Applied Malaria Dynamics

Dynamical Systems for Adaptive Malaria Control

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Foreword

A large fraction of my time over the past 20 years has been devoted to learning about malaria epidemiology, mosquito ecology, and vector control. All the time, I was building and analyzing models that described malaria, or some topic related to malaria. I was looking for a way of organizing and applying the rich body of theory that has been developed over more than a century of malaria research. I wanted a framework that was *extensible* with *plug-and-play* modularity. I wanted models that could scale down for fine-grained simulations, or to scale up to understand regional spatial patterns. To serve the needs of malaria programs, we needed a way of discussing malaria as a changing baseline that was modified by control, so we needed to understand exogenous forcing by weather and vector control. To get integrated malaria control right, we needed to go all in on mosquito ecology. We wanted the software to use the existing theory for malaria spatial and temporal dynamics. Sometime in the fall of 2022, the last few pieces came together, and it was time to write this book.

This book is about applying malaria models. The book fills the gap that comes after an introduction to mathematical epidemiology or infectious disease modeling. What are all the special topics that a student needs to know to be of use in malaria? There will probably never be enough graduate students who are interested in applied malaria dynamics to teach a class on the topic at any university, but if you add it up across the planet, there is a need.

We assume the reader has a solid background in infectious disease models. We assume they've seen the Ross-Macdonald model before. We also assume that the reader will have some technical gaps that they might need to fill. This book does not try to fill those gaps. Instead, we have written some vignettes and lessons to accompany the book.

David L. Smith

Part I

Introduction

Chapter 1

Dynamics for Policy

Malaria is complex and heterogeneous, which makes it difficult to study and manage. A core challenge in both science and policy is the availability of information. Mathematical models can help us understand and analyze all that complexity and make informed decisions despite the data gaps.

In basic research, we develop mechanistic models to understand malaria as a biological process. In malaria epidemiology, the states and parameters describe infection, immunity, infectiousness, disease, and drug taking in response to exposure. Scientists focus on basic biological mechanisms in order to understand differences in malaria across spectrum of transmission. Immunity and drug-taking are important factors to consider, but it may be that differences in epidemiology and disease across settings arise from differences in the local parasite populations. The models are a way of summarizing knowledge in a quantitative form – something like a complex hypothesis. A test of a model's adequacy is whether it can describe malaria accurately after accounting for differences in drug taking patterns and pattern of exposure.

We study mosquito ecology and blood feeding to understand malaria transmission and develop theory for malaria control. Transmission models couple parasite infection dynamics in humans and mosquitoes through blood feeding. Mosquito populations are shaped by the aquatic habitats for immature mosquito populations – standing water bodies shaped by topography, hydrology, land use, and the water chemistry shaped by surrounding rocks, soils, vegetation and pollution. These habitats are filled (exogenously forced) by rainfall and after some eggs are laid, the mosquito dynamics are affected by crowding, predation, and other endogenous dynamics. Larval development and parasite development rates are modified by temperature. Adult mosquito activity rates are affected by temperature and relative humidity. Indoor residual spraying kills mosquitoes when they rest on a sprayed surface, usually after blood feeding or during the process of searching for a host. Insecticide treated nets protect humans from

biting and kill some mosquitoes. By reducing the availability of potential blood hosts, nets can slow blood feeding in some contexts. Larval source management reduces immature population densities.

By studying mosquito ecology and malaria transmission dynamics, we can start to understand malaria as a changing baseline that has been modified by malaria control. This is the problem confronted daily in malaria programs, but it requires a synthesis. The models help translate evidence into information that can be used to make decisions, to make strategic plans, and to mark progress against strategic plans. The models encapsulate information about transmission in context, so it is possible to study how malaria persists in a place over time, and how various factors have modified (or could modify) mosquito population dynamics and blood feeding and thereby suppress transmission. Transmission models help us to set intervention coverage targets based on thresholds.

In policy, we use these models with the expectation that – if we fit the models by adjusting parameters that affect how malaria works in some particular place – they *should* help us understand transmission in some particular context and make good decisions about what to do.

Frustratingly, the heterogeneity and the complexity conspire against us. We would like to be sure about how malaria works across settings before we start using the models to stratify populations, tailor interventions to context, or targeting the interventions. Instead, we must admit that we don't know everything we'd like to, and we probably never will. We must proceed with policy without having satisfactory answers to some basic questions. The models make it possible to fill in the gaps in various ways and evaluate the consequences of having missing data, to assess what missing data would have the biggest effect on malaria, and (ideally) to find a way of filling critical knowledge gaps.

To understand malaria or to give policy advice, we must start simple and then add complexity, layer on layer. To deal with missing information, we start with generic models, and then add details to address concerns about some of the details that we hope to identify by studying the systems as we intervene. This approach – starting simple and then layering on complexity – makes it possible to learn as we go. A question is when it stops making sense to add realism to a model. A model that it too simple and abstract might help us understand the basic dynamics and give generic advice, but we would question the model's adequacy if it can not reproduce the patterns we care about in some particular place at some particular time. As a rule of thumb, a model should be just complex enough to *describe* the patterns we care about and give advice. Practically speaking, it's hard to know you've gone far enough unless, at some point, it's clear that you've gone a bit too far.

Over the past few years, we developed a new framework for building models that would make it possible to start simple and then build models of malaria transmission at any level of complexity. We wanted to be able to build in realism by adding complexity one feature at a time. Through this process we can create

nested, hierarchical models in branching chains. At the ends of the chains, we might find highly realistic models that are, perhaps, overfit. (The cautions against overfitting play out differently if you must act now but also could go out and collect new data.) We call the framework's ability to do this **scalability** and the resulting swarms have **scalable complexity**.

