Comparison of Timed Automata with Discrete Event Simulation for Modeling of Biomarker-Based Treatment Decisions: An Illustration for Metastatic Castration-Resistant Prostate Cancer

Koen Degeling, MSc[1],*, Stefano Schivo, PhD[2], Niven Mehra, MD, PhD[3], Hendrik Koffijberg, PhD[1], Rom Langerak, PhD[2], Johann S. de Bono, MD, PhD[4], Maarten J. IJzerman, PhD[1]

[1]Health Technology and Services Research Department, MIRA Institute for Biomedical Technology and Technical Medicine, University of Twente, Enschede, The Netherlands; [2]Formal Methods and Tools Group, Faculty of Electrical Engineering, Mathematics and Computer Science, University of Twente, Enschede, The Netherlands; [3]Clinical Studies Department, The Institute of Cancer Research, London, UK; [4]Prostate Cancer Unit, The Institute of Cancer Research, London, UK

A B S T R A C T

Background: With the advent of personalized medicine, the field of health economic modeling is being challenged and the use of patient-level dynamic modeling techniques might be required. **Objectives:** To illustrate the usability of two such techniques, timed automata (TA) and discrete event simulation (DES), for modeling personalized treatment decisions. **Methods:** An early health technology assessment on the use of circulating tumor cells, compared with prostate-specific antigen and bone scintigraphy, to inform treatment decisions in metastatic castration-resistant prostate cancer was performed. Both modeling techniques were assessed quantitatively, in terms of intermediate outcomes (e.g., overtreatment) and health economic outcomes (e.g., net monetary benefit). Qualitatively, among others, model structure, agent interactions, data management (i.e., importing and exporting data), and model transparency were assessed. **Results:** Both models yielded realistic and similar intermediate and health economic outcomes. Overtreatment was reduced by 6.99 and 7.02 weeks by applying circulating tumor cell as a response marker at a net monetary benefit of −€1033 and −€1104 for the TA model and the DES model, respectively. Software-specific differences were observed regarding data management features and the support for statistical distributions, which were considered better for the DES software. Regarding method-specific differences, interactions were modeled more straightforward using TA, benefiting from its compositional model structure. **Conclusions:** Both techniques prove suitable for modeling personalized treatment decisions, although DES would be preferred given the current software-specific limitations of TA. When these limitations are resolved, TA would be an interesting modeling alternative if interactions are key or its compositional structure is useful to manage multi-agent complex problems.

Keywords: advanced modeling methods, discrete event simulation, health economic modeling, personalized treatment decisions, timed automata.

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Introduction

There is a long history of modeling in health economics, and its use has had a major impact on resource allocation decisions in various jurisdictions [1,2]. Nevertheless, in the era of personalized or precision medicine (PM), new challenges to the field of health economic modeling (HEM) arise [3]. In particular, modeling of personalized treatment pathways, the use of companion diagnostics, and the likely switches in drug prescriptions are challenging [4,5]. As a consequence, there is a need for models to take into account dynamic behavior and anticipate for patients' and physicians' preferences [6]. This leads to the observation that the most commonly used modeling strategy, that is, (cohort) health state transition modeling [7], with limited flexibility, may not be

optimal for handling such complexity [4,8,9], and there is a need for more advanced modeling technologies [10].

One very specific concern in biomarker-guided treatment decisions is the lack of clinical evidence about the utility of diagnostic testing such as genome sequencing and/or the relative effectiveness of sequences of drug treatment [11]. Such issues particularly arise in clinical conditions in which therapy switches are frequent and when such switches are to be informed by precise information about somatic mutations and molecular expressions. One such condition is metastatic castration-resistant prostate cancer (mCRPC), which is the stage in prostate cancer at which metastases are present and medical or surgical castration no longer controls progression of the disease [12]. A recommended treatment strategy from the European Society for

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Medical Oncology suggests first-line chemotherapy with docetaxel, followed by second-line chemotherapy with cabazitaxel [13,14], although a number of other second- or third-line treatments exist, such as abiraterone, enzalutamide, radium-223, and sipuleucel-T [13,14], which are now increasingly being used before chemotherapy. Because of low treatment response rates [15,16], early recognition of response allows switching from ineffective to possibly effective treatment, which could prevent overtreatment with ineffective and expensive drugs, also reducing treatment-induced morbidity, which may all potentially reduce the health burden associated with overtreatment [17].

Although current decisions to switch treatment are largely based on clinical evaluation, bone scans (BSs), CT scans, and prostate-specific antigen (PSA) tests [18], recent studies indicate that more specific information based on liquid biopsies, for example, circulating tumor cells (CTCs), may be valuable in evaluating treatment response in CRPC [19,20]. A decline in CTCs after treatment has superior performance to PSA, and a composite biomarker panel comprising CTCs is an effective surrogate end point for overall survival [21,22]. The use of this novel molecular information, however, poses a challenge for both physicians and modelers, because currently there are no guidelines for molecular biomarkers and the actual clinical decisions are increasingly based on a combination of imaging biomarkers and laboratory assessments. In addition, both the chance of therapy switches and the transition to other health states are time-dependent and largely determined by physician interpretation and patient characteristics.

