Modeling and simulation the Zika Outbreak under Deep Uncertainty: A Multi-Method Multi-Resolution Approach

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7 January 2015

Abstract: Increased incidences of microcephaly and Guillain-Barré syndrome in areas in the Americas that are hit by the ongoing recent Zika outbreak has alarmed the global community. Health authorities worldwide are urged to take effective action to prevent further spreading, while only having sparse and uncertain information on the problem and the effects of potential solutions. SD is a powerful tool in providing fast yet insightful analysis on pressing problems, however some key aspects of these problems cannot be addressed by this method alone. The objective of our modeling and simulation framework is to provide decision-makers with insights on the prevalence of Zika at different levels of aggregation. Supported by a geographic information system, our approach enables one to look into the evolution of the outbreak from a global, country-level, as well as a province-level perspective. For each province we developed an entity-based model object that allows to switch during runtime between modeling methods. Once the number of interacting individuals has passed a specified threshold, the model object switches from agent-based modeling to System Dynamics. This approach allows to reduce computational requirements dramatically without conceding on disaggregated details where this is of explicit interest, as it is in the beginning of local transmission in another region.

Word count: 3658

1   Introduction: A computational model for the ongoing Zika outbreak

Zika virus infections are a vector borne viral disease transmitted by the *Aedes aegypti* mosquito. It is closely related to dengue and chikungunya. While Zika is usually not life threatening to healthy individuals, this disease is suspected to cause microcephaly as well as Guillain-Barré syndrome. The potential link of Zika to these two severe neurologic conditions has alarmed the global community. In February 2016, the World Health Organization declared the cluster of cases potentially associated with the Zika outbreak in the Americas a public health emergency (PAHO/WHO, 2016). This shows that it is critical to study the potential impacts of the epidemic and implement policies to contain further spreading.

Since the Zika vector is present in tropical and subtropical region across the world, the ongoing outbreak in America has the potential to become a pandemic (Fauci and Morens, 2016; Lucey and Gostin, 2016). This concern seems to be legitimate, Brazil reported the first ever cases of Zika virus infections in May 2015. In the meantime, the disease has spread to at least 23 south and middle American countries. Furthermore, active transmission has also been reported in some parts of Africa, Southeast Asia, and the Pacific Islands. Figure 1 illustrates based on recent confirmed Zika cases the spread of the virus.

Figure 1: Map of Zika cases in the past two-months retrieved from (CDC 2016c)
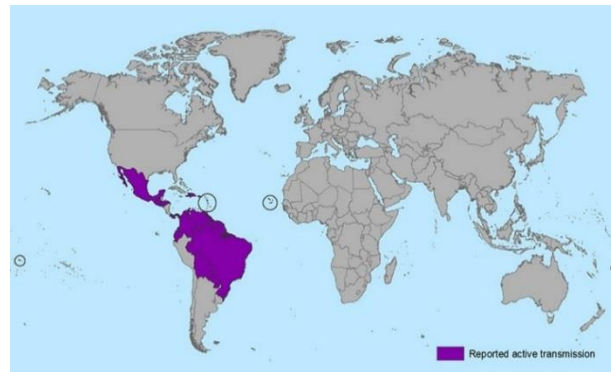
The Zika outbreak in Brazil may contain an especially explosive nature, due to the upcoming Olympic Games that will be hosted in Brazil from 5-21 August 2016. Visitors may bring ZIKV from Brazil to the rest of the world.

Worldwide, health authorities have been urged to take effective action to prevent the spread of this disease, while only having sparse and uncertain information on the problem and the consequences of potential solutions. Currently, there is no cure nor vaccine (ECDC, 2016). Developing a vaccination for ZIKV is expected to take at least 3 to 10 years (Lucey and Gostin, 2016)[1]. Thus alternative policies and their effectiveness are discussed. They can be categorized in vector control, risk communication & personal protection, upgraded Zika surveillance, and travel advise/restrictions.

