Simulating Human Movement in a National-Scale Individual-Based Model of Malaria in Burkina Faso

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Abstract. Malaria due to the *Plasmodium falciparum* parasite remains a threat to human health despite eradication efforts and the development of anti-malarial treatments, such as artemisinin-based combination therapies. Human movement and migration have been linked to the propagation of malaria on national scales, highlighting the need for the incorporation of human movement in modeling efforts. Individual-based models have been used to study how anti-malarial resistance evolves and spreads in response to drug policy changes; however, as the spatial scale of the model increases, the challenges associated with modeling of movement also increase. In this paper we discuss the development, calibration, and validation of a movement model in the context of a national-scale, spatial, individual-based model used to study the evolution of drug resistance in the malaria parasite.

Keywords: agent-based modeling, malaria, migration, movement

1 Introduction

The promulgation of the United Nations Millennium Development Goals, and specifically Goal 6 to combat HIV/AIDS, malaria, and other diseases has resulted in a renewed global interest in malaria eradication. Despite the efforts of the past 20 years, malaria caused by the *Plasmodium falciparum* parasite remains a serious public health concern with 229 million cases and 409 thousand deaths estimated in 2019 [1]. One significant barrier to eradication efforts is the evolution of anti-malarial resistance by the parasite, with resistance to the artemisinin components of artemisinin-based combination therapies (ACTs) being of particular concern [1]. While the primary driver of anti-malarial resistance is the evolutionary pressure applied on the parasite through the use of anti-malarial treatments (e.g., ACTs), a resistant parasite may also appear in a region due to importation though human movement (e.g., temporary travel for work or leisure) or migration (i.e., permanent relocation) [2].

One means of studying the evolution of anti-malarial resistance, and the impact that various drug policies may have upon it, has been through the use of individual-based models (IBMs) that incorporate components such as transmission of the parasite, immune acquisition and response, genotype evolution, and drug intervention strategies

[3]. By incorporating space and geography in these models, it may be possible to evaluate regionally targeted interventions, or observe possible patterns in the development of anti-malarial resistance, allowing for new eradication strategies to be developed. Accordingly, modeling efforts must be accompanied by a model of human movement in order to account for the carriers of anti-malarial resistant parasites. However, national scale simulations may incorporate millions of simulated individuals (i.e., agents), spread across thousands of cells representing simulated space, resulting in challenges of model implementation, calibration, and validation.

1.1 Malaria in Burkina Faso

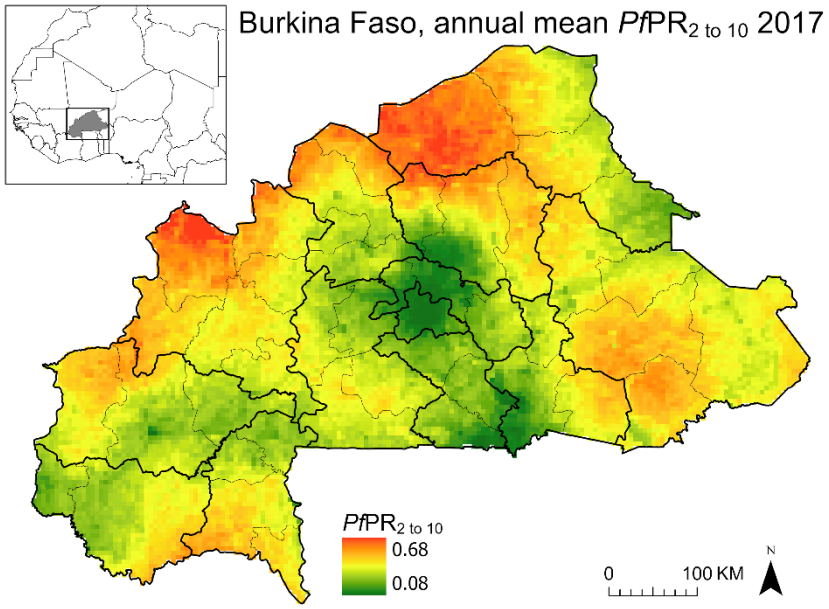

Fig. 1. Annual mean prevalence of *P. falciparum* malaria in Burkina Faso in two-to-ten-year-old children, as of 2017 [4]. Each cell (i.e., pixel) represents a 5 km by 5 km (25 sq.km) block of land and the prevalence scale ranges from 8% to 68%.

