CHAPTER 10

# Mapping the Distribution of Malaria: Current Approaches and Future Directions

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## 10.1 INTRODUCTION

Malaria is an enormous public health and economic problem. In 2010, there were an estimated 219 million cases of malaria and 660,000 deaths, of which 90% occurred in sub-Saharan Africa (WHO 2012). Because malaria is such a substantial burden, predicting transmission risk is a key public health goal. However, accurate prediction is complicated due to a myriad of environmental and human factors that affect transmission. In locations where there are accurate data on these environmental and human factors we can model the distribution of malaria risk. The models can be informed by, and predictions validated by, regional records of malaria cases. Here, we review the range of approaches to understanding malaria transmission, from relatively simple mechanistic models to more complex spatially explicit statistical models.

Malaria is caused by protozoan parasites of the genus *Plasmodium*, with the vast majority of deaths caused by *P. falciparum*. The parasites are transmitted by mosquitoes of the genus *Anopheles*. Of the hundreds of *Anopheles* species described, approximately 70 have been shown to be competent vectors of human malaria (Hay et al. 2010). The dynamics of both the parasites and the vectors, and thus malaria transmission, are largely driven by environmental factors. The two most important of these are the availability of pooled water, often estimated by rainfall, and temperature. The frequency, intensity, and duration of rainfall—combined with factors such as local evaporation rates, soil percolation and slope of the terrain, irrigation, and the availability of other water sources—affect the number, distribution, and stability of pools, and, hence, mosquito population dynamics. Temperature affects the behavior, physiology, and development of mosquitoes and the development of the plasmodium parasite inside the mosquito. Therefore, the intensity and limits of malaria transmission are strongly linked to temperature (Parham and Michael 2010; Mordecai et al. 2013).

Human drivers of malaria transmission include access to and quality of health care, movement of people, malaria control interventions, and the spread of resistance. Many of these factors are associated with poverty. Poorer groups are most vulnerable because they are less likely to use preventive measures (such as insecticide-treated nets and chemoprophylaxis) and have less access to health care (Worrall et al. 2005). Fewer controls on drug distribution in poor areas have led to drug resistance in malaria strains (Artzy-Randrup et al. 2010; Béguin et al. 2011; Lynch and Roper 2011). Finally, human drivers of malaria transmission correlate with environmental factors, leading to what some have called the poverty trap of tropical diseases (Sachs et al. 2004; Bonds et al. 2010).

Models of malaria incorporating the important drivers of disease are important for informing policy and guiding research. The past decade of malaria control programs have saved an estimated 1.1 million lives (WHO 2012), demonstrating progress in the control and eradication of the disease. However, the array of environmental and human/socioeconomic factors that drive patterns of transmission makes malaria a highly complex and multifaceted problem. Models may serve as early warning systems (EWS) for problems such as mosquito resistance to insecticides, parasite

**Table 10.1 Overview of the Advantages and Limitations of the Two Main Classes of Models for Understanding Patterns of Disease Spread**

| Class | Advantages | Limitations |
|---|---|---|
| Explicit (Section 10.3.1) | Utilizes covariance information. Good for predicting at local scales. | Computationally expensive for large datasets, so often less usable for large spatial scale analysis. |
| Implicit (Section 10.3.2) | Many varieties of methods allow exploration of disparate patterns of disease across scales, especially for broad, general patterns. | Spatial correlation relies on correlations between underlying covariates alone. Cannot leverage information about local-scale correlations for fine-grained prediction. |

Examples of each type and how they can be combined to form hybrid models are detailed in Figure 10.1 and in Section 10.3.

resistance to drugs, or climate change–induced distribution shifts. This chapter synthesizes current quantitative methods used to understand the spatiotemporal patterns of malaria and highlights outstanding challenges. We focus on the wide variety of spatial data and modeling, beginning with a review of explicit and implicit spatial methods (including mechanistic approaches, see Table 10.1). We then highlight hybrid approaches, that is, those that combine mechanistic models with sophisticated spatially explicit statistical models. These represent the most promising of the modern approaches. We conclude by examining open questions and possible approaches to address them.

## 10.2 MAPPING AND SPATIAL MODELS

References to malaria's characteristic fevers are found as far back as 2700 BC in China (Cox 2002). It was especially problematic during the decline of the Roman Empire where it was recognized that marshes and coastal and riparian lowlands were particularly high risk areas for "Roman fever" (Sallares 2002). Due to these strong spatial patterns in malaria transmission, mapping the distribution of malaria has long been an important tool for epidemiologists (Gill 1921; Guerra 2007; Omumbo et al. 2005). By indicating the spatial limits of transmission, these maps have given insights into the socio-environmental covariates associated with malaria. These relationships can then be used to estimate malaria transmission in areas where no data are available or to predict changes in the distribution of malaria in the future. They also help identify areas where travelers are at risk of infection and where interventions are most needed to improve public health.

