemics have evolved from a small set of ordinary differential equations (ODEs) to massively parallel computational stochastic agent-based models [22].

Epidemiological models have traditionally been used to study the dynamics of the evolution of diseases from a purely scientific point of view, with an emphasis on understanding the qualitative nature of infection dynamics, such as stability, bistability, and oscillation. Only in recent years have computational models been utilized in epidemiology for making real-time predictions to enable effective decision-making for controlling the spread of epidemics (for example, by determining appropriate disease prevention and containment strategies).

This change in focus away from retrospective analysis, mainly for academic purposes, toward online predictive modeling demands that we place a high premium on the correctness of computational epidemiological models. Specifications for epidemiological models usually originate from the following sources: *i*) historical ground truth observations on past epidemics, *ii*) understanding pathogen virulence and infection prognosis, and *iii*) the availability of health data from a variety of sources, including social networks, personal health-care devices, smart homes, health centers and hospitals.

The problem of validation of epidemiological models has usually been treated as a one-time exercise (performed immediately after model construction) with the primary goal of ensuring that models reproduce the behavior of epidemics observed in the past under appropriate circumstances – in other words, reaffirming historical ground truth [14]. In this paper, we suggest that *model validation be treated as a fundamental part of the model development and use process*, and therefore be performed at periodically during these phases. Such continuous validation of epidemiological models against real-time observations will help maintain user trust in analyses performed using these models.

For users to have confidence in the results generated using simulations from a computational epidemiological model, it is necessary for the model to conform to well-established standards (like meeting industry benchmarks) through a rigorous process of verification and validation. In particular, if a model is unable to compute even short-term predictions (that can be independently corroborated), the user's perception of reliability in the model vanishes, effectively rendering it unusable for any safety-critical scenario that involves predictions over the medium or long-term. As an example, Google Flu Trends – a tool developed by Google Inc. to monitor flu activity in 29 countries – overestimated the number of infected people in the United States during the winter of 2013 [4]. Hence, safety-critical applications like epidemiological models need regular validation for users to retain trust in them. We recommend constant verification, validation and re-calibration of computational epidemiological models using the algorithmic framework of Bayesian statistical model checking [12] to ensure model reliability. Here, we take a first step toward achieving this

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goal by designing a *formal specification language* that can be used to describe agent-based epidemiological models.

II. Related Work

The verification and validation of epidemiological models has recently been a subject of active interest [23]. The literature on model validation contains numerous studies describing graphical and statistical methods to compare computational simulation results and experimental data. These include evaluation metrics like the Akaike's Information Criterion (AIC) and the Bayesian Information Criterion (BIC), that compute the degree of fit of a model with respect to a given set of observations, and weigh it against the model's complexity [1]. These techniques have been used to fit epidemiological models to observed data [17].

Visualization tools [10] that allow two and three-dimensional views of model behavior enable users to select a desired set of properties while synthesizing models that can produce these varying behaviors [3]. As noted earlier, it is essential in terms of reliability and user-confidence, that such models go through a process of formal verification. We feel that there is a significant knowledge gap in the area of validating computational epidemiological models. A fundamental problem is to identify, characterize, and quantify failure conditions of a model to help minimize the social and economic costs should a model fail to provide accurate predictions.

In this paper, we define *EpiSpec*, a new formal specification language for representing correctness specifications of epidemiological model behaviors and suggest the use of Bayesian statistical model checking to validate stochastic parameterized computational epidemiological models against spatio-temporal specifications written in EpiSpec.

III. Background

A. Epidemiological Agent-Based Models

Deterministic epidemiological models often fail to effectively explain the spatio-temporal relationships and the interaction between individuals (in their neighborhoods), and the effect of human behavioral response on the disease spread process. The need for an understanding of the *local dynamics* of the disease, tracking the movement of relevant individuals and evaluating the plausible control strategies under different conditions has led to the development of agent-based models [2]. ABMs allow individuals of a population to be represented as by first-class objects (the *agents*). A set of simple interaction rules for the agents and the environment give rise to a complex emergent behavior. ABMs have been extensively used for studying a variety of infectious diseases, including influenza and measles. With the availability of a variety of ABMs for describing the dynamics of an epidemic, identifying a model that best describes the outcome of the epidemic becomes essential.