Burkina Faso is a landlocked country in western Sub-Saharan African (SSA) with endemic malaria (i.e., persistent transmission of the infection in the population), which is the leading cause of hospitalization in the general population (45.8% of hospitalizations) as well as for children under five (48.2% of hospitalizations) [5, 6]. During periods of seasonal rainfall, the *P. falciparum* prevalence rate in the two- to ten-year-old population (called *Pf*$PR_{2\text{-}10}$) may increase significantly in relation to the annual mean *Pf*$PR_{2\text{-}10}$ which ranges from 8.0% to 67.6% using 2017 estimates [4]. The primary first-line therapies

for uncomplicated malaria are ACTs, such as artemether-lumefantrine or dihydroartemisinin-piperaquine, which have been recommended since 2005 in accordance with WHO guidelines [7]. ACTs are used in conjunction with other malaria intervention programs such as insecticide-treated mosquito nets (ITNs), indoor residual spraying (IRS), and intermittent preventative treatment of pregnant women (IPTp). As a result of ACT usage and these other interventions, the general worldwide trend since 2005 has been a reduction in the prevalence of malaria [8].

1.2 Movement Models

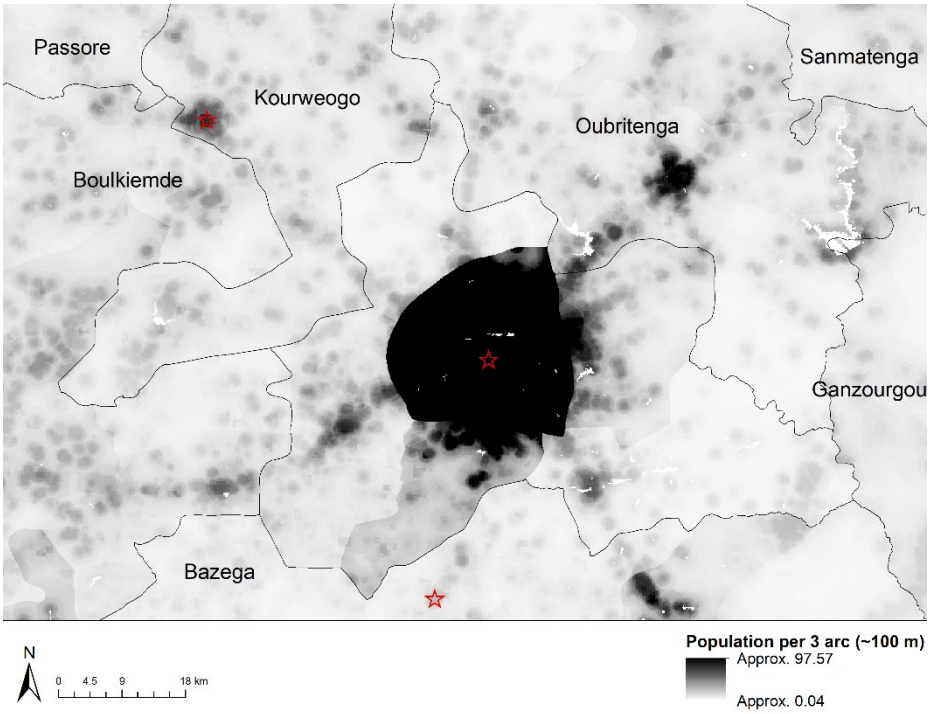

Fig. 2. Site of surveys by Marshall et al. [9], where red stars represent the approximate locations of the survey sites. The densely populated region in the center is the capital Ouagadougou. (Map prepared by the authors, population data from WorldPop [10])

Since human movement and migration has been linked to the migration of drug-resistant genotypes [2], incorporation of human movement is a relevant component of an IBM. The two most common mathematical models of human movement in the SSA region are the gravity and radiation models [11, 12]. Gravity models are constructed with the assumption that movement rates between two points (e.g., cities) increase in relation to the size of the point populations and decrease with the square of the distance between them; similar to the physical laws of gravitation. Gravity models may be modified with functions that account for other parameters, such as mode and cost of travel.

Radiation models draw their inspiration from physical processes (i.e., particle diffusion), but differ from gravity models in that the underlying assumption is that individuals move outward from their origin and are "absorbed" by a given destination, within a given distance, with a probability that is proportionate to the population of a given destination.