Modeling and simulation methods can be used to assess the potential (speed of) spreading as well as to test measures. Useful modeling and simulation approaches for doing so include System Dynamics Modeling (SD) and Agent-Based Modeling (ABM). While SD enables a fast yet insightful study of pressing problems, such as the Zika outbreak in the Americas, some key aspects of these problems cannot be addressed by this method alone. For instance, SD does not necessarily support the study of geographically explicit components of a problem. In order to do so, data-interfaced methods need to be developed both on the input side (e.g., pulling in geo-spatially specific data from geographic information systems) and the output side (e.g., plotting geo-spatial outputs on maps). Moreover, the highly aggregated unit of analysis of SD modeling and simulation complicates the study of the initial transition of the disease. It may be better to represent the initial stage as a highly disaggregated process with probabilistic events occurring within networks of individual agents, each of whom can have significant effects on the system. Therefore, it could be argued that the nature of ABM would be better suited to capture the initial stage of an outbreak. The rationale behind this is supported by the fact that initial local transmissions are unfortunate successions of discrete events which in turn depend on combinations of unfortunate factors that need to be present for an outbreak to occur. In other words, whether it comes to local transmission in many regions around the world is a probabilistic chain of events which is hard to study using SD in isolation.

However, after the initial stage, individual agents cannot prevent a further outbreak from happening. From then on, SD enables one to more efficiently simulate the further outbreak of the disease in a particular region. Consequently, modeling and simulation studies of epidemiological processes may

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[1] More detailed background information about the ongoing ZIKV outbreak and available policy options can be found in Fauci and Morens (2016), Lucey and Gostin (2016), Schuler-Faccini et al. (2016), and Ventura et al. (2016).

benefit from the integration of SD with other methods, namely, ABM and geographic information systems (GIS).

In this article, we present a hybrid modeling and simulation approach which integrates SD, ABM, and GIS to study epidemic transmission on multiple levels of aggregation. We demonstrate the approach for the current Zika outbreak. The objective of our modeling and simulation framework is to provide decision-makers with insights on the spread of a given infectious disease at different levels of aggregation. This approach enables one to look into the evolution of the outbreak from a global perspective, from a country-level perspective, as well as from a province-level. By combining the advantages of SD and ABM (more precisely the disaggregation, stochasticity, network structures and machine learning capabilities), our approach allows for building a spatially explicit set of images of plausible futures and testing policies across these plausible futures.

While working on this project, we discovered similar research by Bobashev et al. (2007), which confirms the relevance and feasibility of our approach. While the work of Bobashev et al. (2007) was ground-breaking in the development of modeling and simulation tools for the study of epidemiological processes, it seems there has not been much follow-up research. Our research could, in the light of their work, be seen as a further expansion and extension of their studies.

The remainder of this article is structured as follows. First, in section 2, we present our hybrid approach that combines SD with the complementary methods ABM and GIS. In section 3, we describe the implementation on a simplified model. In section 4, we depict preliminary findings of this ongoing research and the potential applications of the framework. Finally, in section 5, we conclude by summarizing case-specific and framework-specific findings.

2 Methodology: Combining Agents and Equations, Object-oriented modeling, Regions and Networks, and Knowns and Unknowns

Our Zika-study required the development of a methodology which integrates different modeling and simulation approaches and concepts from other disciplines. Given the Zika case, we developed a hybrid framework which allows for switching dynamically during runtime between SD and ABM models for many different regions. Building on long-term best practices in computer science, we adopted an object-orientation approach for doing so. We also adopted techniques from graph theory for dealing with the interconnectivity of regions. Finally, we use the exploratory modeling and analysis methodology to simulate our models under deep uncertainty, explore the resulting simulations, and identify robust solutions.

2.1 A Multi-Method Approach

SD and ABM are two widely used modeling and simulation methods to study complex systems. In recent years, many have ventured into integrating these two methods. Combining their complementary characteristics could provide a more complete representation of complex systems, since shortcomings of one method can be dealt with by the other method (Borshchev and Filippov, 2004; Scholl, 2001b). However, since SD and ABM differ conceptually and operationally, integration is not straightforward. Alternative implementations have been proposed.

The idea of swapping, depending on the conditions, from AB to SD and back during run time was first introduced by Bobashev et al. (2007). They describe that the AB model can be used to dynamically parameterize an aggregated SD component. Furthermore, an aggregated SD component can again be decomposed into heterogeneous agents linked in a network structure. The motivation for an

implementation like that is the heavy performance burden of an ABM implementation compared to a SD implementation. The possibility to switch to an SD implementation of the model after the number of interacting individuals has reached a threshold allows to reduce runtime dramatically without conceding on disaggregated details where this is of explicit interest. Detailed representation of heterogeneous populations is then critical when these populations are very small. However, if the number of agents is large and we do not assume strongly clustered agent network structures, disaggregated simulation produces similar results as an aggregated population averaged approach (Bobashev et al., 2007; Rahmandad and Sterman, 2008). Moreover, the different representations also allow for explicitly studying different dynamics. Processes at the local level as well as at very large-scale can both be modelled, which allows for exploring the consequences of policies at the local and global level, using one and the same model.