To make this possible, we needed modular software with *plug-and-play* functionality and a high degree of structural flexibility. We needed the framework to be extensible. After making a lot of mistakes, the primary design phase is over, and the algorithms have been published in two software packages. We are currently extending the library of *base models*, which includes some simple or classical models that are instructive or of historical interest. We are also fine-tuning the design requirements for models as we develop protocols that streamline fitting models to data. The software avoids the mistakes we made over the past few years, reuses models, and streamlines the model building process. We hope this software has dramatically lowered the costs of building and analyzing these complex, realistic models.

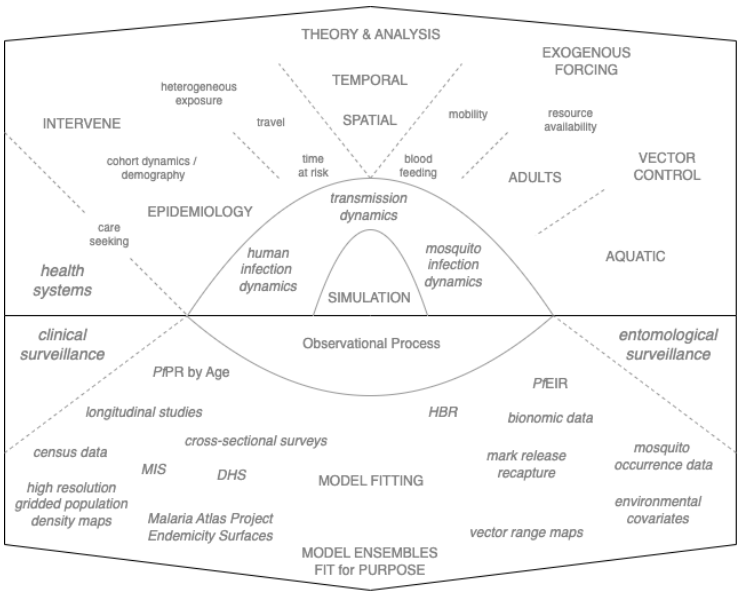


Figure 1.1: A schematic diagram of the elements in the framework (top half) and the process of model building and model fitting (bottom half)

This book has been written to introduce the features of the framework (see Figure 1.1). The book itself is embedded in the RAMP-Model-Library, which was set up during the primary design phase. The RAMP-Model-Library is where we made all our design mistakes: was the software truly plug-and-play, and was the framework truly extensible? As the primary design phase came to a close, the library that was once the laboratory became a classroom and a museum.

The library is being transformed into a resource for any developer who wants to add new base models to the library or add functionality. Most of all, it is being set up for the end user, someone in a malaria program or working with a malaria program who wants to use simulation based analytics to analyze policies. This book is structured into a set of lessons that teach concepts. Some of the concepts build on one another, and others take on new challenges. We combine these lessons into some examples where we show some algorithms to build models fit for purpose. When a topic deserves a deeper dive, we have supplemented this book with vignettes or lessons.

In malaria epidemiology (narrowly defined as a study of infection and disease in humans), the relationship between exposure, infection, immunity, disease, and infectiousness changes in populations as they age, and it is affected by drug taking. This picture grows more complex as we consider intervening with vaccines or monoclonal antibodies, or as we look at interactions with anemia, nutritional status, and human genetics. Our models need to interface with data from clinical settings and research, so they will need to consider diagnostics, parasite counts, detection, and transmission. Combining these factors can give rise to an overwhelming amount of complexity. We have developed some new models that manage the complexity. While these models are suitable for computation, we still need to understand and explain some of the basic relationships.

We are interested in using these models to guide policy, which requires both solid computation and good communication. In this book, we lay a foundation for understanding the complexity by studying some simple compartmental models. We will review classical queuing models for superinfection and the multiplicity of infection (MoI); new models for the age of infection (AoI) or stage of infection (SoI); immunity; parasite densities, fever, disease, and detection; gametocytes and transmission, and drug taking. To end up with models that can handle all the complexity, we build probabilistic models that combine these factors. In doing so, we find that we can do some powerful analysis, and we can map the states in these models onto outcomes that matter for research and policy: test positivity, parasite counts, infectiousness, and disease. With patience, we can combine these factors and develop a framework for understanding malaria in populations that match the features of individual-based simulation models. We end up with a sensible understanding malaria epidemiology as ontogeny – development of immunity as a part of an organisms history. We back this view with some very usable models that capture the changing character of malaria in cohorts of humans as they age.

We are interested in understanding malaria control in context, which requires delving into mosquito ecology and behavior. In this book, we start with a simple model for mosquito ecology and parasite infection dynamics in mosquitoes. We add aquatic population dynamics, mosquito population regulation, and exogenous forcing by weather. Later, we worry about adult mosquito behavioral states such as mating, sugar feeding, and egg laying. We introduce the concept of resource availability, and we develop an understanding of mosquito search and movement

in response to resource availability. We take some deep dives to understand how mosquito spatial dynamics work at a fine spatial grain, and then we scale up to understand mosquito populations on landscapes.

At first, we describe mosquito blood feeding and transmission with a few simple parameters. Later, we develop a new model for mosquito blood feeding in a dynamically changing host population with parameters that allow host strata to be more or less available. We also modify our understanding of heterogeneous exposure to biting. We develop a methods for modeling environmental heterogeneity, heterogeneous exposure by age, and a generalized way of handling failty– other sources of heterogeneous biting – through stratification.

We must take a detour to understand how to handle the effects of temperature on the parasite's extrinsic incubation period (EIP). We need a way of dealing with mosquito survival and dispersal through the EIP. This problem has been effectively solved.

To round out this picture, we need a way of dealing with other aspects of human ecology that affect malaria transmission dynamics, including human mobility, human demography, bed net usage, adherance to drugs, and care seeking. Differences among humans call for a synthesis of studies that have identified traits that affect malaria, stratification, and simulation to identify useful ways of propagating the heterogeneity through analyses.