In the most recent study of movement in Burkina Faso, Marshall et al [9] surveyed three sites (Ouagadougou, Saponé, and Boussé) during the rainy season of July 2011 (Fig. 2), recording the number of trips by both source and destination. The survey data were then used to fit mathematical models, and the authors concluded that a gravity model with a power-law distance kernel had the most predictive power in relation to the observed movement patterns [11]. However, in the context of SSA it has been suggested that countries may follow unique patterns that are not perfectly explained by either the gravity or radiation model in their unmodified forms [12], indicating that further work may be needed in order to ensure that a mathematical model is appropriately fit to a given country.

2 Model Design

2.1 Mathematical Model

The general success and application of gravity models for human movement and migration in SSA, coupled with the recent work by Marshall et al. [9,11], motivated us to use the modified gravity model suggested by Marshall et al.:

$$Pr(j|i) \propto Pop_j^{\tau} k(d_{i,j}) \tag{1}$$

$$k(d_{i,j}) = \left(1 + \frac{d_{i,j}}{\rho}\right)^{-\alpha} \tag{2}$$

Where $Pr(j|i)$ describes the probability of travel from the source i to the destination j, given the product of (1) the population of j raised to τ and (2) the distance kernel, which takes the form of a power law containing the scale parameter ρ, and the power-law parameter α.

A limitation of the model constructed by Marshall et al. [11] is the lack of consideration for the time, distance, or complexity in traveling to a given destination. One means of capturing the difficulty associated with travel is through the use of a friction surface, which quantifies the ease or difficulty in traversing surfaces (e.g., road types) or natural barriers such as mountainous terrain [13]. An alternative is the use of a travel time map (or surface) which estimates the time to reach the nearest city (or high-density urban area [14]) from a given location on the map. The use of travel time map, such as the one prepared by the Malaria Atlas Project [14], is appropriate in the context of malaria interventions since rural communities may lack local medical resources, necessitating travel to seek care [2, 15].

Accordingly, the probability of movement can be adjusted to use travel times as follows:

$$Pr(\mathrm{j|i})' = \frac{Pr(j|i)}{(1+t_i+t_j)} \tag{3}$$

Where *Pr(j|i)'* describes the new probability of travel from source *i* to the destination *j*, by dividing the original probability *Pr(j|i)* by the sum of one plus travel time to the nearest city of the source t_i and destination t_j. This has the effect of biasing the model's movement towards destination cells that are located in or near cities, but still allowing travel between rural locations, or from a city to a rural location.

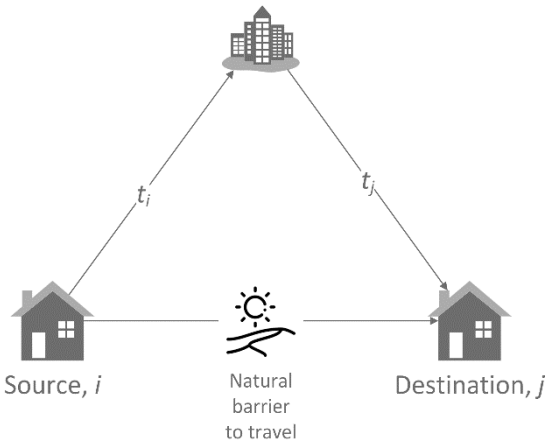

Fig. 3. Inclusion of source t_i and destination t_j travel time allows for the probability of indirect or blocked routes to be determined. If the travel time from one or both rural destinations to the city is large, this means that travel around the rural locations is high-friction (i.e., neither easy nor fast). As a result, the probability of movement to or from locations *i* and *j* is decreased via Equation 3.

Incorporation of both the source t_i and destination t_j in the denominator of Equation 3 is necessary as it properly accounts for indirect travel routes. For example, in Fig. 3, direct travel between the source *i* and destination *j* is blocked by a barrier and thus travel must be routed through a city or circuitous road. Conversely, since the travel time map is based upon the time to the nearest city, when travel is unrestricted (i.e., the destination is in a city) the value of t_j would be zero representing direct unrestricted travel. Finally, when both *i* and *j* represent cells within a city, the original probability *Pr(j|i)* remains unadjusted. As a result, during model calibration, care must be taken to ensure that the number of trips within a city or province, or between cities, are properly modeled.