2.2 Global-multi-regional model

Our objective is to realize a global-multi-regional model. To do so, we use object-orientation programming, which allows for generating reusable components. Similar to the concept of classes and instances in computer science, model entities can be created when they are needed. Once formulated and tested, a model component developed for one region can be cloned and reused for many similar regions. By using the same core model components, the structure of every region is identical but its properties are parametrized differently. To some extent, this is similar to the entity-based approach in Ventity (Yeager et al., 2014). The use case of object-oriented or entity-based formulation of SD models is not restricted to multi-regional models but can be applied to many complex dynamic systems. Our entity-based global-multi-regional model also enables us to compute key performance indicators on different aggregation levels: Provinces can be aggregated to countries and these in regions and eventually to global parameters.

2.3 A GIS-Based Graph-Theoretic Visual Approach:

Mathematical modeling of infectious disease at a global level requires modeling of outbreaks in different regions and to exchange information across regions during run-time. Dealing with many regions explicitly is usually outside of scope for traditional SD modeling. Fortunately, related academic disciplines have invested heavily in geographic modeling and geographic information systems. Some of their concepts are adopted here to model the interconnectivity of regions and to visualize and animate the simulation results on maps.

Our model assumes that epidemic transmission occurs at three different levels of aggregation. First, within each model object that represents one province, disease transmission occurs at individual level from infectious to susceptible. Second, each model object is linked with an adjacency list of geographical neighboring objects. Depending on the weight of the link between neighboring objects in the network, initial local transmission occurs as probabilistic event. Finally, each province can be aggregated to a country which is assumed to be connected with other countries by air travel. Air travel is retrieved from an external database and dependent on seasonal effects as well as an internal model that controls the incoming flights based on how many people are infectious in the destination country. Likewise, to infecting adjacent countries, the population is exposed by external infectious individuals and local transmission occurs probabilistic.

2.4 An Exploratory Approach: ...dealing with knowns and unknowns...

The Zika outbreak and its potential consequences are also deeply uncertain. In this research we want to take deep uncertainty explicitly into account. We therefore decided to embrace an Exploratory Modeling and Analysis (EMA) approach (Kwakkel and Pruyt, 2013; Lempert, 2003). EMA is a methodology that supports the exploration of a wide variety of scenarios and even alternative model

structures in view of identifying robust policies under deep uncertainty. EMA builds on the realization that policy models that can predict future states cannot be built, however computational models are extremely powerful as analysis tool that allows to test various hypothesis how the world works under a specific set of assumptions. Hence, using models a wide range of plausible futures are created and explored using smart algorithms and other analytical tools (Bankes, 1993).

Beyond uncertainties in parameters and model formulation, we are interested to explore the methodological uncertainty - meaning different threshold values, between the two extreme ends, pure ABM implementation and full SD implementation. Other interesting aspects to explore are inherent assumptions made during the construction of the ABM with respect to the agent activation scheme. Research has shown that asynchronous and synchronous scheduling of agents may produce considerably different results and conclusions (Caron-Lormier et al., 2008). Nevertheless, many ABM research projects do not explicitly deal with their agent activation process.

The presented multi-method approach that is able to swap depending on a condition from AB to SD is particular valuable in the field of exploratory modeling. Since, the core of exploratory modeling and robust decision making is to evaluate alternative actions across a wide variety of plausible future. In order to be able to execute many thousand simulation runs, models with a relative short runtime are required (Walker et al., 2013).

3   Simplified model to present general concept

The research is still ongoing and therefore the presented concept is preliminary and under revision. This section presents a simplified model to illustrate the currently implemented design.

At the end of the project the complete code will be made accessible with all details and documentation at https://github.com/philippschw

The model was implemented in Python. A number of reasons motivate this choice. First, across many scientific disciplines Python is a widely used programming language for scientific computing and quantitative data analysis. The open source environment allows to foster transparency and reproducibility of research. Further, Python achieves a balance between full flexibility of general-purpose programming languages and ease of use. In addition, as object-oriented programming language agent-based and multi-model approaches are feasible. Finally, since Python supports the integration of different libraries it provides an unprecedented rich ecosystem of modules that can be utilized and recomposed in novel ways (Pérez et al., 2011).