Simple maps categorizing geographic risk or providing travel guidelines using only country-wide presence/absence data can be very effective. However, to identify local populations at risk and establish or improve intervention, prevention, or control, that

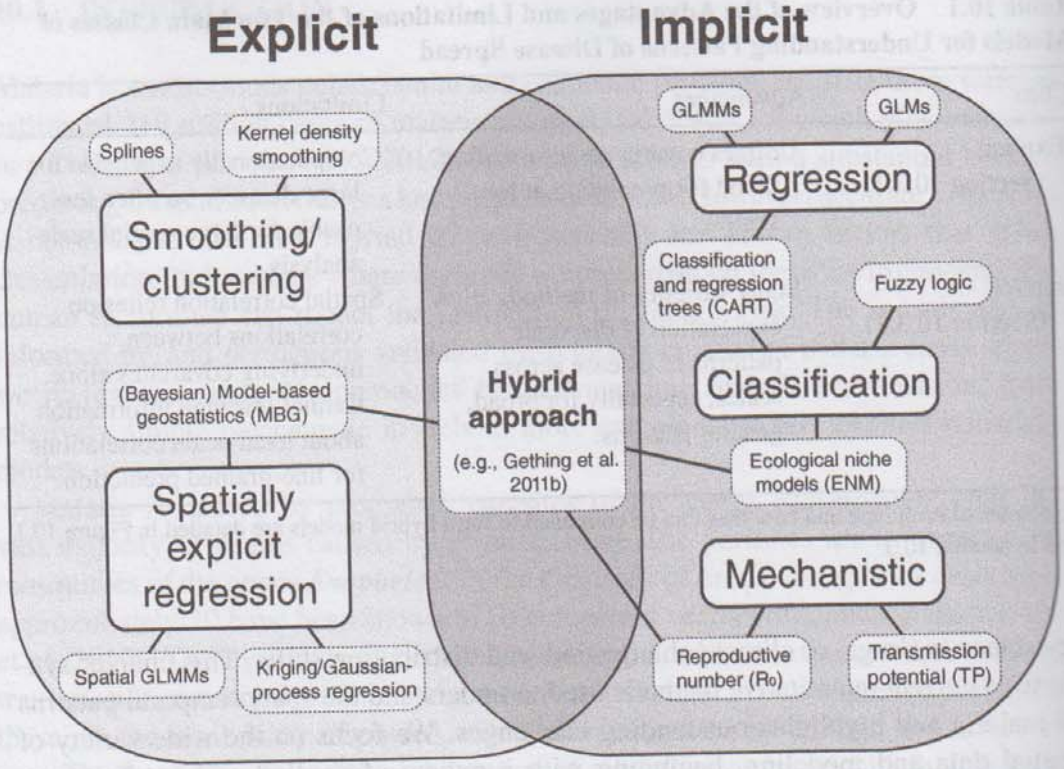


**Figure 10.1** Schematic representation of the methods and approaches used to model patterns of disease transmission, such as malaria. Further details of the explicit methods can be found in Section 10.3.1, implicit in Section 10.3.2, and hybrid methods in Section 10.3.3

is, specifically for public health policy applications, requires more detailed data and maps. In this section, we review the current state of malaria mapping and modeling, highlighting both advances and limitations.

### 10.2.1 Types of Data and Covariates Used for Spatial Analyses of Malaria

The simplest malaria maps are pictorial, spatial representations of observed data, summary statistics, and indices. Many "evidence-based" or "expert opinion" and "medical intelligence" maps fall into this category. For instance, data on number of cases or deaths can be aggregated by country and mapped as an index of the relative impact of malaria compared with other countries (WHO 2012; Le Sueur et al. 1997). Finer scale mapping can represent differences in prevalence among regions within countries based on data from individual clinics. These types of data and maps are frequently used for informal reports, or as visual tools for presenting travel and health guidelines. Various types of medical intelligence can supplement case and prevalence data in order to build maps that better represent regional risk of disease. These maps can be useful as rough guides for development of disease policy. However, their lack of transparency and formality limit their reproducibility for scientific questions and their use in prediction across space and time (Hay et al. 2010; Sinka et al. 2012).