2.2 Implementation

The mathematical model described in Section 2.1 was incorporated, along with other spatial changes such as the ability to read raster-based data files, into an IBM previously developed by Nguyen et al. [3] in C++.[1] As an organizational matter, the movement model was implemented as a new class, which implements an abstract class defined by the IBM for movement models. The integration of the movement model into the IBM can be summarized as follows. First, geographic data (i.e., population, travel times) is read from disk into memory using an object that implements the singleton pattern. Next, for each daily model timestep following execution of other population events (e.g., infections, births, deaths), iterate through each cell in the model and calculate the number of individuals leaving the cell. This follows the calculation of *Pr(j|i)'* from the current cell *i* to every other cell, and the resulting vector is used to perform a random multinomial draw for each individual, indicating their destination cell. Individuals are then moved to their destination cell with a timer set for when they will return to the original cell simulating movement, or with no timer indicating permanent migration to the new cell. Model execution then proceeds to the next timestep.

The incorporation of the movement model into the IBM resulted in a number of time and space complexity challenges, and analysis of the source code suggests an algorithmic complexity of $O(n^3)$ with a space complexity of $O(n)$ for the calculation of travel-time probabilities. During implementation of the movement model, static memory along with a singleton design pattern was used to eliminate the need to reload or copy geographic data, which is represented in memory as either a matrix or a flat array. While it was originally hypothesized during development that the probability of movement could be calculated once at model initialization based upon the initialization parameters, doing so resulted in artifacts appearing in agent movement over time. However, when the probability is calculated during each timestep (i.e., in a manner consistent with population growth in the simulation) the model performed as expected suggesting that caching of calculated movement probabilities is unlikely to be possible. This suggests that most optimizations are likely to come from careful programming and code organization to minimize the number of times that movement probabilities need to be calculated per timestep.

Finally, in preparing the spatial data used for the calibration of Burkina Faso, the limiting factor of the spatial resolution is the cellular size of the reference $Pf\text{PR}_{2\text{-}10}$ values provided by the Malaria Atlas Project [4], resulting in a cell size of 25 sq.km. This results the approximately 273,000 sq.km of Burkina Faso being converted into 10,936 pixels (or cells). Initial population data comes from WorldPop [10], which was aggregated using the sum function of ArcMap 10.7.1 to 25 sq.km cells, resulting in pixel level populations ranging from 1 to 206,607 individuals per cell. The travel time map uses the Malaria Atlas Project travel time to cities map [14]; however, the original 1 sq.km cells are aggregated up to 25 sq.km using the mean function with a cell factor of 5.

[1] The source code for the simulation is hosted on GitHub at https://github.com/rjzupkoii/PSU-CIDD-Malaria-Simulation and the work described in this manuscript uses the version 4.0.0 release of the simulation.

3 Calibration and Validation

Model calibration and validation took place in two parts following implementation and initial verification of code correctness. Outside the work done by Marshall et al [9] introduced in Section 1.2, there is a lack of quantitative travel data for Burkina Faso that can be used to robustly calibrate and validate the model. Furthermore, the work by Marshall et al [9] is limited due to three factors. First, the section of survey sites is clustered in the central region around the capital Ouagadougou and does not incorporate other regions such as Houet in south-west Burkina Faso. Second, the sampling sites used in the survey resulted in travel between most of the provinces in Burkina Faso not being captured in the respondent data, limiting the overall predictive power of any models derived from it. Finally, the time of the survey during the rainy season also introduces biases due to seasonal migration patterns. As a result, model calibration and validation were performed with these limitations in mind and the objective was not to ensure complete model fidelity to the survey data, but rather to ensure that agent movement does not deviate significantly from expectations.

With the limitations of the underlying validation data in mind, parameterization of the movement equations proceeded by first selecting the value for the scale parameter ρ based upon the $\log_e(\rho)$ range of values suggested by Marshall et al [11]. To do so, a "synthetic survey" was performed in Matlab 2019b which approximated the sampling of the Marshall et al. [6] survey.[2] This was done by applying the gravity model fit by Marshal et al [7] (Equations 1 and 2) using population of the province as Pop_j, the distance from the sampling site to the centroid of the province as $d_{i,j}$ iterating through values 0.05 to 1.8 by steps of 0.05 for $\log_e(\rho)$, and then performing a random draw of samples equal to the number of survey participants. This was done for a total of 1,000 trials for each value to ensure sufficient statistical power. The results of the synthetic survey were then compared to the survey data from Marshall et al. [9] and the number of matches and inter-quartile ranges (IQR) were compared. While Marshall et al. [11] suggests $\log_e(\rho) = 0.45$ as the best fit, the value $\log_e(\rho) = 0.20$ was selected here as it offered the most IQR matches along with a low mean squared error. To further validate this result, the $\log_e(\rho)$ parameter was input as a simulation parameter and the frequency of trips and distanced traveled where then compared to the survey data resulting in generally favorable results (Fig. 4). However, it is important to note that agreement between model and data will always be difficult in a calibration like this when the total number of trips is very low (e.g., <5 trips during a survey period).