From this large toolbox of Python modules *mesa* was used to implement the ABM (Masad and Kazil, 2015) and *PySD* (Houghton, and Siegel, 2015) was used for an simple conversion of a SD model implemented in Vensim ® into an equivalent equitation based model in Python. Furthermore, the complete architecture was embedded into the Python based Exploratory Modeling and Analysis (EMA) Workbench (Kwakkel and Pruyt, 2015). EMA is used to set up experiments and perform advanced result analysis.

3.1   The System Dynamics Model

The core of the SD model is a SIR–model (i.e., a Susceptible-Infectious-Recovered-model). An individual is considered to be in one of the following three states/compartments/stocks: susceptible (S), infectious (I), and recovered (R) in the model. The flow from susceptible to infectious is described by the simple equitation:

$$\frac{Susceptible * Infected * probability\ for\ transmission}{Total\ Population}$$

The recovered are assumed to have obtained permanent immunity and do no longer infect others. In this first iteration model, no further complexity was introduced for the sake of simplification. In the future, the model will be extended to account for incubation time and asymptomatic individuals. Furthermore, the interaction between human and vectors (mosquitos) will be incorporated by means of a second SIR chain for mosquitos. In addition, the strong effect of temperature on the expansion of the *Aedes aegypti* population will be included in the final model (Brady et al., 2013; Watts et al., 1987). As a consequence, the disease transmission rate will become coupled to the season.

3.2 The Agent-Based Model

Likewise, agents in the agent-based model are in one of the three stages: susceptible, infectious, and recovered. The model is defined as a cellular automaton and conceptually similar to the forest-fire model (Drossel and Schwabl, 1992). Agents have a fixed position on a two-dimensional grid which represents a simple network structure. The grid strictly enforces one object per cell and is toroidal, meaning the top and bottom, and left and right, edges wrap to each other. A small set of simple rules govern disease spreading. According to probabilistic discrete events, an infectious individual is capable of infecting its susceptible direct neighbors in either 8-cell Moore or 4-cell Von Neumann neighborhoods. The density of agents, the number of susceptible to total population and the probability of disease transmission per contact determines the pace and possible stalemate of the spread of the epidemic. For model testing and debugging a deterministic version was implemented.

To illustrate the conceptual mechanics of switching between ABM and SD formalisms, no further complexities were introduced. In future iterations, the model could be enriched by adding more complexities. Particularly promising seems to utilize ABM's inherent benefits over other modeling methods. For example, constructing a heterogeneous population with adaptive behavior embedded in a social network would yield interesting insights and make use of the multi-layer complexity for policy exploration. Furthermore, agents could be made mobile and interact with other according to their daily routine.

To keep the computational requirements at a minimum, the susceptible and recovered agents are kept inactive, since their interactions are irrelevant to the epidemic process. Another possible implementation could be to dynamically create agents and their associated network of susceptible and recovered agents in line with the evolving outbreak.

3.3 Switching Between ABM and SD

Proper interfacing between ABM and SD models is a precondition to allow to switch between ABM and SD system representation. Of At the beginning of each time step, a condition is checked based on the latest computed (or initial) values. In the present model it is tested whether the number of infectious agents are above a certain threshold value. If there are only few infectious agents, a AB is initiated with the latest values from the data set. If there are many agents, then instead an equitation based model is set up. Both models are advanced only a single time step and write at the end of each step their (aggregated) system values to the shared single data frame.

1. **AB <-> Data** <-> SD (check input data t_1: if few infectious agents, then AB)
2. **AB <-> Data** <-> SD (check input data t_2: if few infectious agents, then AB)
3. AB <-> **Data <-> SD** (check input data t_3: if many infectious agents, then EB)
4. AB <-> **Data <-> SD** (check input data t_4: if many infectious agents, then EB)
5. …
n. **AB <-> Data** <-> SD (check input data t_n: if few infectious agents, then AB)