Models for the spatial distribution of malaria consider a suite of environmental and socioeconomic variables. Beginning in 1920, Gill (1921), created maps representing broad-scale environmental constraints on global malaria distribution using bands of temperature and rainfall. This provided a template for later approaches to mapping malaria endemicity/transmission risk by defining areas where malaria transmission is likely to be constrained by environmental suitability. These maps of environmental constraints have increased in complexity and sophistication over the past century (Thomson et al. 1999). Remotely sensed data has been particularly important for gathering environmental variables even in inaccessible places (Thomson et al. 1997). Environmental covariates for malaria include air, ground, or water temperature (Paaijmans et al. 2009; Garske et al. 2013; Kleinschmidt 2001); rainfall, humidity, and soil moisture (Hay et al. 2000; Hoshen and Morse 2004; Kleinschmidt 2001); and vegetation greenness (as a proxy for soil moisture/water source) (Ayala et al. 2009; Kleinschmidt 2000; Thomson et al. 1999; Hay et al. 1998; Suzuki et al. 2006). Physical variables such as the location of water bodies, proximity to those water bodies, and elevation (Kleinschmidt 2000, 2001; Pascual et al. 2008; Minakawa et al. 1999; Ayala et al. 2009), are also important. A wide variety of socioeconomic covariates can be included, ranging from measures of poverty to population/settlement data, urbanization, land use, and land cover (Ayala et al. 2009; Thang et al. 2008; Vanwambeke et al. 2007; Tol et al. 2007; Hay et al. 2005; Omumbo et al. 2005; Snow et al. 1996).

Although the types of data needed for analyses are well known, in many cases these data are not yet standardized or accessible, and they vary in quality (Hay et al. 2000). Further, the spatial resolution of the data covariates are often disparate and mismatched (Gotway and Young 2002; Valle et al. 2011). Combining data of different types, scales, and resolutions is an open challenge (Gotway and Young 2002; Valle et al. 2011). However, efforts have been underway to make databases on parasite and vector distributions and disease available to the public (Moffett et al. 2009). Early efforts included the Mapping Malaria Risk in Africa (MARA), and now the Malaria Atlas Project (MAP) leads the way in compiling, synthesizing, streamlining, and geo-referencing datasets (Hay and Snow 2006; Le Sueur et al. 1997), including data on prevalence. The increasing availability of these data should expand the types of analyses that are possible, and improve fitting and testability.

## 10.3 MODERN MAPPING APPROACHES AND METHODS

Many quantitative approaches are available for modeling spatial processes and building maps, ranging from simple interpolation of point observations to complex spatiotemporal statistical models. A more complete overview of the wide variety of methods for the statistical analysis of spatial data can be found elsewhere (Cressie 1993; Stein 1999; Pfeiffer et al. 2008; Graham et al. 2004; Kitron 1998). Here, we review the methods that are available for spatial analysis of diseases in general; then we examine the methods that have been applied specifically to malaria, and evaluate their effectiveness.

### 10.3.1 Spatially Explicit Models

Spatially explicit statistical models seek to understand spatial patterns by modeling how observations relate to each other directly, sometimes without any covariates. Following Tobler's law of geography, the assumption is that observations that are located near to each other should be more alike than those that are far from each other. Models of this type include splines or smoothers, spatial clustering algorithms of various flavors (Cressie 1993), and kriging or Gaussian process (GP) regression (Stein 1999; Rasmussen and Williams 2006) (which are two names for the same approach). Most spatially explicit models that are applied for diseases in general, and malaria in particular, focus on modeling how climate or other factors influence transmission or prevalence and combine this with a spatially explicit model to allow localized deviations from what would be obtained from a regression model that does not include space (Brooker et al. 2004; Mirghani et al. 2010; Bousema et al. 2010; Yeshiwondim et al. 2009). One simple, if unsatisfying, way to do this is with a two-step process to first link malaria prevalence with climatic variables using logistic regression (Kleinschmidt 2000) or generalized linear mixed-effects models (GLMMs) (Kleinschmidt 2001), and then refining the model in space by kriging the residuals. This allows the model to take into account unmodeled local factors that could be affecting patterns of transmission, and improve prediction. However, by using a two-step process, there is a possibility that portions of the response are miscategorized as "noise" or "trend." Instead, a single model where both portions are fit simultaneously is more robust, though more computationally intensive.