B. Validation of epidemiological models

Model checking is a popular technique for the verification and validation of models arising in numerous applications including software, hardware and computational systems biology [5]. Given a model expressed as a transition system and its behavioral specification represented in a temporal logic, model checking algorithms explore the entire state-space of the model and check if it meets the specification. If a scenario exists where the model does not satisfy the specification, it also provides a *counterexample* – a trace showing how a specification can be violated [5].

The application of model checking techniques (including symbolic approaches based on binary decision diagrams and satisfiability solving) to epidemiological modeling has had limited success due to the state-space explosion problem. Since a model with n Booolean variables can have as many as 2^n states, a typical epidemiological model with 100 32-bit integer variables has as many as 2^{500} states! To enable the validation of such large *probabilistic* models, Bayesian statistical model checking algorithms can prove useful [12].

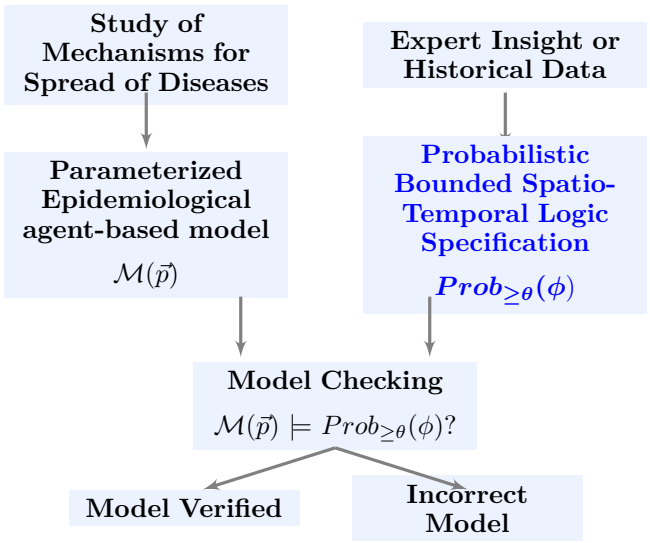

Fig. 1: Formal verification of stochastic epidemiological models requires designing specifications languages that can describe desired behavioral properties of the model.

Bayesian Statistical Model Checking: Given a stochastic model $\mathcal{M}$, a formal specification ϕ, and a confidence threshold θ, the *probabilistic model checking problem* is to determine if $\mathcal{M}$ satisfies ϕ with probability at least θ (denoted $\mathcal{M} \models Prob_{\geq\theta}\ \phi$). Numerical methods for probabilistic model checking [18] compute the probability of a stochastic model satisfying a specification (usually with high-accuracy) and compare this numerical estimate with the desired threshold. These methods are memory intensive and fail to scale to systems with large state spaces (more than 100 integer-valued variables). Hence, symbolic model checking algorithms have not been successful in validating large computational epidemiological models [23].

Statistical model checking (SMC) methods [9] generate independent and identically distributed (iid) samples from the stochastic model and use runtime monitoring to determine whether each sample trajectory satisfies the given specification [24]. SMC algorithms use the results of the monitoring algorithms to determine the answer to the

probabilistic model checking problem. Further, they can be divided into methods that require a *fixed sample size* [9] and those that do not (and are known as *adaptive*) [29]. Adaptive algorithms use the result of the monitoring algorithm on the sampled trace to determine whether or not the model meets the specification with the required confidence or if more samples are required to establish either fact with the necessary certainty. Such adaptive statistical model checking algorithms operate iteratively to provide a *statistical approximation* to the probabilistic model checking problem. They are often used in computational systems biology since they scale better than exact estimation-based probabilistic model checking methods [12].

Deployment of statistical model checking techniques in computational epidemiology requires significant advances in two areas: *a*) the development of fast algorithms to analyze large models and, *b*) the design of specification languages capable of capturing detailed behavioral properties of computational models in epidemiology.

The first problem has gained attention recently in the model checking community. One approach to statistical model checking uses Wald's Sequential Probability Ratio Test (SPRT) [28] to decide between two simple hypotheses: does $\mathcal{M}$ satisfy specification ϕ with probability $\theta - \delta$ or with probability $\theta + \delta$? Here, $2 * \delta$ $(0 < 2 * \delta < 1)$ is user-specified and is known as the indifference region [29]. Our Bayesian statistical model checking algorithm takes a adapted finitely monitorable specification and uses the sequential version of the Bayes Factor test to decide between two composite hypotheses, hence not requiring any indifference region [12].

