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From puddles to planet: modeling approaches to vector-borne diseases at varying resolution and scale

Philip A Eckhoff[1], Caitlin A Bever[1], Jaline Gerardin[1], Edward A Wenger[1] and David L Smith[2,3]

Since the original Ross–Macdonald formulations of vector-borne disease transmission, there has been a broad proliferation of mathematical models of vector-borne disease, but many of these models retain most to all of the simplifying assumptions of the original formulations. Recently, there has been a new expansion of mathematical frameworks that contain explicit representations of the vector life cycle including aquatic stages, multiple vector species, host heterogeneity in biting rate, realistic vector feeding behavior, and spatial heterogeneity. In particular, there are now multiple frameworks for spatially explicit dynamics with movements of vector, host, or both. These frameworks are flexible and powerful, but require additional data to take advantage of these features. For a given question posed, utilizing a range of models with varying complexity and assumptions can provide a deeper understanding of the answers derived from models.

Addresses
[1] Institute for Disease Modeling, 1555 132nd Ave NE, Bellevue, WA 98005, USA
[2] Spatial Ecology and Epidemiology Group, Department of Zoology, University of Oxford, Oxford OX1 3PS, UK
[3] Fogarty International Center, National Institutes of Health, Bethesda, MD 20892, USA

Corresponding author: Eckhoff, Philip A (peckhoff@Intven.com)

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Introduction

Modeling mosquito transmission of pathogens has a long history starting with the foundational work of Ross [1] and Macdonald [2,3], who established the mathematical formalisms for modeling the transmission of malaria between a vector and a host population [4]. The Ross–Macdonald model identifies five key quantities: mosquito population density, mosquito survival probabilities, mosquito blood feeding frequency, mosquito host preferences, and parasite development in mosquitoes. This basic model was extended first for modeling the Garki project [5] and later in the cyclical feeding models [6,7]. From 1970 through 2010, there was a rapid proliferation of mathematical models of vector-borne disease, but most of these models retained the basic Ross–Macdonald structures and assumptions, as cataloged and analyzed in the comprehensive review by Reiner *et al.* [8••].

As described in that review [8••], several of the simplifying assumptions of the Ross–Macdonald model structure become important to address including well-mixing of vectors and humans, representation of the aquatic stage ecology, spatial dynamics, multiple vector species, and heterogeneous biting rates. Over the past decade, several new model structures have emerged that build off of the foundation built by Ross and Macdonald but extend modeling of vector transmission to new levels of realism. These are described below, and range from improved representation of larval aquatic habitat driving transmission [9,10] to continental-scale maps for the distribution of important vectors [11,12] or parasite and transmission rates [13]. As analyses range in scale from puddle to planet, one of the biggest challenges has been to model transmission at intermediate spatial scales, and this review examines several new model frameworks that have been recently developed to address this challenge.

Elaborations on Ross–Macdonald

Even though Ross and Macdonald developed their models by 1910 and the 1950s, respectively, recent work has continued to elaborate details and implications of theory based on these established model structures [4]. Work by Smith and McKenzie demonstrated that the effect of adult vector mortality may be even greater than that predicted by Macdonald [14]. Recently published work by Brady *et al.* demonstrates the importance of larval populations and the impacts of adult mortality and combined interventions including larval control on both juvenile and adult populations and ongoing transmission [15]. At much broader spatial scales, transmission rates varying by location can be estimated from mapped estimates of parasite rate using Ross–Macdonald theory [13].

Implicit assumptions in standard Ross–Macdonald theory involve details of the vector life cycle including population densities and simple descriptions of adult feeding behavior. Recent mathematical models have relaxed these assumptions and introduced a new level of detail

and realism to vector-population simulations. Depinay *et al.* developed a model framework with exceptional realism in the mosquito life cycle, with full representation of aquatic stages and explicit responsiveness to temperature in both larval and adult life stages [9], with potential to add in spatial structure. Bomblies *et al.* went even further with a detailed, spatially explicit hydrology simulation of puddle and pond formation and volume, with explicit effects of temperature, rainfall, humidity, soil, and slope [10]. Another model framework maintained this explicit aquatic stage and detailed feeding behavior, but added in the ability to track multiple species simultaneously, with the potential for each to have separate larval ecology responses to rainfall and feeding preferences [16].