To go along with a theory of transmission, we need a theory of control. We compute effect sizes and evaluate area effects. We develop a generalized concept of effect modification that considers the total effect of a single unit of control. We modify basic processes by including the effects of vector control and mass medical interventions (*e.g.* seasonal malaria chemoprotection, mass drug administration, vaccines, and monoclonal antibodies). Relying on behavioral state models and the concept of resource availability, we develop a models for integrated vector control.

In doing all this, we are building on an enormous body of work that started with Ronald Ross. While Ross is better known for identifying malaria parasites in a mosquito gut, which proved that malaria is mosquito transmitted, we are more interested in the academic work that followed.

After winning the Nobel Prize in 1902, Ross was instrumental in building solid quantitative foundations for malaria transmission and its measurement. Ronald Ross wrote the first models describing malaria transmission. In his writings from 1899 to 1908, it's clear that he was searching for quantitative way of saying something simple – if there are not enough mosquitoes, the malaria transmission can't be sustained. There must be a critical mosquito density, above the cutoff malaria transmission would be sustained, and below it malaria would be eliminated. Ross was looking for a formula that encapsulated his intuition: how were thresholds related to the fact that it took two bites for a mosquito to

complete its life cycle? Eventually, Ross wrote down some systems of equations that would describe malaria. The ideas, mathematics, and identification of parameters and processes were extended by other scientists later, most notably Alfred Lotka and George Macdonald.

It seems that the challenge of malaria control was what pushed Ross toward modeling. Ross's first model was a discussion of adult mosquito movement to guide larval source management [1]. The first model describing malaria transmission appeared in a book, *The Prevention of Malaria in Mauritius* [2]. When it came to thinking through control, Ross found it useful to do the math.

This is a book about how to do the math that is required for malaria programs. The goal is to use all the data available, but especially the data generated by malaria programs, to paint a clear picture of malaria transmission as a changing baseline that has been modified by control. The software is structured into three major domains: the humans and malaria epidemiology, including the effects of treating malaria with drugs; the mosquitoes and the way they have been changed by weather and vector control; and parasite transmission through mosquito blood feeding. Within each domain, there are multiple sub-domains, and there are built in ports and junctions to deal with heterogeneity and other features for malaria control. After a 140 years of studying malaria, there's a lot of detail that could be important in some way. Part of what we need to do is sort through all that detail to find what is most relevant.

We have organized the concepts in this book around a narrative that allows us to introduce the core concepts – those that make modular computation possible – in an order that minimizes the need to draw on unfamiliar concepts. We start with the Ross-Maconald model, but our next task is to update the model for mosquito blood feeding.

Our philosophy has been to design a framework for model building that can be used by programs. The material in this book is designed to be used by non-experts too, so in this context, *model building* means applying a set of tools to to computational tasks we wish our brains could do.

The software we have developed is meant to lower the costs of building and using models. We want programs to be focused on the decisions, the data, the concepts, and the analysis. As a metaphor, some students learn a numerical method for approximating $\sqrt{2}$ in school, but after learning it once, they stop worrying about *how* it is computed and they punch buttons into a calculator. Knowing how to compute something is sometimes useful, but worrying about how to compute it each time would interrupt the process that called for computing it. Instead, we punch the formula into a scientific calculator or any software that does computation confident that the machine knows how to do it. In applying models, the same kind of logic applies. People need to understand the concepts, but like a calculator, the tools should hide the technical details that

don't add to a discussion. The software we have developed is a reliable interface for calculations designed to support policy.

To lean how to use that software, we need to get through a lot of material. The background material in the following presentation is fairly sparse. We are trying to introduce just *enough* mathematics to teach users the critical concepts so they know what the software can do. We assume that the work will be done by teams that include a few people who understand the mathematics, who can guide others through the process. To fill in some of the gaps and technical, we have written (or can write) vignettes. On occasion, the text includes links to these vignettes for those who might find them useful. Please send suggestions about new vignettes to smitdave@gmail.com.

The first model we present is a Ross-Macdonald model.

Chapter 2

A Ross-Macdonald Model

This chapter introduces one version of the Ross-Macdonald model, which is the simplest way to get started [3]. This particular system of delay differential equations traces back to a 1982 book chapter written by Joan Aron and Robert May [4].

We chose this model because it is *extensible.* Most other versions of Ross-Macdonald are difficult to extend. Why? The variables in some versions of the Ross-Macdonald represent fractions, so the equations are difficult to modify when the denominators change. Most Ross-Macdonald equations are *autonomous* (time is never used in computing derivatives), but these equations are already non-autonomous (*i.e.* time drives a seasonal pattern). Malaria transmission dynamics are forced by exogenous variables (*e.g.*, weather), so why start by assuming it isn't?

Please skim this chapter, even if you're familiar with the Ross-Macdonald model. In writing the equations, we introduced some concepts and conventions that became important for the software design.

2.1 Aron and May's Equations

The simplest quantitative description of malaria dynamics tracks the number of infected and infectious mosquitoes and the number of infected and infectious humans. To develop systems of equations, we assign names to variables that represent these quantities: the number of infected and infectious people is denoted $X(t)$ (out of H total); the number of mosquitoes is $M(t)$; the number of infected mosquitoes is $Y(t)$ (out of $M(t)$ total); and the number of infectious mosquitoes is denoted $Z(t)$ (out of $M(t)$ total).

In dynamical systems, we ask how these variables change over time. For our

first equation, we start with adult, female mosquito populations. (It is tiresome to repeat *adult, female* each time, and we're ignoring male mosquitoes at this point anyway, so *mosquito* hereafter means *adult, female mosquito*, unless we say otherwise.) The number of mosquitoes is changing as new adults emerge from aquatic habitats or die.