More recently, Bayesian spatial models that consider both portions simultaneously have been applied for disease mapping (Best et al. 2005; Patil et al. 2011). Like classical methods, Bayesian approaches are likelihood based. However, they add a second component, the prior probability distribution, also called the prior. Bayes' rule is used to combine the likelihood with the prior in order to obtain a posterior probability distribution that is then used to draw conclusions about the data and model being considered (Carlin and Louis 2008; Clark 2007; Clark and Gelfand 2006). Bayesian methods have the advantage that uncertainty in parameter estimates and predictions are straightforward to obtain in the analysis, and external information (i.e., information outside of the data under immediate consideration) can be included through the prior distribution (Clark 2007).

Most of the Bayesian models for disease mapping, especially for malaria, fall under the classification of Bayesian "model-based geostatistics" (MBG), which extends regression models for spatial, non-Gaussian data using spatial GLMMs (Diggle et al. 1998) based on "Bayesian kriging." Applications are typically local scale, for instance within a single country or region, and tend to focus on either environmental (Kazembe et al. 2006; Gosoniu et al. 2009) or socioeconomic factors (Diggle et al. 2002) affecting measures of prevalence. Recent work by MAP models endemicity using MBG as well (Patil et al. 2011; Hay et al. 2009). This approach is used to categorize endemicity via parasite rate over space using a spatial model *without* any covariate information (Hay et al. 2009). Climate factors are only incorporated indirectly by limiting the model to be within "stable spatial limits of *P. falciparum transmission*"

(Hay et al. 2009) as determined in previous studies (Guerra 2007; Guerra et al. 2008).

One weakness of spatially explicit methods for disease mapping is that they usually assume that the response being modeled is stationary—that is, spatial correlation depends only on distance between locations, not on location itself. Various workarounds for this are possible. For instance, Gosoniu et al. (2009) divide space into chunks a priori and fit a separate spatial model in each section. However, more modern variants of GPs, such as treed GPs (Gramacy and Lee 2008), facilitate non-stationarity by dividing the space probabilistically, allowing the data to inform whether or not splits are needed, and then averaging over all likely splits. Another drawback of spatially explicit methods is that their computational costs increase rapidly as the number of observations increases and their performance can be poor when data are clumped (Cressie 1993). This relegates their utility to local scales. For continent-wide or global analyses implicit models are usually the better choice. However, as computation becomes less expensive, and easy-to-use tools more available, we expect Bayesian spatial models to become more commonplace.

### 10.3.2 Implicit Models

Most mapping and spatial modeling approaches for malaria, especially those that address continent-wide or global distributions, are implicit spatial models. Implicit methods link a modeled quantity with a set of covariates that are spatially dependent, such as environmental or socioeconomic factors. This can be done with a mechanistic model, such as a mathematical model for the basic reproductive number $R_0$ (see Section 10.3.2.2). More typically, a response, such as disease prevalence, is modeled by a statistical model, for example, regression (such as linear or generalized linear models (GLMs)) or classification (niche modeling, discriminate analysis, classification trees, etc.). Maps are then constructed by plotting the predicted value of the response at each location as a function of the values of the covariates that were included in the model. Thus, the predicted values of the response at various locations may exhibit spatial correlation and structure, but only when such structure already exists in the underlying covariates.

#### *10.3.2.1 Classification Methods*

Transmission outcomes are often categorized into endemic/epidemic/malaria free or simple presence/absence categories of disease, parasites, or vectors. Classification approaches are a way to integrate large amounts of data and try to associate specific combinations of environmental and socioeconomic conditions with specific levels of transmission or risk. For instance, "pattern matching" or discriminant analysis has been used to classify the climate factors associated with presence or absence of disease (Rogers and Randolph 2000, 2006) and to classify levels of the childhood parasite ratio (Omumbo et al. 2005). Another approach is classification trees (or classification and regression trees, CART), which predict classes or categories by creating recursive, axis-aligned partitions informed by the data (Breiman et al. 1993). CART has mostly been used for local-scale modeling of factors affecting individual

risk of infections such as wealth or other socioeconomic factors (Thang et al. 2008), malnourishment in children, location, or environmental covariates (Protopopoff et al. 2009; Sweeney et al. 2006). Although CART approaches have not been widely used for malaria, they are powerful and general approaches that deserve greater attention as an alternative to "expert opinion."

Ecological niche modeling (ENM, Hirzel et al. 2002), which refers to classification methods based primarily on environmental covariates, has become popular to describe geographical limits of disease (Peterson 2006). The goal of a niche model is to produce a set of rules that describe the distribution of species, specifically to understand geographical limits. The data modeled are simple presence/absence data, and a variety of inferential approaches can be used, from expert opinion (Guerra 2007) to sophisticated machine learning methods (Levine et al. 2004). For malaria, niche models are usually used to understand the environmental factors that constrain the distributions of malaria vectors for the parasite–vector complex more generally (Ayala et al. 2009; Moffett et al. 2007; Peterson 2009).