In practice, it is easier to switch from disaggregated to aggregated system representation than the other way around. For the switch from ABM to SD, all agent conditions (susceptible, infectious, recovered) simply need to be aggregated, afterwards, the stocks in SD are initialized with the aggregated values. One the other hand, switching from SD to ABM requires enriching the aggregated information by means of assumptions about the geo-spatial distribution of different agents as well as possibly the distribution of other agent properties.
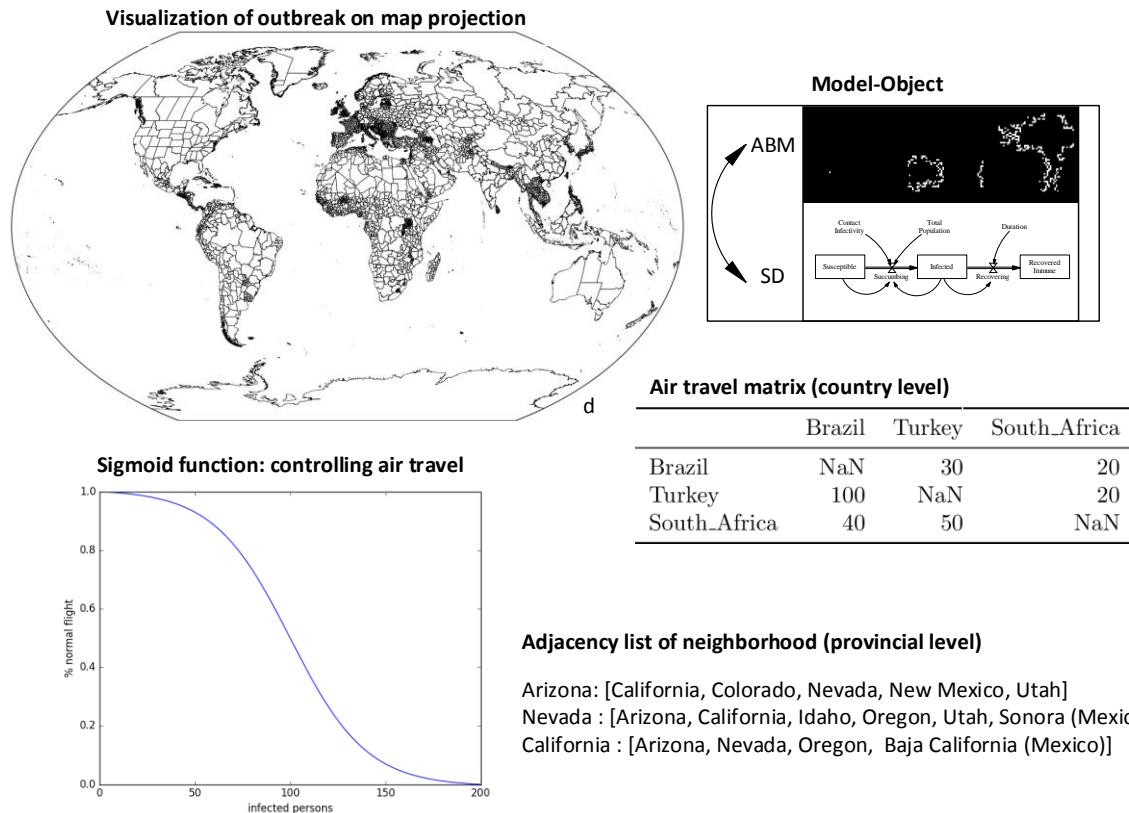
For a single hybrid model object, the model could also be simply advanced until a condition is fulfilled. However, multiple interacting model objects require some form of synchronization. Since, it was observed that the SD model outcomes are insensitive to the selected time step, despite the problem that this approach may not always be legitimate, a global time step of one was chosen.

3.4 Creating a global epidemic model

The *Aedes aegypti* mosquito as main vector that transmits the Zika virus is persistence in nearly all regions of the world with tropical and subtropical climate. As a consequence, nearly half of the world's population lives in regions with potential local transmission (Brady et al., 2012). These regions were defined as scope for our simulation model.

Figure 2 illustrates the elements required for the global epidemic model. It is based on embracing multi-resolutions and data-interfacing both on the input side and the output side. In a nutshell, it is formed by multiple instances of the hybrid model object and a model controlling the air travel, these elements are supported by several underlying external data source, including maps, air travel data in matrix from, and socioeconomic and weather data on provincial aggregation level.