The Bayes Factor describes the confidence of the observations in one hypothesis as opposed to the other. Given samples $x_1, x_2, \ldots x_n$ generated from the model $\mathcal{M}$, where u is the unknown probability of $\mathcal{M}$ satisfying ϕ (so that we have $H_0 : \mathcal{M} \models Prob_{\geq\theta}\phi$ and $H_1 : \mathcal{M} \models Prob_{<\theta}\phi$) and $g(.)$ the Bayesian prior representing existing information about the system, the Bayes Factor is given by the following expression: $B_n = \frac{\int_\theta^1 f(x_1|u)\ldots f(x_n|u)g(u)du}{\int_0^\theta f(x_1|u)\ldots f(x_n|u)g(u)du}$. At any point during the statistical model checking process, if the Bayes Factor exceeds a threshold T (>1), the algorithm accepts the null hypothesis H_0. Similarly, if the Bayes Factor falls below the threshold $1/T$, the alternate hypothesis H_1 is accepted. Thus, the Bayesian statistical model checking algorithm is a scalable model checking approach for verifying epidemiological models against specifications with any desired degree of confidence [15]. We have formally proven results on the termination and accuracy of the Bayesian statistical model checking algorithm [12], [15].

The second problem, which is the focus of this paper, requires *designing languages for specifying properties in epidemiological models*. The aim is to design languages that have sufficient expressive power to allow users to express important properties about the dynamics of epidemics and also have a well defined syntax and formal semantics that facilitates the development of compilers and analyzers for the language. It is also beneficial to have a language that facilitates formal reasoning, so that software verification and formal methods tools can be used to validate programs written in the language.

C. Time model for epidemiological model specification

Another dimension in the choice of a specification framework is to select an appropriate model of time [6]. We use the *linear time model* where the flow of time is defined by a structure $(T, <)$ such that: *a*) the elements of T are referred to as *time points*, *b*) $<$ is a binary relation on T that is transitive and irreflexive, and *c*) if $s, t \in T$ and $s < t$, then s is said to be *earlier* than t.

It should be noted that flows of time are partial orders, and naturally define the future of t by the set $\{s \in T \mid t < s\}$. Similarly, the past of a time point t is defined by $\{s \in T \mid s < t\}$. The flow of time T can be discrete or dense; dense flows of time may be continuous or include points of discontinuity. The EpiSpec specification language has homogeneous, continuous, and dense flow of time that is isomorphic to the real numbers.

D. Framework for expressing spatio-temporal properties

As the EpiSpec specification language will be used to reason about events in three-dimensional space, it is essential to make a choice about the formal model of space and time employed in our specification framework. We propose the use of four-dimensional Minkowski spacetime models [21] to capture detailed physical properties of evolving epidemiological behavior.

The n-dimensional Minkowski spacetime T^n is the tuple $(R^n, \preccurlyeq, A, v)$, where: *i*) spacetime points $(x_1, \ldots x_n)$ are elements of R^n, *ii*) given $\boldsymbol{x} = (x_1, \ldots x_n)$ and $\boldsymbol{y} = (y_1, \ldots y_n)$, $\boldsymbol{x} \preccurlyeq \boldsymbol{y}$ if and only if $x_n \leq y_n$ and $\sum_{i=1}^{n-1}(x_i - y_i)^2 \leq C(x_n - y_n)^2$, where C is a constant, *iii*) A is a countable set of atomic propositions, and *iv*) spatio-temporal valuation map v from A to R^n such that $p \in A$ holds at $x \in R^n$ if and only if $x \in v(p)$. For epidemiological models, the Minkowski spacetime framework is appropriate because it enables the description of evolving space and time patterns of susceptible, infected, and recovered individuals. It is also capable of expressing fine-grained and nuanced distributions of populations such as those classified by gender, age, color or race.

The Minkowski spacetime framework also creates a bound on the speed with which information can pass from one point to another in a physical system, and serves as a realistic framework for describing human contact during the spread of epidemics. In particular, $\boldsymbol{x} \preccurlyeq \boldsymbol{y}$ holds if and only if the temporal component of x is smaller than the temporal component of y and the spatial distance between these two spacetime points is small enough for information reach from one point to the other without having to travel beyond the speed of light.