2.1.1 Mosquito Ecology

We assume the following:

- mosquitoes emerge at the rate of $\Lambda(t)$ adults, per day;
- mosquitoes die at a constant rate, g. The fraction surviving one day is e^{-g}; and the average lifespan is $1/g$.

Our first equation describes changes in the number of mosquitoes:

$$\frac{dM}{dt} = \Lambda(t) - gM \tag{2.1}$$

2.1.2 Infected Mosquitoes

Mosquitoes become infected after blood feeding on an infectious human. Here, we describe blood feeding using a few simple parameters.

To describe *blood feeding*, we assume the following:

- mosquitoes blood feed at the rate f, per mosquito, per day; in this model, this implies that the waiting time to a blood meal is $1/f$ days.
- a fraction of all mosquito blood meals, q, is taken on humans; we call this the *human fraction*
- the human blood feeding rate is the product of these two parameters, fq, which is defined as the number of human blood meals, per mosquito, per day.

The number of human blood meals by a population of vector mosquitoes, per person, per day is called the human biting rate (HBR). In this model, HBR is given by a formula:

$$\text{HBR} = \frac{fqM}{H}$$

Later, we can worry about how to map that onto an estimated HBR value, but not right now.

In the mosquito population, we need to know what fraction of blood meals end up infecting a mosquito that has not already been infected.

To describe *infection rates*, we assume the following:

- a fraction of human blood meals, infects mosquitoes. We call this quantity *net infectiousness* (NI) and (for reasons that we will discuss in a moment), we give it a name, κ:
$$\kappa(t) = c\frac{Xt}{H}$$
- infected mosquitoes die at the same rate as uninfected mosquitoes.

We can now write down our second equation describing changes in the number of infected mosquitoes:

$$\frac{dY}{dt} = fq\kappa(M - Y) - gY \tag{2.2}$$

2.1.3 Infectious Mosquitoes

To become infectious, a mosquito has to become infected and then survive through the extrinsic incubation period (EIP). We assume:

- mosquitoes become infectious after a fixed delay, τ days, called the EIP. The fraction of mosquitoes that survive through the EIP is $e^{-g\tau}$.
- infectious mosquitoes die at the same rate as other mosquitoes.

For a mosquito to become infectious, it must have become infected τ days ago and survived through τ days with probability $e^{-g\tau}$. To write this in equations, we use a subscripted τ to denote the value of a variable (M, Y or X) or term (κ) at time $t - \tau$. For example X_τ is the number of people who were infected and infecious at time $t - \tau$, and M_τ is the number of mosquitoes at time $t - \tau$.

The number of infectious mosquitoes that are added to the population at a point in time includes all the mosquitoes that became infected at time $t - \tau$ and survived the EIP. This is our third equation describing changes in the number of infectious mosquitoes:

$$\frac{dZ}{dt} = fq\kappa_\tau(M_\tau - Y_\tau)e^{-g\tau} - gZ \tag{2.3}$$

Here, Z represents the number of mosquitoes with *sporozoites* in their salivary glands. The *fraction* of mosquitoes with sporozoites in their salivary glands has been called the *sporozoite rate* (SR), which in our notation is

$$z = \frac{Z}{M}$$

The number of bites by vector mosquitoes, per person, per day is called the entomological inoculation rate (EIR). It is defined as the product of the HBR and the SR:

$$\text{EIR} = \text{SR} \times \text{HBR}$$

In our notation, the EIR is:

$$\text{EIR} = z\frac{fqM}{H} = \frac{fqZ}{H}$$

As with the HBR, we would like to know how to connect estiamted values of the EIR to our formulas. Since that's *really* complicated, we've spent a lot of time in the following sections discussing it.

2.1.4 Infected Humans

Humans become infected after being bitten by an infectious mosquito. We assume the following:

- A fraction b of all bites by infectious mosquitoes cause an infection.
- The hazard rate for infection, also called the *force of infection* (FoI) and denoted h is $b\times$ EIR:
$$h = fqb\frac{Z}{H}$$
- Infections clear at the rate r, per infection, per day (the average time to clear is $1/r$ days), and after clearing an infection a person becomes susceptible to infection again.

We can now write down our fourth equation describing changes in the number of infected humans:

$$\frac{dX}{dt} = h(H - X) - rX \tag{2.4}$$

2.1.5 . . . as a System

While we presented these equations one at a time, they work as a system. To see it all at once, we write it here as a system with four equations and two terms:

$$\begin{array}{rl} \frac{dM}{dt} & = \Lambda(t) - gM \\ \frac{dY}{dt} & = fq\kappa(M - Y) - gY \\ \frac{dZ}{dt} & = fq\kappa_\tau(M_\tau - Y_\tau)e^{-g\tau} - gZ \\ \frac{dX}{dt} & = h(H - X) - rX \end{array} \qquad (2.5)$$

$$\begin{array}{rl} \kappa & = c\frac{X(t)}{H} \\ h & = bfq\frac{Z(t)}{H} \end{array}$$