Detailed feeding behaviors such as feeding location and host preference can also be important details of the transmission system, especially in the context of introducing interventions such as insecticide-treated bednets (ITNs). Host-selection in the presence of alternate hosts was described in a model framework built on a cyclical adaptation of Ross–Macdonald theory [17]. The impact of shifts in vector behavior for feeding location, timing, and host preference on interventions was recently explored in even more depth [18•]. Detailed feeding behavior by species in the contexts of multiple species is explored in [16] and this framework was recently used to explore the effect of feeding behavior on the impact of combined interventions [19]. Competition between species in the larval stage is being studied [20], along with the impact of sugar-feeding behavior [21].

Filling in the intermediate spatial scales

Between the scales of the very short spatial-scale aquatic habitats modeled in mechanistic detail [10] and the global patterns of mosquito species habitat [11,12] lie many spatial scales containing important dynamics. Two generalized model concepts that facilitate questions at scales between puddles and the planet are patch models [22] and continuous space models (Figure 1). Patch models function as metapopulations dividing landscapes into smaller subareas, or 'patches.' Hosts and vectors within the same single patch can interact strongly, and connectivity on the landscape is determined by weaker interactions among patches occurring through time spent at risk by hosts, or migration of hosts, vectors, or both [23]. Other frameworks utilize a continuous space in which feeding and oviposition locations are single points. The relationship between continuous space and patch models can be seen in Figure 2.

Successfully extending beyond non-spatial or single-patch dynamics, in which all vectors and hosts in the model are able to interact, to higher-spatial resolution or

Figure 1

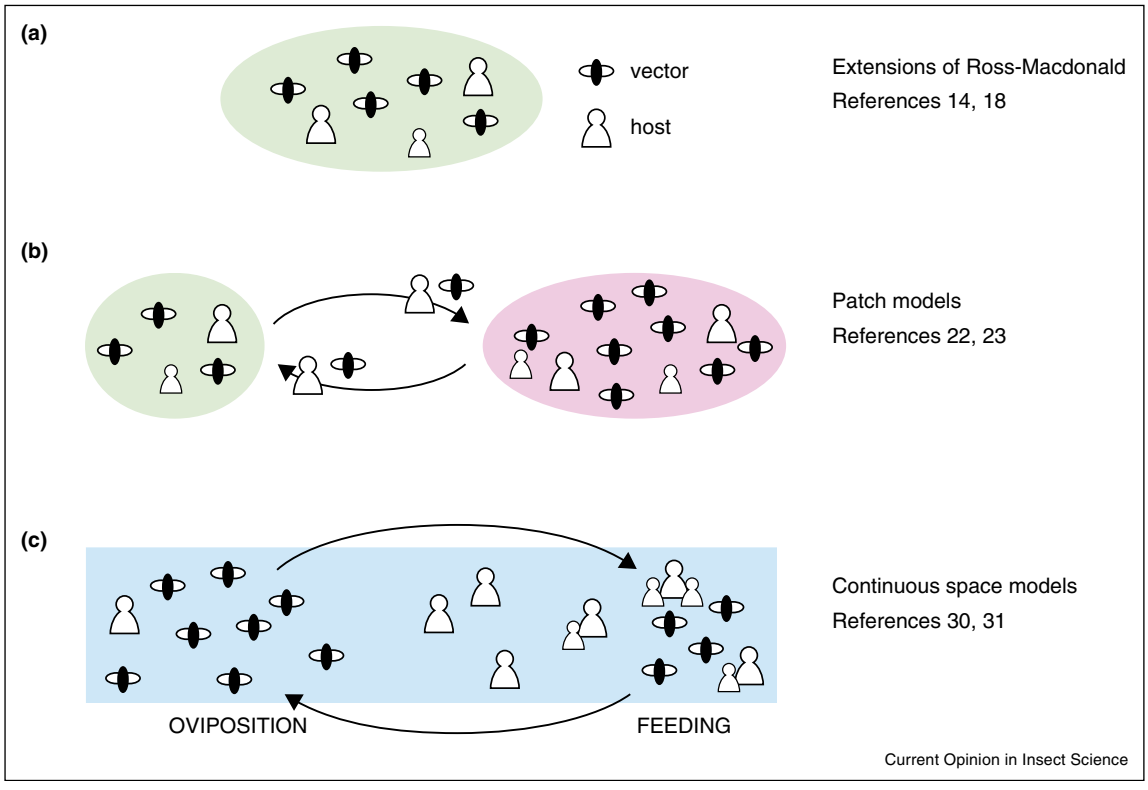
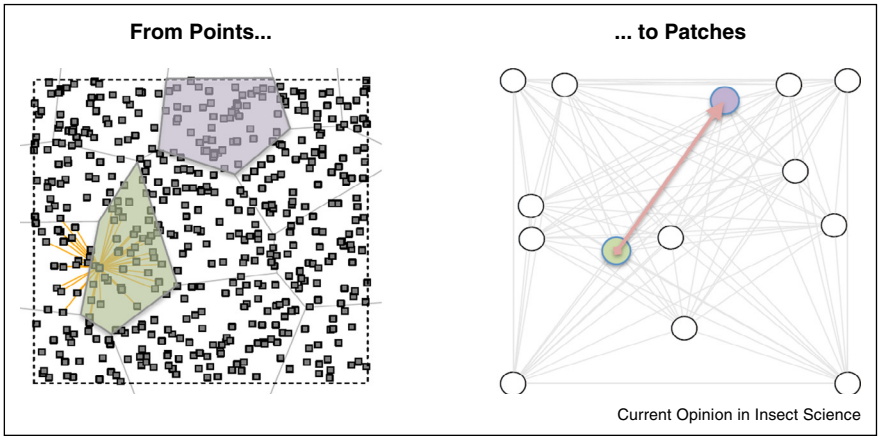