[2] The source code for the synthetic survey can be found at https://github.com/rjzupkoii/PSU-CIDD-Burkina-Faso/tree/master/Analysis/Movement

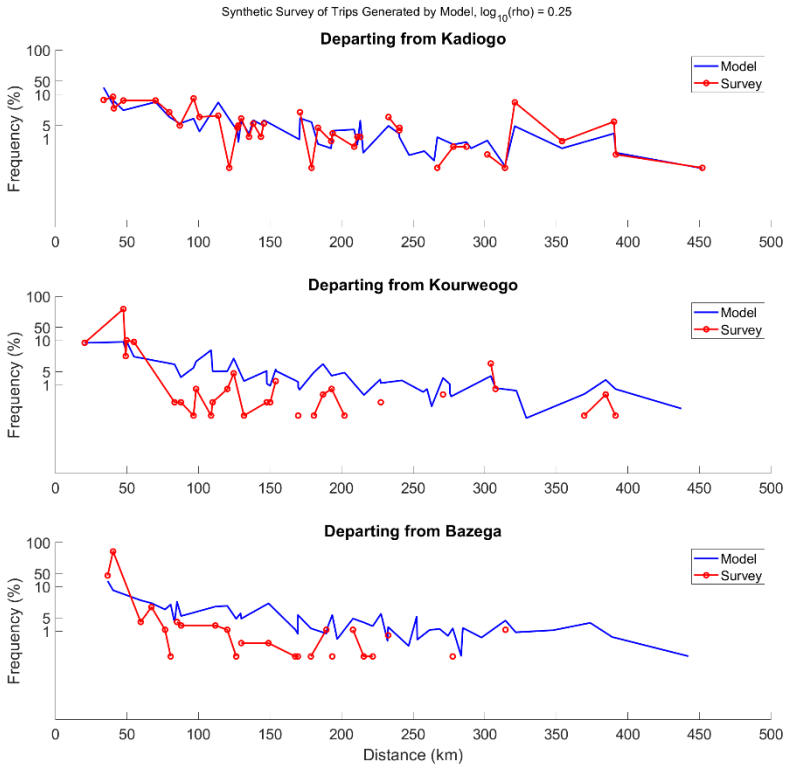

Fig. 4. Frequency plot of simulated trips from a source to destination province, plotted against the distance between the province centroids. Note that in the case of Kadiogo, containing the capital Ouagadougou, the results compare favorably to the survey data. However, the mathematical model's predictive power is worse for Kourweogo and Bazega, where less respondent data was available.

Following selection of the scale parameter ρ, the inferred values $\alpha = 1.27$ and $\tau = 1.342$, as fit by Marshall et al. [11], were used as part of a simulation of the entire country for 12 months with a population of approximately 19 million individuals wherein all travel between cells was logged. The cell-to-cell travel was aggregated up to the province level to allow for comparison to Marshall et al. [9] survey data, and also plotted as a monthly heatmaps of arrivals. The process of doing so revealed that that $Pr(j|i)'$ provides a reasonable probability of movement from the source to destination in regions of high, geographically dispersed populations.

However, in Kadiogo province, containing the capital Ouagadougou, the model was biased towards movement remaining within the district. Examination of the probabilities calculated for the cells within the province showed a higher likelihood as a result of the higher local population density in relation to the rest of the country, thus biasing

the results. In order to correct this bias, an intra-province travel penalty was introduced wherein *Pr(j|i)'* is divided by the penalty *p* when the source and destination cells are both within the capital province. A 12-fold intra-province penalty was determined for Kadiogo following additional calibration runs of the model which is applied by dividing *Pr(j|i)'* by 12 when the source *i* and destination *j* is within the capital province.

The final point of calibration and validation for the movement model was the number of trips taken. The survey by Marshall et al [9] indicates that about 29.1% of the population travels on a yearly basis with a mean number of 3.42 trips. This suggests a daily circulation rate (i.e., the daily probability of an individual traveling) of 0.002727 for travelers leaving their home province. However, since the model allows for intra-province travel, it is necessary to introduce an adjustment to this value. Individual movement was tracked in the model and various circulation rates trialed until the national level annual rates (29.1%) were matched by a daily circulation rate of 0.00336. As a result, approximately 19% of all simulated trips are to cells within the same province while the remainder leave the province. Ultimately the movement model and its parameterization results in individual movement within the model that is consistent with movement focused on major population centers and following national transportation networks (Fig. 5).