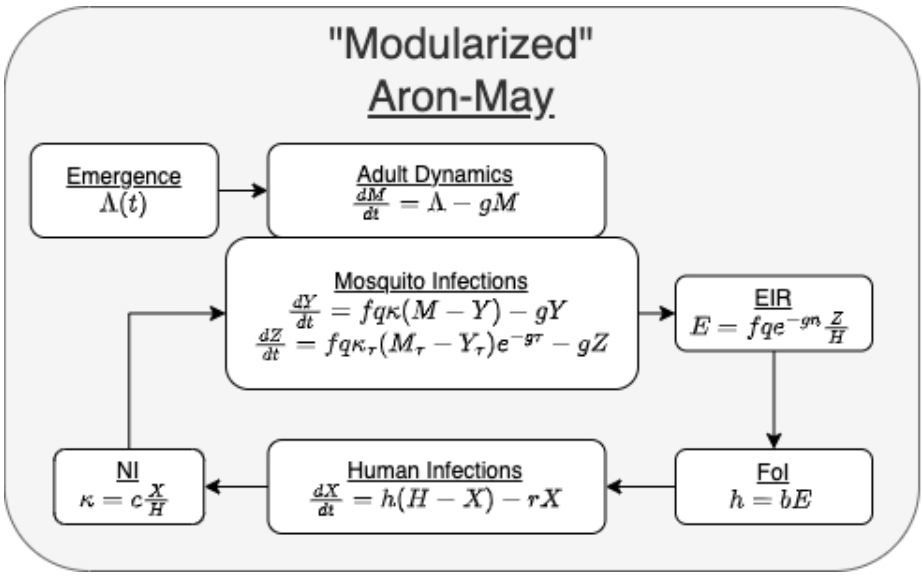


Figure 2.1: A diagram of the a version of the Ross-Macdonald model, using equations from Aron and May [4]

These equations describe processes in three domains (Figure 2.1):

- adult mosquito ecology (M);
- parasite infection dynamics in mosquito populations (Y and Z);
- parasite infection dynamics in human populations (X).

The equations describing parasite infections in mosquito populations also include the variable M, so the mosquito infection dynamics are coupled to the mosquito population dynamics. The way we've written the equations, each compartment has an input term (*i.e.*, Λ, κ, or h) that depends on something else. We've passed Λ as a parameter. For the infection dynamics, the terms κ and h couple two separate systems. For adult mosquito dynamics, emergence is passed to the model as a parameters.

There are, of course, more compact ways of writing these equations. We have written the equations this way to emphasize a few things. First, the terms make it clear exactly how the equations in one domain are connected to another. Second, if we wanted to start *changing* some of the assumptions, these terms help to isolate the parts we might like to change. By writing the equations in this modularized form, we can start to understand how we might be able to write software that would allow us to represent mosquito infection dynamics with different systems of equations.

The next step is to find solutions.

2.2 Solutions

What does a **solution** to these equations look like?

Solutions to these equations are values of the variables over time $(M(t), Y(t), Z(t), X(t))$ that satisfy the system of four equations described above. We call these solutions *orbits.* To put it another way, if we took the derivatives of the orbits for any variable at any point in time using the basic definition

$$\lim_{h \to 0} \frac{x(t+h) - x(t)}{h},$$

and then we used the values of the orbits at time t to compute dM/dt, dY/dt, dZ/dt, and dX/dt (*i.e.*, using the formulas on the previous page), they would be the same.

It is important that these orbits are unique: after specifying the *initial values* of these variables, there is one and only one set of orbits that solves the equations. When we solve the equations, we tend to produce orbits forward in time, but the orbits are defined for all time – *i.e.* the process implies the existence of solutions far back into the past. These are deterministic equations, after all.

As written, the equations do not define a *model,* though it is an easy mistake to make (and one we'll probably make repeatedly when we can get away with it). Instead, the equations define a process or a **model family.** A model is something that *can* produce orbits, and we can't possibly produce orbits until we assign specific values to the parameters.

To find solutions of equations we use an R software package called `deSolve`. Because of the delay for the EIP, these are called *delay differential equations,* which are handled using a function called `dede`. An important part of these delay differential is that the values of variables at a time lag are retreived using a function called `lagvalue()`.

A very important part of solving a delay differential equation is that we must specify the initial conditions for an interval of time, not just at a point. (Since the equation for dZ/dt looks back τ units, we must specify values of $M(t)$, $Y(t)$,

and $X(t)$ for all values of $t \in (-\tau, 0)$.) This forces an awkward choice, since we would need to know the solutions back in time to use them. What is typically done – and we've done it here – is to specify a constant set of initial values. Doing this introduces a little *numerical slop*. These values are *not* what we would get if we ran the equations backwards in time. We're happy to acknowledge this little problem and find ways around it, but we should never forget it is there.

2.2.1 Derivatives

With `deSolve`, solving differential equations is not difficult. The first step is to write down the equations to compute the derivatives. (Many users will find that reading this code is like learning how to compute $\sqrt{2}$. If so, feel free to skip it.)

The solver expects a function with three required arguments (in this order):

- `t` is time
- `y` is the list of variables
- `params` is a set of parameters

The derivatives are computed and returned in the same order as 'y' in a `list`. To make code that is easy to read, we make `params` as a `list` with parameter names (see below), so that inside the function `with(params,{...})`, the parameter names are visible.

```
dAronMay = function(t, y, params){with(params,{

  # Variables
  if(t<=tau) ylag<-y0 else ylag <- lagvalue(t-tau)
  M=y[1]; M_tau = ylag[1]
  Y=y[2]; Y_tau = ylag[2];
  Z=y[3];
  X=y[4]; X_tau = ylag[4]

  # Terms
  kappa = c*X/H; kappa_tau = c*X_tau/H
  h = b*f*q*Z/H

  # Dynamics
  dM = Lambda(t) - g*M
  dY = f*q*kappa*(M-Y) -g*Y
  dZ = f*q*kappa_tau*(M_tau-Y_tau)*exp(-g*tau) -g*Z
  dX = h*(H-X)-r*X

  return(list(c(dM, dY, dZ, dX)))
})}
```

2.2.2 Initial Values

To run the model, we must supply initial values. A useful convention for simple models is to pass the initial values as a named list. Later, we can turn the outputs into a data frame, and then we can retrieve the variables by name. If you're writing code yourself, remember that the initial values and the return value for the derivatives must occur in the same order.

```
y0= c(M=60, Y=0, Z=0, X=1)
```

2.2.3 Parameter Values

We pass the parameters as a list. It might seem like overkill, but we have written a function that takes default values and generates the list. This makes it easy to generate a new set of parameter values with alternative values, and it also helps us to write and pass function $\Lambda(t)$ with parameters we like. By passing the parameter as a list, the parameter values are available to the function `dAronMay` when we use `with(params, {})`.