IV. The EpiSpec specification language

As a first step toward fully automated verification and validation of computational epidemiological models, we discuss our specification language (EpiSpec) that is

capable of expressing properties in such models, and give illustrative examples to demonstrate its expressiveness.

The epidemiological specification language EpiSpec will be defined on the probabilistic spatio-temporal structure $\boldsymbol{E} = (\boldsymbol{S^3}, \boldsymbol{T}, \preccurlyeq, \boldsymbol{A}, \boldsymbol{v}, \boldsymbol{P})$, where

- $\boldsymbol{S}^3$ denotes the three-dimensional space that represents the geographical location of the epidemiological agents.
- $\boldsymbol{T}$ denotes the homogeneous, dense, and continuous linear flow of time.
- Given $\boldsymbol{x} = (x_1, x_2, x_3) \in \boldsymbol{S}^3$, $\boldsymbol{y} = (y_1, y_2, y_3) \in \boldsymbol{S}^3$, and $t_1, t_2 \in \boldsymbol{T}$, $\boldsymbol{x} \preccurlyeq \boldsymbol{y}$ if and only if $t_1 \leq t_2$ and $(x_1 - y_1)^2 + (x_2 - y_2)^2 + (x_3 - y_3)^2 \leq C_s(t_1 - t_2)^2$. Here, C_s is a constant indicating the square of the speed with which the fastest moving agent or infection can move in an epidemiological model.
- $\boldsymbol{A}$ is a countable set of atomic propositions, representing properties over different types of subpopulations describing, for example, the number and types of susceptible, infected, recovered individuals.
- $\boldsymbol{v}$ denotes the spatio-temporal map from the finite set of attributes $\boldsymbol{A}$ to $\boldsymbol{S}^3 \times \boldsymbol{T}$ such that $p \in \boldsymbol{A}$ holds at the spatial co-ordinates $(x, y, z) \in \boldsymbol{S}^3$ at time $t \in \boldsymbol{T}$ if and only if $(x, y, z, t) \in v(p)$.
- $\boldsymbol{P}$ denotes the probability space (Ω, F, P) where Ω is the set of all possible outcomes, F is the set of events (that represents groups of outcomes), and P is the assignment of probabilities to events, and is implicitly determined by the computational epidemiological model in our setting.

The probabilistic spatio-temporal structure $\boldsymbol{E}$ combines the notion of linear time and the idea of a Minkowski space-time into a unified probabilistic framework. Any trajectory of a computational epidemiological model can be stated in terms of the elements of this probabilistic spatio-temporal structure. We now define the EpiSpec specification language.

A. Syntax of the EpiSpec Language

EpiSpec is built from atomic propositions and expressions over real-valued variables. We first define EpiSpec expressions, that can be used to compute various quantities of interest in an epidemiological computational model, including the ratio of values of infected to susceptible individuals at a given location at different points of time, the number of new infections at a given location in a given period of time, the rate at which an infection is spreading at a given location, and the time at which the infection reaches a local extremum value at a given location.

Definition 1 (EpiSpec expressions)**.** *Given spatial co-ordinates $(x, y, z) \in \boldsymbol{S}^3$ over time $t \in \boldsymbol{T}$ and real-valued functions $r(x, y, z, t)$ EpiSpec expressions are given by:*

$$
\begin{aligned}
\langle esexpr \rangle \ ::= \ & r(x, y, z, t) \\
\mid \ & \langle esexpr \rangle + \langle esexpr \rangle \mid \langle esexpr \rangle - \langle esexpr \rangle \\
\mid \ & \langle esexpr \rangle \times \langle esexpr \rangle \mid \langle esexpr \rangle \div \langle esexpr \rangle \\
\mid \ & \sin(x, y, z, t) \mid \cos(x, y, z, t) \\
\mid \ & \arcsin(x, y, z, t) \mid \arccos(x, y, z, t) \\
\mid \ & \tfrac{d\langle esexpr \rangle}{dt} \mid \tfrac{d\langle esexpr \rangle}{dx} \\
\mid \ & \tfrac{d\langle esexpr \rangle}{dy} \mid \tfrac{d\langle esexpr \rangle}{dz} \\
\mid \ & \log(\langle esexpr \rangle) \mid \exp(\langle esexpr \rangle) \\
\mid \ & \langle esexpr \rangle^{\langle esexpr \rangle} \\
\mid \ & \textstyle\int_{t_1}^{t_2} \langle esexpr \rangle dt \mid \int_{x_1}^{x_2} \langle esexpr \rangle dx \\
\mid \ & \textstyle\int_{y_1}^{y_2} \langle esexpr \rangle dy \mid \int_{z_1}^{z_2} \langle esexpr \rangle dz \ \square
\end{aligned}
$$