Closely related to the ENM is the "fuzzy logic" approach used by the MARA model that seeks to classify geographic areas as suitable or not suitable for malaria transmission (Craig et al. 1999; Ebi et al. 2005). Instead of the standard binary indicator of suitable/not suitable, this model uses a sigmoidal fuzzy membership curve to rank climate variables derived from spatially interpolated weather station data (Hutchinson et al. 1995) according to a scale of climate "suitability", where this scale ranges from 0 (not suitable) to 1 (completely suitable). The "fuzziness" indicates uncertainty in the spatial boundaries of transmission. Unlike other classification models, the MARA model uses nonlinear temperature responses for many (though not all) of the parasite and vector traits. However, the fuzzy logic, and other classification methods like the MARA model, do not model the magnitude of transmission within suitable areas.

MAP is the best known effort focusing on building comprehensive maps of malaria transmission. The goal of MAP is to overlay maps of estimated transmission on population distributions to indicate the number of people at risk. The main metric of transmission that MAP predicts is "parasite rate," or the incidence of infection in the human population, standardized to ages 2–10. MAP has developed a variety of techniques to refine its inferences of transmission. However, the backbone is a niche model classifying areas as stable/unstable/no risk of malaria (Guerra 2007; Guerra et al. 2008). MAP starts with medical reports of malaria at the country level, to determine which regions should be considered in more detail. Within countries where malaria is known to occur, surveys of malaria are used to estimate spatial distributions of risk. From this, estimated environmental limits of malaria transmission based on local annual temperature and aridity are developed. This is further refined using "medical intelligence" to identify specific areas, like islands or cities, that might not fit the larger regional patterns.

#### *10.3.2.2 Mechanistic Models of Malaria Transmission*

An alternative to the niche, pattern matching or statistical approaches is mechanistic models that link environmental factors with transmission/population processes. The

most common approach is to model pathogen transmission with an SEIR (susceptible, exposed, infected, recovered) or similar model, which describes the spread of disease through host and vector populations over time using coupled ordinary differential equations (Keeling and Rohani 2008; Mandal et al. 2011). The behavior of these types of models is summarized by the basic reproductive number $R_0$. The value of $R_0$ determines whether or not a disease invades and spreads through a naïve population (Diekmann et al. 1990; Dobson 2004).

Predicting the transmission of malaria over space and time is challenging because the mosquito vectors have a complex, stage-structured life history (Rogers and Randolph 2006; Tabachnick 2010). This means that environmental factors such as temperature and precipitation can influence disease dynamics in multiple ways. One solution is to embed a stage-structured model (Dobson et al. 2011) of mosquito population dynamics in the standard SEIR framework (Anderson and May 1991; Rogers and Randolph 2006). However, this makes the model analytically intractable, preventing extrapolation of local transmission dynamics across geographical space. A simpler approach is to model the dependence of the $R_0$ equation on environmental factors directly (Mordecai et al. 2013; Molnár et al. 2013). $R_0$ has been shown to be well correlated with actual disease prevalence (Smith et al. 2007), and it is relatively easy to estimate (Keeling and Rohani 2008).

Consider a commonly used form of $R_0$, derived from MacDonald's extension of the Ross model (Ross 2006; MacDonald 1957):

$$R_0 = \frac{Ma^2bce^{-\mu E}}{Nr\mu}. \tag{10.1}$$

Here, $M$ is mosquito density, $a$ is the per-mosquito biting rate, $b$ is the proportion of bites by infective mosquitoes that infect susceptible humans, $c$ the proportion of bites by susceptible mosquitoes on infectious humans that result in mosquito infection (and thus $bc$ is a measure of vector competence), $\mu$ is adult mosquito mortality rate, $E$ is incubation period of the malarial parasite in mosquitoes, $N$ is human density, and $r$ is the rate at which infected humans recover and acquire immunity.

Other quantities, such as the ratio of vectors to hosts required for disease persistence, transmission or epidemic potential (TP, EP), and vectorial capacity, can also be used to understand the spatial distribution of malaria (Rogers and Randolph 2006). For instance, Martens et al. developed the MIASMA model based on TP to examine the spatial distribution of malaria (and other vector-borne diseases), and the impact of climate change in the distribution (Martens et al. 1995, 1997, 1999). TP has also been used to determine suitability thresholds ((van Lieshout et al. 2004); see (Rogers and Randolph 2006) for an in-depth critique of this approach). These alternative measures can have advantages in that their simplifying assumptions allow us to ignore components of the process for which data are not readily available (such as the size of the mosquito or human population). However, their interpretability can be more difficult as they provide relative, rather than absolute, measures of transmission.