Note that we have also attached the initial values of the variables as a parameter set, which are the return values for `lagvalue(t)` when `t<0`.

```
makeParams = function(y0,
                      g=1/12, f=1/2.5, q=0.95,
                      c=0.15,
                      b=0.55, r=1/200, H=1000,
                      m=.05, ss=1,
                      tau=10
                      ){
  ss = min(1,max(0, ss))
return(list(y0=y0,g=g,f=f,q=q,c=c,H=H,tau=tau,b=b,r=r,
  Lambda = function(t){m*H*(1 + ss*sin(2*pi*t/365))}))
}
params = makeParams(y0)
```

To make it absolutely clear, we are assuming:

- $g = 1/12$: mosquitoes live about 12 days, on average
- $f = 1/2.5$: mosquitoes feed every 2.5 days, on average
- $q = 0.95$: the human fraction is 95%; mosquitoes feed on humans 95% of the time
- $c = 0.15$: about 15% of bites on infectious humans infect a mosquito
- $b = 0.55$: about 55% of bites by infective mosquitoes cause an infection
- $r = 1/200$: human infections last about 200 days, on average

- $H = 1000$: we're simulating transmission in a population of a thousand humans
- $\tau = 10$: the extrinsic incubation period is about 10 days
- For emergence, we tune the average value using m and it is scaled to H:
  - The parameter m in the function above has been set to 0.05 by default.
  - The parameter ss affects the amplitude of the fluctuations. We force it to take on values between 0 and 1.
  - Emergence is modeled as a sinusoidal function with a yearly cycle.

$$\Lambda(t) = mH\left(1 + \sin\left(\frac{2\pi t}{365}\right)\right)$$

2.2.4 Solving

This code solves the equations:

```
require(deSolve)
tt = seq(0,5*365, by=5)
yout <- dede(y=y0, times=tt, func=dAronMay, parms=params)
```

2.2.5 Visualizing

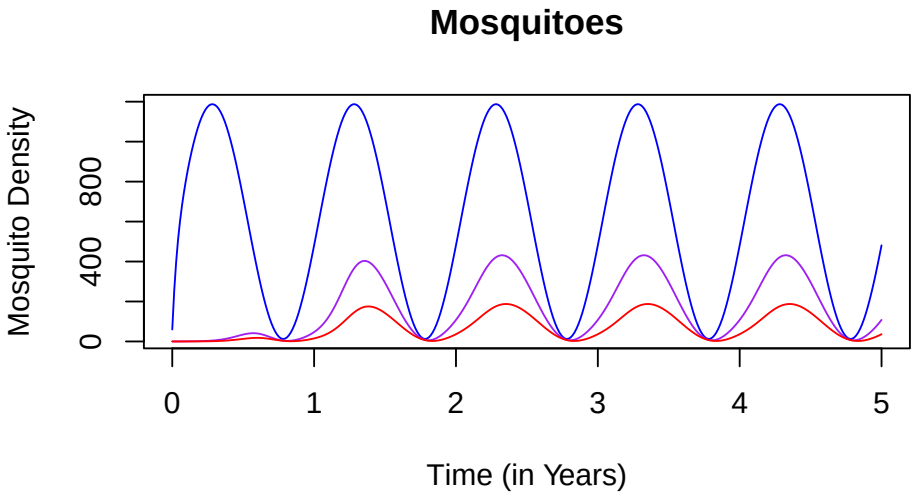
We write a function so that we can plot things easily:

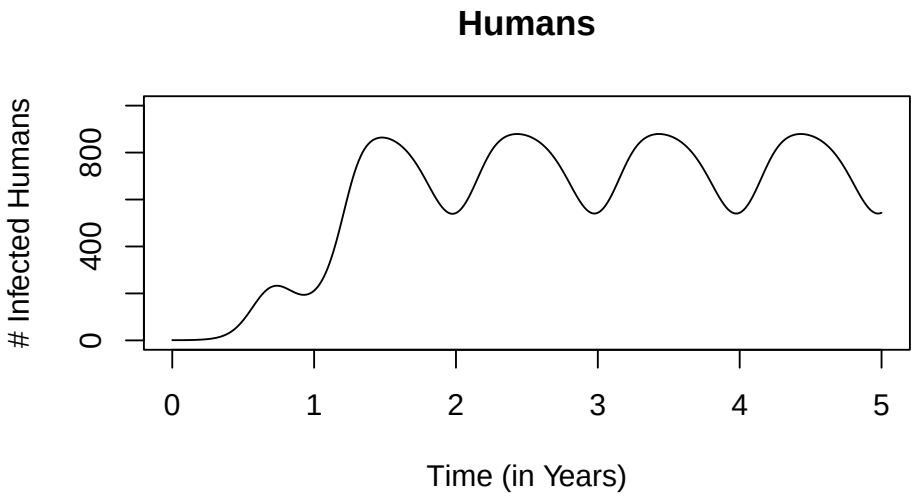
```
plotTS_AronMay = function(yout){with(data.frame(yout),{
  par(mfrow = c(2,1))
  plot(time/365, M, type = "l", col = "blue",
       xlab = "Time (in Years)",
       ylab = "Mosquito Density",
       main = "Mosquitoes")
  lines(time/365, Y, col = "purple")
  lines(time/365, Z, col = "red")

  plot(time/365, X, ylim = c(0,1000), type = "l",
       xlab = "Time (in Years)",
       ylab = "# Infected Humans",
       main = "Humans")
})}
```

This code plots the outputs:

```
plotTS_AronMay(yout)
```


Mosquitoes
Mosquito Density
0
400
800
0
1
2
3
4
5
Time (in Years)


Humans
Infected Humans
0
400
800
0
1
2
3
4
5
Time (in Years)

2.3 Understanding the Dynamics

- The idea of stability and basins of attraction.
  - Stable states
  - Stable orbits
- Long-term average *vs* steady states

2.3.1 Thresholds

2.3.2 Parameters

Chapter 3

Extending Ross-Macdonald

In this chapter, we modify the Ross-Macdonald model by adding a fully defined model for mosquito ecology. The process is actually quite simple:

- We define terms that describe egg-laying by adult mosquitoes;
- We write a basic equation that determines how eggs develop in aquatic habitats and then emerge as adults;
- We incorporate seasonality into the aquatic model;
- We replace the parameter $\Lambda(t)$ from the Aron-May model with a term that describes emergence of adults from aquatic habitats.