Given EpiSpec expressions, we define EpiSpec formulas using classical first-order logic augmented with bounded temporal logic and spatial operators, that allow the specification of spatio-temporal properties.

Definition 2 (EpiSpec formulas)**.** *An EpiSpec formula is given by:*

$$
\begin{aligned}
\langle esformula \rangle \ ::= \ & p^{1} \\
\mid \ & \langle esexpr \rangle \leq \langle esexpr \rangle \\
\mid \ & \langle esexpr \rangle \geq \langle esexpr \rangle \\
\mid \ & \langle esformula \rangle \wedge \langle esformula \rangle \\
\mid \ & \langle esformula \rangle \vee \langle esformula \rangle \\
\mid \ & \langle esformula \rangle \implies \langle esformula \rangle \\
\mid \ & \neg \langle esformula \rangle \\
\mid \ & F^{[t_1, t_2]} \langle esformula \rangle^{2} \\
\mid \ & G^{[t_1, t_2]} \langle esformula \rangle^{3} \\
\mid \ & P^{[t_1, t_2]} \langle esformula \rangle^{4} \\
\mid \ & H^{[t_1, t_2]} \langle esformula \rangle^{5} \\
\mid \ & \langle esformula \rangle \ U^{[t_1, t_2]} \ \langle esformula \rangle^{6} \\
\mid \ & E^{[r]} \langle esformula \rangle^{7} \\
\mid \ & S^{[r]} \langle esformula \rangle^{8} \\
\mid \ & \exists w \ \langle esformula \rangle^{9} \\
\mid \ & \forall w \ \langle esformula \rangle^{10} \ \square
\end{aligned}
$$

EpiSpec formulas can be used to capture complex spatial information about epidemiological models, including the rate at which infections spread across geographical regions. They can also help identify natural spatial barriers to the spread of the diseases, and generate statistical data about an epidemic in a given area of interest. By combining space and time, these expressions can capture involved descriptions of the behavior of the model such as the rate of spread of the disease in a given area, the contribution of specific locations in creating new infections in a region, and the local extrema of the infection at a particular location.

In order to express properties of stochastic agent-based models in epidemiology, we allow the specification of properties that are true with a desired level of confidence.

[1] $p \in \boldsymbol{A}$.

[2] The bounded temporal logic formula $F^{[t_1, t_2]}\phi$ that indicates that ϕ is true some time between the next t_1 and t_2 time units.

[3] The bounded temporal logic formula $G^{[t_1, t_2]}\phi$ that indicates that ϕ is always true between the next t_1 and t_2 time units.

[4] The bounded temporal logic formula $P^{[t_1, t_2]}\phi$ indicates that the ϕ was true some time between the previous t_1 and t_2 time units.

[5] The bounded temporal logic formula $H^{[t_1, t_2]}$ indicates that ϕ was always true between the previous t_1 and t_2 time units.

[6] The bounded temporal logic formula $\phi_1 U^{[t_1, t_2]} \phi_2$ indicates that ϕ_2 is true sometime within the next t_1 to t_2 time units, and ϕ_1 holds until ϕ_2 becomes true.

[7] The spatial logic formula $E^{[r]}\phi$ indicates that ϕ is true everywhere in a neighborhood of radius r around the current point.

[8] The spatial formula $S^{[r]}\phi$ indicates that ϕ is true somewhere in a neighborhood of radius r around the current point.

[9] Here w occurs free in the formula.

[10] Here w occurs free in the formula.