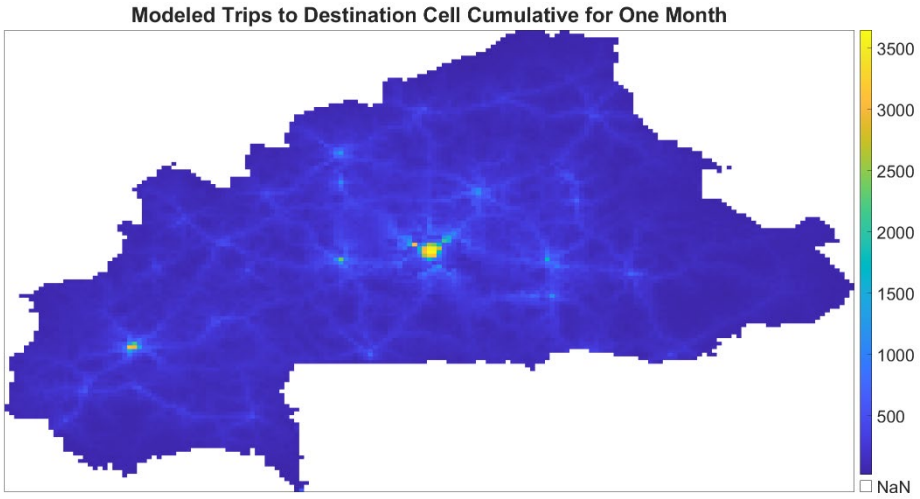

Fig. 5. Heat map of trips to the destination cell over the course of month. Note that destination for trips approximates the population distribution of the country with Ouagadougou (central) and Bobo-Dioulasso (west) being distinguishable along with smaller towns and villages.

4 Discussion and Conclusion

For individual-based epidemiological models of malaria, an appropriate model of movement by individuals is necessary due to the role that human migration plays in the

spread of anti-malarial resistance. However, the development, calibration, and validation of IBMs incorporating such a movement model, particularly at the national scale, remains a challenge. These challenges can be further compounded by the lack of quantitative data available for a given country of interest. Despite this, IBMs and mathematical modeling more broadly still play an important role in malaria control with national scale models offering possible insights for surveillance and drug policy response [16].

One of the advantages of geospatially coupled malaria models is that they can offer projections for where anti-malarial resistance surveillance efforts may be focused. Given the parameterization and the sub-models necessary in a malaria IBM (e.g., transmission, human immune progression, human movement patterns, etc.) the ability to project where drug resistance is more likely to emerge is a natural by-product when genotype evolution is incorporated. However, the validity of these projections is dependent, in part, upon the movement model being appropriate for a region and properly calibrated.

An important application of malaria IBMs is evaluation of how changes in drug policy (e.g., changing the partner drug in an ACT or introducing multiple first-line therapies [see 3, 17, 18]) impact the emergence of drug resistance by the parasite. The connection between antimalarial drugs and *de novo* emergence of resistance has been well established [19-21], accordingly it is not a matter of "if" drug resistance will emerge, but rather when. However, the role that human migration plays in introducing an anti-malarial resistant parasite to a region remains unclear. This question can only be addressed through the incorporation of a calibrated and validated model of human movement and migration.

A standard equation or a regionally calibrated movement model, such as the one developed by Marshall et al. [11], is unlikely to meet the needs of a model developer "out of the box." While a published parameterization may offer a useful starting point for model developers, additional algorithm development, parameterization, and calibration steps are necessary to ensure that the model is appropriate for expected movement in a region, and the goals of the model. This movement model demonstrates one approach that can be used to improve fidelity though the use of a travel time map. As always, model developers should be diligent during the calibration and validation process to ensure that model outputs make sense in the context of quantitative and qualitative data that is available.

In summary, while the introduction of an anti-malarial resistant *P. falciparum* parasites to a region through human movement and migration is just one mechanism by which resistance can appear; it is necessary that IBMs modeling malaria epidemiology properly account for it. As this paper has demonstrated, it is possible to scale-up mathematical models to be utilized in national-scale IBMs; however, performance, calibration, and validation are all challenges that require careful investigation. Furthermore, the availability of data for a region of study can place limitations on the extent of validation that is possible, necessitating some caution in the claims that can be made by simulating specific scenarios.

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