3.1 Aquatic Dynamics

3.2 Understanding Mosquito Dynamics

Chapter 4

Modularity and Software

Hundreds of publications have described new models of malaria [5,6]. The challenge we have taken on is to find a new way of building models for malaria that draws from all those good ideas to build models at any level of complexity. We want to do this with reusable, professional quality software. Ideally, the models that we develop would be sufficiently complex to address policy questions, yet remain amenable to analysis. To get there, we took a step back to try and understand *malaria models*, and to put this into a birds-eye view of the process of model building.

From Ross's first published model in 1905 to the first draft of this book, 117 years have passed. The story of malaria models can be summarized in three epochs.

Ross's models, and contributions to mathematical study of malaria made by Alfred J Lotka (1912-1923), George Macdonald (1950-1968), and Garrett-Jones (1964-1970) take us to the end first epoch, which is marked by the end of the Global Malaria Eradication Programme (GMEP, 1955-1969). As part of the GMEP, Macdonald's formulas were extended by Garrett-Jones into the concept of *vectorial capacity* and a rudimentary theory of vector control. By 1970, the *Ross-Macdonald* model was more than just a set of equations. It was a theory for malaria dynamics and control supported by a well-developed set of concepts, parameters and metrics [3].

Over that same period of time, mathematical theory for directly transmitted diseases took a parallel path, with important mathematical contributions from Kermack and McKendrick, NTJ Bailey, and Bartlett. Sometime around 1980, mathematical epidemiology began a period of innovation and synthesis, particularly after the publications of Robert May and Roy Anderson made it a mainstream activity in departments of ecology.

In malaria and mosquito-borne diseases, Klaus Dietz publications span the second epoch (1971-2006), including development of a mathematical model with immunity for the Garki Project [7], work on the dynamics of malaria under treatment by drugs [8], seasonality [9], and heterogeneous biting [10,11]. During this time, theory developed for malaria borrowed concepts and methods. In spatial dynamics, the patch models of Yorke and ** were modified to by Dye and Hasibeder to describe mosquito-borne pathogens [12,13].

The last epoch of malaria, which starts around 2006, is marked by two major developments: a maturing theory of malaria control; and the rise of branded, individual-based models.

The publication of *OpenMalaria* in 2006 marks the beginning of the last epoch of malaria. Some important antecedents were Dana Fochs models for *Aedes* dynamics and dengue virus transmission, as *CIMSiM* and *DENSiM*. In malaria, several within-host models had been developed [14,15]. *OpenMalaria* traces its history back to an intrahost model developed by Dietz and Louis Molineaux [15]. After *OpenMalaria,* two other branded individual-based models were developed. One was developed by a team at Imperial College called *Malaria Tools.* Another was developed by a team at the Institute for Disease Modeling called *eMod.* The fact that the models were named and branded was significant – the authors had developed software that they would maintain and that they were willing to stand behind. The models had finally dealt with *disease* in a serious way, and through publications, the fitted models demonstrated a fidelity to evidence. The branding signaled continuity and consistency.

Around 2007, new models of vector control began to appear that related inteven-tion coverage levels to effect sizes. Macdonald's work had focused on sensitivity to parameters, and the GMEP emphasized technical efficiency to achieve very high coverage (with IRS). Garrett-Jones developed vectorial capacity as a way of understanding vector control and effect modification by insecticide resistance. The new models extended Garrett-Jones ideas. The need for new models was motivated, at least in part, by the goal of achieving universal coverage with ITNs. What were reasonable coverage targets? The new generation of vector control models introduced the concept of an effect size on transmission as a function of intervention coverage levels, where coverage had one definition for operations (*e.g.* something like ownership) and another for effect sizes (*e.g.* related to vector contact rates with interventions). The goal of achieving very high coverage with ITNs bumped into the reality that nets are not durable, so new models have been devised to look at intervention coverage in relation to distribution schemes and product durability. While these concepts had been considered during the GMEP design phase, they did not appear in Macdonald's models.

If we want to take advantage of all the research that has been done, we need a way of understanding malaria models and the whole business of model building.

4.1 Model Building

Model building is a fairly involved process that includes several unavoidable steps:

- There must be some motivation for building a model, which usually starts with a conversation, boxes and arrows drawn on paper or a chalkboard or whiteboard. The process involves refining the questions, until there's a well-formed idea – a reason for building a model.
- The idea gets translated into mathematics. The boxes get translated into variables, the arrows are rate parameters, a mathematical formalism is selected.
- The model gets analyzed. In some cases, when the model complexity exceeds a very low threshold on complexity, this is done with pencil and paper. It is only possible to analyze individual parts of the model this way.
- The model gets translated into pseudo-code, and then it gets implemented as software that can produce output. This is followed by a long and painful process of verifying that the software does what the pseudo-code says it *should* do. After awhile, the software is trusted, and it's time to use it.
- Some thought is given to the correspondence between the variables in a model, observable quantities, and the observational process itself. This process can be a part of what happens above, but at some point, the models need to be fitted to data.
- The software produces output and then: the outputs are visualized; models are fitted to data; graphs are made; papers or reports are published; and careers advance.