To assess whether advanced modeling technologies indeed empower modelers to address these challenges, we used two advanced modeling techniques, discrete event simulation (DES) and timed automata (TA), for modeling the personalized treatment process of mCRPC.

The TA modeling paradigm has been developed originally in computer science for modeling distributed systems, such as networks of computers [23]. A typical TA model consists of several automata, which can model agents (e.g., patients or physicians) or other process components (e.g., tests or guidelines). Distinctive of these models is the automata's potential to communicate and interrupt each other, for example, a patient and physician taking a joint decision, while being capable of acting independently. Each automaton can transition between states if prespecified conditions are met (e.g., a treatment ends) or by incentives from other automata (e.g., according to the guideline, a patient should be tested on disease status). The compositional structure of TA has contributed to successful applications of modeling and analyzing complex systems and multi-agent models [24], although to our knowledge, TA has not yet been used for the health economic evaluation of health care interventions. In addition to TA's patient-level discrete handling of time and state transition structure, which naturally represents clinical pathways, its compositional structure and straightforward modeling of interactions are expected to be particularly useful for modeling patient-level and preference-sensitive decisions, such as those present in the dynamic treatment process of mCRPC.

TA's compositional structure and straightforward representation of interactions distinguish it from DES models, which are generally structured around one system or process. In DES the behavior of a system (e.g., clinical pathway) is translated into an ordered sequence of well-defined events [25]. These events correspond to specific changes in the system's state at a specific point in time (e.g., when a test is performed). DES is known from operations research and has been applied in various industries, including health care [26,27], showing to be well suited for modeling clinical processes, including their resources, constraints, and interactions, while making efficient use of computer

resources. Although DES is not new to the field of HEM, its value might increase now that models need to take into account the preference-sensitive, patient-level, interactive, and dynamic clinical processes associated with PM [4,5,28]. Particularly its ability to represent dynamic processes and include patient-level histories makes DES suitable for modeling dynamic application of biomarkers, such as the use of CTCs for response monitoring in mCRPC treatment.

The objective of this study was to illustrate the utility of TA and DES for modeling personalized treatment decisions. Both modeling paradigms were assessed qualitatively, on the basis of the population of both models in terms of complexity and data requirements, and quantitatively regarding the simulated intermediate and health economic outcomes. The specific case study on mCRPC treatment was chosen to achieve the aforementioned objective because early response prediction is an unmet clinical need and because incorporation of novel promising biomarkers, such as CTCs, to guide decision processes at the patient level must be evaluated in HEM.

Methods

Case Study

Current guidelines for monitoring treatment response in patients with mCRPC who only have bone metastases involve a combination of PSA and BSs [13,29,30]. Although approved for monitoring disease progression by the US Food and Drug Administration in 1986 [31], the most recent opinion is that PSA alone is not a reliable biomarker of treatment effectiveness [22,32]. Therefore, clinical decisions to switch treatment are commonly made on grounds of PSA, BSs, and clinical progression, although there is a high likelihood of overtreatment or treatment with ineffective drugs.

Liquid biopsies, such as CTCs, have the potential to be used as alternative response markers. CTCs can be detected from blood and have been shown to be prognostic for survival in different tumors [33–35]. CTCs are expected to be useful as a response marker, allowing early detection of drug response or to enable earlier treatment switching from an ineffective treatment, compared with current practice [19,36]. Although the ability of CTCs to associate with survival has been illustrated [19,21,22,37] and CTCs have been approved by the Food and Drug Administration for disease monitoring in advanced disease [38], a clinical trial to evaluate the utility of CTCs as a response marker in mCRPC is yet to be conducted. In advance of the CTC-STOP trial [39], which has recently started and should fill this evidence gap, an early simulation study, that is, in a context in which evidence is limited, was performed to provide an estimate of the potential health economic impact of applying CTCs as a response biomarker in mCRPC treatment.

DES Model

A DES model was developed using AnyLogic multimethod simulation software (AnyLogic, St. Petersburg, Russia) [40]. The model was structured by the four mCRPC process states as shown in Figure 1A, that is, first-line treatment with docetaxel, postdocetaxel follow-up, second-line treatment with cabazitaxel, and postcabazitaxel follow-up.

Simulated patients' characteristics (e.g., treatment response based on the treatment effectiveness) were assigned at model start-up. Test results were generated on the basis of the patient's response to current treatment and the diagnostic performance of the applicable test. These results were recorded to inform future treatment decisions. The moment at which tests were performed and treatment decisions (i.e., whether to continue or stop current treatment on the basis of progression of the disease) were made