Illustration of single-mixed population extensions of Ross–Macdonald, patch models, and continuous space models.

Figure 2



An example of a tiling process to move from points in continuous space to patches.

broader geographic extents requires careful addressing of the spatial scales of transmission. What is the patch size, within which one can assume all hosts and vectors can interact, with heterogeneity of biting rate a potential additional feature within this scale? How are patches connected through movement of hosts and vectors, and what spatial and temporal resolution is required for accuracy?

A patch framework can facilitate the implementation of heterogeneity within and across patches. Within a single patch, the variation of biting by age and body surface area and the impacts on transmission and the patterns of clinical disease were explored [24]. Heterogeneous biting, in which a subset of individuals within a local area receive a disproportionate share of mosquito feeds, was explored for its impact on transmission and interventions [25]. Patches can facilitate implementation of models for spatially varying transmission intensity, often known colloquially as 'hotspots,' and the impact of focusing control efforts on hotspots was modeled [26] using extensions of a model for malaria transmission and combined interventions [27]. The effects of spatial heterogeneity on the impact of larval source management can be modeled with an elegant and simple implementation of multiple habitats for oviposition [28].

The previously discussed mechanistic hydrology model framework [10] is spatially explicit. In the original application, it was constructed for a single village with spatial resolutions ranging from 10 m at the center to 80 m at the edges of a 2.5 km^2. Heterogeneous soil and slope determined the puddle dynamics, and vectors connected the landscape through host-seeking dynamics driven by wind and CO_2 plumes. After the original parameterization to a single village, this framework was able to be ported to another village in the Sahel and capture the dynamics there with good fidelity [29]. This framework for malaria can work very well in landscapes with well-understood soil and slope mapping and transmission driven primarily by *An. gambiae s.l.*, although the computational and data challenges and other assumptions in the model may limit the scaling much beyond villages.

In the context of these questions of appropriate spatial scale and the difficulties of parameterizing more fully detailed or mechanistic hydrology-driven models, Perkins *et al.* created a generalized spatial framework for vector-borne transmission [30••]. This model is continuous in space, with a set of points for possible feeding locations and oviposition sites, with movement allowed for both vectors and hosts. Mosquito movement is driven by alternation of feeding and oviposition, with a spatial dispersion of hosts and vectors determined by their respective kernels. This framework can be parameterized to match a given landscape along with locally applicable data-driven functions for host and vector movement in order to explore vector-borne transmission at a variety of spatial scales.