$R_0$ can vary across the landscape because the ambient temperature influences the physiology of mosquitoes and the plasmodium parasite. While the models we mention

use mean temperatures, temperature variation can also affect the transmission of vector-borne diseases (Paaijmans et al. 2009; Lambrechts et al. 2011; Molnár et al. 2013). Temperature-sensitive malaria models vary in complexity. Many are primarily static models of transmission measures (e.g., EP, (Martens et al. 1997); a fraction of vectors surviving parasite development (Craig et al. 1999); or $R_0$ (Parham and Michael 2010; Mordecai et al. 2013)). More complex dynamic transmission models that include temperature have also been developed (Hoshen and Morse 2004; Pascual et al. 2008; Ikemoto 2008; Alonso et al. 2010; Gething et al. 2011a; Ermert et al. 2011; Lunde et al. 2013). The models are also differentiated by the parameters they treat as temperature sensitive, how mosquito population size responds to temperature, and how rainfall is included (Craig et al. 1999; Hoshen and Morse 2004; Parham and Michael 2010; Alonso et al. 2010; Ermert et al. 2011). They tend to share the common assumption that most rates increase monotonically with temperature, following degree-day or Detinova functions (Detinova 1962; Craig et al. 1999). They also tend to ignore the important effects of temperature variation.

Although monotonic functions are attractive for their simplicity, most life-history traits of ectotherms show a unimodal response to temperature because they are directly determined by metabolic rate (Huey and Berrigan 2001; Thomas and Blanford 2003; Frazier et al. 2006; Deutsch et al. 2008; Dell et al. 2011; Amarasekare and Savage 2012). A recent study showed that all mosquito and parasite traits involved in malaria transmission peak at temperatures between 25°C and 35°C (Mordecai et al. 2013); and several previous models have demonstrated this unimodal relationship between temperature and malaria transmission (Martens et al. 1997; Craig et al. 1999; Parham and Michael 2010; Mordecai et al. 2013; Lunde et al. 2013). As a result, malaria transmission is expected to peak at a temperature warm enough for fast development but not so warm that mosquitoes die before they can transmit the parasite.

There is still substantial variation in how authors model the response of parameters to temperature. A relatively simple way to capture the unimodality and asymmetry of thermal responses of traits underlying $R_0$ (Equation 10.1) is with the Brière equation:

$$B = B_0 T(T - T_0)\sqrt{(T_m - T)}, \tag{10.2}$$

where B is the trait value, $B_0$ a constant, $T$ is temperature (°C), $T_0$ is the minimum temperature for the trait, and $T_m$ is the maximum temperature. Equation 10.2 is purely phenomenological, with none of the parameters having an explicit, mechanistic, metabolic interpretation. A more mechanistic model would be unimodal extensions of the Boltzmann–Arrhenius (BA) equation for the thermal response of rate-limiting metabolic enzymes (Dell et al. 2011; Amarasekare and Savage 2012). Which equation to use depends upon the objectives of the study. The advantage of the Brière equation is that it is more analytically tractable than unimodal extensions of the BA equation (Dell et al. 2011; Amarasekare and Savage 2012). Whatever the approach, incorporating physiological constraints directly into $R_0$ can provide important insights into existing empirical patterns of malaria transmission predictions of future changes (Mordecai et al. 2013; Molnár et al. 2013). For example, Mordecai

et al. (2013) found that using unimodal instead of linear responses lowers the predicted optimal transmission temperature from 31°C (Parham and Michael 2010) to 25°C, a value consistent with field transmission data (Martens et al. 1997; Craig et al. 1999). Such efforts to more realistically incorporate physiological responses to temperature can greatly alter maps of transmission suitability (Gething et al. 2011a; Ryan et al. 2014).

The importance of temperature fluctuations for transmission in malaria is increasingly well accepted. Fluctuations can increase transmission at marginal temperatures, reduce transmission at the optimal temperature, and even change the optimal mean transmission temperature if the thermal response of transmission is asymmetric (Paaijmans et al. 2009; Lambrechts et al. 2011; Molnár et al. 2013). To make more accurate predictions, malaria transmission models must include physiologically accurate thermal responses to daily, seasonal, and interannual variation in temperature. Further, it has been widely recognized that local adaptation can result in differences in the thermal responses between species and even within species in different areas (Joy et al. 2008; Harris et al. 2012). While phenomenologically more accurate, the increasing complexity of this type of modeling quickly loses generality in projecting over larger areas.