Figure 2: Schematic representation of all modeling components for global epidemic model

Visualization of outbreak on map projection

Model-Object

Sigmoid function: controlling air travel

Air travel matrix (country level)

	Brazil	Turkey	South_Africa
Brazil	NaN	30	20
Turkey	100	NaN	20
South_Africa	40	50	NaN

Adjacency list of neighborhood (provincial level)

Arizona: [California, Colorado, Nevada, New Mexico, Utah]
Nevada : [Arizona, California, Idaho, Oregon, Utah, Sonora (Mexico)]
California : [Arizona, Nevada, Oregon, Baja California (Mexico)]

The in the preceding section described model object that switches flexible between ABM and SD is cloned and reused for each province on the map. The model object is parameterized from an external database with the province specific features such as population, temperature etc. The provincial aggregation level is justified because many countries (outside Europe) are so large that they span over several climate zones and therefore, have too different characteristics.

Besides, interconnectivity between regions is achieved at different levels. First, each model object (province) is associated with a list of adjacent regions. The geographical neighbors are computed based on the polygons of the provinces. The weight of link in this network with adjacent regions could potentially be specified but for now is assumed to be uniform. Second, air travel connects the regions on a national level. Travel is defined as travel flow stored in matrix form. It is derived from an external data source and influenced by seasonality and extraordinary events (such as the Olympic Games in the Summer 2016 in Rio de Janeiro). In addition, number of incoming flights to a destination is impacted by the simulation model itself. Following a normalized sigmoid function (y between 0 and 1), where x is the number of infectious persons in a destination country, and y the percentage of normal flights. Disease transmission through the air transport network occurs according to probabilistic rules based on based on the share of infectious population and the number of travelers.

Ultimately, the approach facilitates the dynamic visualization of spatially explicit outbreak over time. The created decision support system goes way beyond conventional systems. Different scenarios can be projected on a map and are therefore more accessible for users than line graphs.

3.5   Results

Figure 3 demonstrates outcomes produced by the described method switch approach. Several model objects are simulated in parallel and plotted. Due to the stochasticity, the ABM model produces ragged lines, once the model has switched to SD the curves are smooth. Furthermore, it is apparent that the switch mechanics are independent from one another. One model object can be simultaneously be in ABM mode while others are in SD. Note, the present implementation is a one-way switch, implying that the model object switches from ABM to SD but not back.

Figure 3: Simulation Results – illustrating ABM SD method switch
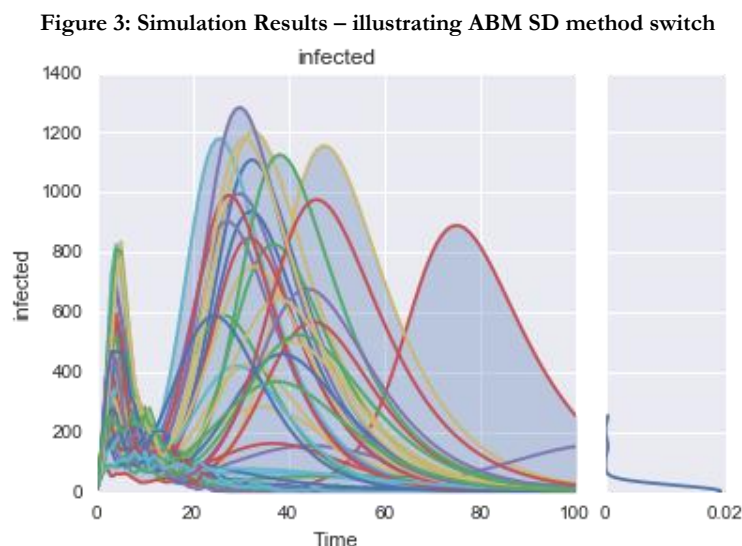
4 Discussion

We have presented a conceptual model for modelling and simulating the Zika outbreak under deep uncertainty. Supported by GIS, our approach provides insights into the evolution of the outbreak at different resolution levels. We presented an example of a simple implementation of a threshold hybrid model that switches between ABM and SD system representations. The presented approach allows to describe appropriately the process of initial local transmission in a region while fostering an efficient description of the epidemic process of an ongoing outbreak.

Numerous literature reviews on ABM and SD concluded that one the one hand, tradeoffs between ABM and SD exist and on the other hand, the methods are highly complementary (Behdani, 2012; Macal, 2010; Schieritz and Grobler, 2003; Scholl, 2001). Beyond the specific case of epidemiological modelling we see great potential in matching ABM and SD models to switch by condition between the two methods. The set out approach shows one promising way to combine the advantages of SD with the benefits of ABM, namely disaggregation, stochasticity, network structures and genuinely learning capabilities of agents (adaptive behaviour patterns).

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