Another continuous space framework was developed by North *et al.* to study the spatial spread of homing endonuclease genes in a mosquito population [31••]. This framework has vectors that move between blood-feeding and oviposition locations that can change over time in response to stochastic and seasonal dynamics. This framework was used to show the impact of varying the density of larval sites, the density of blood-feeding sites (houses), and the degree of clustering or dispersion of houses.

The past half-decade has been an era of remarkable expansion in the available model frameworks for simulation of these spatial dynamics, beyond those mentioned so far. Skeeter Buster extends previous dengue models to be spatially explicit and stochastic [32,33] with the ability to incorporate genetic structure [34]. It implements a list of house and breeding container locations to define the

landscape. The mechanistically detailed vector-borne transmission model for multiple vector species [19] can be simulated spatially as a patch model. A spatial model built to analyze the potential impact of a dengue vaccine [35] represents houses and workplaces within a 20 km × 30 km region, with houses placed randomly within 1 km^2 based on population density. Vector distribution can be heterogeneous, and vectors can move to adjacent locations [36•].

Measuring mosquitoes for control

Increasing realism in models has been accompanied by development of new methods for disease control. The great number of possible interventions inevitably raises questions about how they could be optimally deployed or combined. The increased degree of realism and its spatial dimensions in multiple independently derived models has also come with alternative ways of representing adult mosquito behaviors relevant for control, including searching for places to feed or lay eggs, resting between flights on substrates of various kinds, mortality occurring as a result of these activities, host choice, and insecticide detection and avoidance. Modeling studies link these behaviors to transmission and highlight their importance for control, but they also raise questions about the adequacy metrics commonly used to measure mosquitoes.

These expanded descriptions of adult mosquito behavior could help to explain variability in the responses to interventions deployed in combinations in different ecological settings. Mosquito searching and resting behavior during blood feeding could determine, for example, how well insecticide treated bednets or spraying work alone or in combination in different ecological contexts, or with insecticide resistance. The number, carrying capacities, permanence, connectivity, and ecology of mosquitoes and their predators or competitors in larval habitats affect the intrinsic growth rate of mosquito populations and benefits of genetic modification of mosquitoes, responses to adult vector control, and larval source management. Other behavioral parameters affect the probably success of oviposition traps, area repellants, and toxic sugar baits, and other parameters.

The phenomenological approach of the Ross–Macdonald model provides little basis for understanding how the parameters vary in different ecological settings and under various modes of control, and answers are unlikely to come from purely empirical approaches. Despite one century of mark-release-recapture studies of mosquitoes, for example, the evidence base to address questions about parameter values in different contexts remains thin [37•]. Beyond responses to temperature and humidity, which can be measured in the lab, what determines survival probability and feeding rates of mosquitoes in different ecological contexts? A careful reconsideration of the basic parameter set considered important for control could help unify the study of transmission dynamics and control in the field and *in silico*.

Conclusions

The explosion in models of vector-borne diseases has recently begun to include a broader set of frameworks for modeling spatial effects and dynamics that include spatially heterogeneous landscapes knit together by host and vector movement. Moving beyond models of a single population of vectors mixing with a single population of hosts to capture spatial dynamics and variability requires data on human and mosquito movement [38], human population patterns [39], and pathogen distribution at broad geographic scales [13,40] or within-city microscales [41]. This review has focused on framework details for vector life cycle, behavior, distribution, and movement, but depending on the question being posed to models, more detail on the infection and immunity component beyond the basic Ross–Macdonald framework may be required. Driven by this necessity, there have been strong recent advances in models of infection and immunity for malaria [42•,43,44,45•,46] and dengue [47–49].

It is important to bear in mind that much model complexity may not be relevant for a given question posed, and thus choosing the question-appropriate level of complexity, detail, and realism is essential. It is also important to remember that relevant insights can often be obtained from very simple models or analytic structures [50]. Exploring the same question with models of varying complexity and assumptions can thus cross-check the results and implications and result in a deeper level of understanding. As such, an essential next step given the recent advances in spatial modeling frameworks for vector-borne disease will be to map results across multiple frameworks.

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