Using mechanistic models to build predictive maps can have many advantages. For instance, they can be used to predict gradations in severity that are not feasible with classification methods. Further, since they are built from first principles and usually parameterized from lab data, they can be validated with independent field data. Maps built with mechanistic models are ideal for indicating potential distributions under future climate scenarios as they are tractable and explicitly link key biological processes and abiotic factors. Their utility beyond this is constrained by two major weaknesses. The first is that all mechanistic models are simplifications of biological systems, and there is always the chance that important processes, such as economics, or land-use patterns, have not been included, impairing their predictive power (Rogers and Randolph 2006). The second is that it is difficult to generate measures of risk in the same currency as available data. Even so, process-based models will remain important tools for developing spatial models as they are the only way to quantitatively understand the connections between climate and biological variables, and to explore quantitative effects of intervention strategies (Rogers and Randolph 2006).

### 10.3.3 Hybrid Approaches

A hybrid approach to malaria mapping combines a mechanistic transmission model with statistical or niche-based spatial modeling. The most comprehensive modeling of this type is performed by MAP (Gething et al. 2011b). We use the specific approach by Gething et al. (2011b) as an example of an effort to assemble the multiple lines of inference discussed above, including mechanistic modeling and implicit and explicit spatial modeling, to create a single, hybrid map for the global distribution of falciparum malaria transmission.

The approach of Gething et al. begins by revisiting their previous analysis (Guerra 2007; Guerra et al. 2008) to describe the limits of stable/unstable/no risk falciparum

malaria transmission using improved (implicit) methods and extended datasets. Then, as in Hay et al. (2009), they use a Bayesian model-based geostatistical approach to make a spatial prediction of the intensity of transmission, as measured by parasite rate, PR, within the regions of stable transmission. They obtain posterior distributions over the map, which allow understanding of uncertainty in this prediction. Gething et al. (2011b) then use complex models to connect PR to two other measures of malaria transmission that have their basis in mechanistic models—Entomological Inoculation Rate (EIR) and $R_c$ ($R_0$ under current control efforts). Using independent data, they infer the model parameters that link PR, EIR, and $R_c$ to each other. They then use the posterior distributions of PR from the Bayesian analysis with the mechanistic component to obtain posterior distributions of EIR and $R_c$. Thus, they take three distinct modeling approaches—mechanistic, implicit spatial modeling, and explicit spatial modeling—and combine them into a single, powerful analysis.

MAP has been successful in producing global maps of falciparum transmission that can be updated in future years to track changes in the distribution of malaria. A strength of their approach is the use of data for validating model predictions and on understanding uncertainty in these predictions. However, they do not aim to identify the environmental factors that determine the level and severity of transmission as part of either the mechanistic or spatially explicit statistical portions. This may be due to the fact that computational costs for spatially explicit analyses using methods such as these typically scale with the cube of the number of data points. Further, the climate factors that determine transmission are effectively decoupled from their mechanistic model—climate factors are used only in the initial classification step, but not incorporated in the mechanistic model. Thus, this *particular* hybrid approach is not well suited for predicting the future spatial extent of malaria under climate change or developing spatial control strategies. Despite this, their hybrid framework is a good example of the direction we expect the field to move in the near future.

## 10.4 FUTURE DIRECTIONS AND CONCLUSIONS

Malaria transmission depends on many biotic, abiotic, and socioeconomic factors, and understanding how all of these factors interact to produce observed patterns of malaria in space and time is an important challenge. An expansive literature of techniques developed to understand these patterns has grown over time. Different approaches are suitable for different questions and at different scales. With increases in computing power and access to spatial data, the sophistication and utility of malaria maps will continue to improve.

However, there are still many unanswered questions, particularly with respect to how to use tools for prediction and understanding in the face of climate change. For instance, as climate changes, we expect an increase in both mean temperature and variability of temperature, as well as an increase in the incidence of extreme weather events with associated increases and decreases in the distribution and severity of malaria (Lafferty 2009). This may mean that more severe and frequent epidemic

malaria could occur at some locations, with significant policy implications. However, much current modeling work focuses on understanding the limits of endemicity (Guerra 2007; Guerra et al. 2008; Hay et al. 2009), and many of the tools that are developed for this purpose are not appropriate for understanding epidemic malaria. Instead, approaches that have been developed for other diseases, especially those that include mechanistic modeling, should be adapted (Grassly and Fraser 2006; Pascual et al. 2008; Alonso et al. 2010).