Definition 3 (Probabilistic EpiSpec formulas)**.** *Given an EpiSpec formula* $\langle\phi\rangle$ *and a confidence level* $\theta \in [0,1]$*, a* probabilistic *EpiSpec formula is given by:*

$\langle esprobspec\rangle ::= Prob_{\geq\theta}(\phi)\ \square$

B. Illustrative Specifications

We demonstrate the expressive power of the EpiSpec specification language in describing complex correctness specifications in computational epidemiological models using three examples:

Disease progression: There is an 80% chance that if the number of infected people (I) reaches a critical mass (C), then within 3 weeks, the number of infected people will exceed 90% of the total population (N). $Pr_{\geq 0.8}(N > C) \rightarrow F^{[0,3w]}(N \geq 0.9 * T)$.

Minimal steady-state infections: The likelihood that always within radius r of the current location, the number of infected people (I) would exceed 1 percent of the total population (N), is at least 70%. $Pr_{\geq 0.7} G^{[0,\infty]} S^{[r]}(N \geq 0.01 * T)$.

Clustering in disease-prone areas: With a 50% probability, at this spatial location, if the number infected people (I), exceeds a threshold L, but are less than another threshold H, then always within the next two months, within a radius of 55 distance units there will be some location where the number of infected people exceed 10% of the total number of infections. $Pr_{\geq 0.5}(L < I < H) \rightarrow G^{[0,2m]} S^{[55]}(I > 0.1 * N)$

V. Applications of EpiSpec in model validation

The process of validation and verification (V&V) is an essential part of predictive modeling in epidemiology. We suggest the use of EpiSpec for writing epidemiological properties that researchers want to investigate. With the availability of high-performance computing (HPC) architecture and fast model checking algorithms and tools implementing them, epidemiological models can be analyzed in real-time to respond to emergencies like finding containment strategies for pandemics. We now describe two focus areas where EpiSpec should be used.

A. Model calibration against behavioral specifications

The problem of model calibration and variable selection in epidemiological analysis continues to attract the attention of researchers [8]. We have extensively studied the problem of finding parameters in stochastic computational models, so as to calibrate them in order to meet desired behavioral specifications [11]. The EpiSpec language can be used to write desired epidemiological properties that the modeler is interested in, and then use algorithms and tools for automated model discovery against behavioral specifications to calibrate the model appropriately.

B. Discovering rare behaviors

The mathematical problem of finding large deviations [27] has extensive applications in the field of epidemiology. For example, in the Summer of 2014, several cases of people infected by the Middle East Respiratory Syndrome (MERS) corona-virus, that had been hitherto confined mainly to certain countries in Western Asia, were found in the United States and raised serious concerns among heath-care providers and the wider community [20].

We have earlier used two approaches to address the problem finding rare behaviors in stochastic computational models: *a*) using decision procedures [7] and *b*) by employing change of measures arguments [13], to search for and expose the conditions under which these behaviors can occur in the model. These techniques can be combined to produce powerful algorithmic tools that can find such pathologically rare (but critical in terms of health-care) behaviors in epidemiological models and can potentially have a vital impact in providing early warning about the possibility of serious epidemics. Again, EpiSpec can be used to write the specifications describing the rare behaviors that we are interested in detecting.

Formal verification for analyzing epidemiological models

Note that our techniques for solving both the model calibration and rare behavior discovery problem involve statistical model checking [12] and the use of powerful constraint solvers [16]. We translate any given set of behavioral specifications written in EpiSpec into a form that can be checked during model simulation using *monitoring algorithms* [26]. These formal methods based techniques, combined with our work on algorithms to handle extreme-scale data [25] can be used to create powerful tools to solve the aforementioned problems.

VI. Conclusion

In this paper, we described a new probabilistic spatio-temporal logic that combines the notion of linear time with Minkowski space-time in a probabilistic framework. We showed that the language is capable of expressing complex correctness specifications for computational epidemiological models.

Several opportunities for future work remain open. First, one needs to investigate runtime monitoring algorithms for verifying the EpiSpec specification language against traces obtained from computational models. The nature of the Minkowski space-time framework naturally suggests opportunities for distributed verification of large models on multiple nodes.

We also plan to investigate the algorithmic discovery of such specifications from complex unstructured big data sets, and the communication of these specifications to the end-user using a suitably flavored language that employs the ontology of epidemiological modeling.

Finally, the use of first-order logic in EpiSpec requires an investigation into new statistical model checking algorithms that can reason about non-propositional probabilistic specifications. We believe that Bayesian model

checking provides a very natural framework for such an investigation.

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