One key challenge is to add economics into statistical and mechanistic models of malaria. The observed distribution and intensity of malaria is a consequence of poverty and ecological constraints (Gallup and Sachs 2001) as they act as strong controls on disease (e.g., Béguin et al. 2011; Snow et al. 1996; Tol et al. 2007; Hay et al. 2005). This combination of environmental and socioeconomic controls, as well as changes in drug resistance, land-use/urbanization, and climate makes for extremely high spatial heterogeneity of malaria transmission (Snow et al. 1996). The human factor—evolving resistance of the parasites to malaria drugs and vaccines, or the vectors to pesticides, repellents, and climate, and the impact of intervention strategies more generally—has been tackled in few mapping studies to date or has only been addressed separately from climate factors.

Understanding the factors that influence transmission, especially climate, is the focus of most studies discussed here. What is less generally discussed are the big methodological issues of what to model and what approach to take. These choices are, of course, driven by the particular questions being explored by the model and the spatial and temporal scales of interest. However, we argue that an emphasis should be placed on hybrid models that incorporate data-driven mechanistic models for biotic elements together with statistical models to improve prediction. The inclusion of mechanistic models is key for two reasons. First, good mechanistic models are preferred for making predictions outside the range of observed data (Rogers and Randolph 2006; Bayarri et al. 2009). Further, human interventions have "decoupled" climate from transmission in many parts of the world (Gething et al. 2010), making statistical models (or niche-type models) less reliable for identifying key climate drivers. Combining approaches will be especially important for making predictions of large-scale spatial patterns—across countries or continents—in the face of climate change. It also allows the consideration of variation in traits between species or populations of vectors and parasites in a straightforward way. However, for local-level analyses including the mechanistic models of transmission may be less important because socioeconomic factors are more likely to dominate.

In the previous section, we discussed the approaches of MAP, which demonstrates the power of current hybrid methods. The more recent combination of mechanistic models and Bayesian inference is a powerful tool as it allows the quantification of uncertainty in both parameters and processes and the inclusion of prior information (Clark 2007). Understanding uncertainty is especially important for effective and efficient control of infectious diseases (Merl et al. 2009). Another promising approach that allows this kind of hybrid modeling is structural equation modeling (SEM), which provides a straightforward way to combine mechanistic (or generally causal) models with likelihood-based inference (Grace et al. 2012).

Regardless of the particular approach or scale, we argue that there are two key considerations that should be emphasized in any mapping of malaria: transparency and testability.

### Models and Maps Need to be *Transparent*

Maps developed from "expert opinion" or medical intelligence are very useful, but difficult to reproduce or assess for reliability. It is not clear how to improve this aspect of malaria modeling without calling for systematic reporting within and among nations. For maps developed through statistical or modeling methods, details of the methodology and open-source code should be standard practices. As for all scientific products, the aim should be to allow the reader to repeat the methods used to create the map.

### Models and Maps Should be *Testable*

Many models (especially mechanistic ones) are difficult to test directly, but doing so allows a better understanding of what drives malaria transmission. For mechanistic models, connecting modeled quantities with data (e.g., $R_0$) is difficult, or the data are not available. For statistical models it is usually the latter case—there are limited data available and thus partitioning data for training and testing is not feasible. Further, subsampling spatial or temporal data has its own issues, whereby the scale at which the data are subsampled can obscure correlation structure (Hall 1985). One way to facilitate model testing is to make databases of malariometric and physiological data publicly (and freely) available, and simultaneously develop "standard" datasets at multiple scales (local, country, continental, and global) for both training/fitting and testing of models to allow the efficacy of different methods to be compared. Some of the detailed and robust maps of current malaria transmission being developed by the MAP collaboration may fall into this category. Further, a focused effort to develop sets of standardized and policy relevant measures of prevalence, transmission, and risk would provide a framework enabling researchers to test and compare their predictions in a more transparent way while giving policy makers more usable information.

To conclude, there are few diseases more important to map than malaria. Different mapping efforts have increased our understanding of the spatial distribution of malaria, and the reasons behind the spatial distribution. With better knowledge about what drives the geography of malaria, we can make maps of how transmission will change in the future. Developments in remote sensing, data sharing, mapping techniques, and statistical methodologies will lead to more accurate and instructive maps. These maps will make it easier to target interventions, and, we hope, help further global decline of malaria.

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