That's the simple story of model development. What happens next is could be one of the following:

- Someone re-examines an existing model and notices it is inadequate in some way: it is missing some features, or it might make an assumption that ought to be modified. Simple models become spatial models, single populations are structured.
- Someone decides to implement the model in a different way, perhaps with a different mathematical formalism. Continuous time models are translated into discrete time models. Deterministic models become stochastic. Autonomous processes become non-autonomous.

Through this process, hundreds of malaria models were published.

A problem with this process has been that the software is often developed for bespoke tasks (*i.e.* to publish a paper). The software is often poorly documented and difficult to reuse. The costs of building a model for one task limited the complexity of the model. It was difficult to combine elements of one model

developed for one purpose, with someone else's model developed for another purpose.

In malaria, this *ad hoc* process of writing new models was found to be inadequate to serve the broad range of policy questions. One way of dealing with the complexity was to build individual-based models, but individual-based models have some of the same limitations as reality.

4.2 Modular Computation

Before *OpenMalaria*, most models of malaria modified the Ross-Macdonald model in one way [5]. The innovation was focused on specific themes or questions: how long would an infection last in models with superinfection?

4.2.1 `exDE`

We have written the software that solves these equations in a package called `exDE`.

Part II

Blood Feeding, Exposure, and Transmission

Chapter 5

Adding Realism to Models

The kind of realism we want to include in our models is the kind that has been documented by research studies.

Malaria is complex. The Ross-Macdonald model is a good start, but we want to add the features of real systems: exogenous forcing by weather; spatial heterogeneity; multiple mosquito species with different behaviors; integrated vector control; and models of malaria epidemiology that have the features programs need.

5.1 Blood Feeding and Heterogeneous Exposure

Transmission occurs during blood feeding, a process that implies that requires humans and mosquitoes to be in the same place at the same time. Blood feeding is among the most difficult problems to simulate. By way of contrast, Macdonald's description of human blood feeding is simple: a single parameter describes human blood feeding rates. We end up describing human blood feeding in terms of a blood feeding rates (denoted f) and a human fraction (denoted q). A question for us is how these rates vary by context, and the consequences for exposure. To do this, we need to rethink the mathematics of blood feeding.

Over the past two decades, several papers have drawn attention to the way blood feeding is constrained by the availability of vertebrate hosts. It may be fine to assume that the density of vertebrate hosts doesn't change, but *something* should change when a large fraction of people are using bednets. Even with static parameters, we should think through the limiting cases: if there are no vertebrate hosts, then there blood feeding should not occur (*i.e.*, $f = 0$); if there are no human hosts, then there should be no human blood meals ($q = 0$); and if there are no alternatives to humans, all blood meals should be on humans

($q = 1$). On the one hand, the mosquitoes should blood feed at a slower rate. On the other hand, human biting should become heterogeneous.

To deal with heterogeneous exposure and many other phenomena, we need a sensible way of segmenting humans into population **strata**. Stratification makes it possible to deal with population heterogeneity.

A new model of **blood feeding** is based on a model of blood feeding as the endpoint of a search for a blood host [16]:

- Each sub-population has a *search weight* (w), and the total *availability* of humans for blood feeding (W) is the sum of the sizes of the strata weighted by their search weights.
- We also consider the availability of alternative vertebrate species for blood feeding (O).
- To compute total availability, we add a scaling parameter on alternative hosts, because mosquito preferences can translate into different patterns of search; total availability is $B = W + O^{\zeta}$.
- Mosquito blood feeding rates are computed using a *functional response* to total availability of vertebrate hosts ($f = F_f(B)$).
- The human fraction is proportional to the relative availability of hosts $q = W/B$.

If the models do a proper accounting, then the total number of human blood meals taken by mosquitoes should equal the number of blood meals received by humans. The concepts we devised for blood feeding must, therefore, translate into a model for heterogeneous exposure:

- The *search weights* thus translate into a kind of **Frailty**, which is one component of *heterogeneous exposure.* Important sources of frailty include bednet use, housing type, and age.
- We also want to consider *variability* in exposure within a stratum – what is the distribution of the *expected* number of bites over time? We have already discussed frailties, so this is a different kind of heterogeneous exposure that we call **Environmental Heterogeneity**. This helps us to align models with data: mosquito counts data tend to be described well by *negative binomial* distributions, so it is likely that the distribution of infectious bites also follows a negative binomial distribution. We introduce a function that translate the EIR into the FoI:

  $$h = F_h(E)$$

  In the Ross-Macdonald model, the underlying assumption is consistent with a Poisson distribution, but we have also derived *negative binomial hazard rates.* Environmental heterogeneity can arise from two sources:

  - the aggregated distributions of mosquitoes in micro-habitats, and the redistribution of mosquito populations by wind and weather;
  - random movements of humans around mosquito micro-habitats that affect their risk in a way that doesn't tend to change the mean;

5.2 Space

Space is big, so we start by drawing boundaries around a part of the world we want to study, that we call the *spatial domain.*

5.2.1 Human Travel and Mobility

The notion of a spatially distributed risk for humans and the modalities of human travel.

- Humans move around, so we develop a model of *time spent.* Time spent is sub-divided into three parts:
  - time spent at home;
  - time spent traveling, when a night is spent away from home;
  - human mobility, which describes time spent around home when not traveling.
- For travel, we estimate a travel FoI.
- For time at home and mobility, after weighing time spent and mosquito diurnal activity patterns by time of day, we modify time spent to get a notion of *time at risk*
- After modifying time at risk by search weights, mosquito blood meals are distributed among all hosts according to their availability.

5.2.2 Mosquito Dispersal

To describe mosquito spatial dynamics, we

5.3 Time

5.4 Epidemiology

5.5 Mosquito Ecology

5.6 Control

5.7 Context

Chapter 6

Heterogeneous Exposure

For humans, exposure to malaria means exposure to the bites of infectious mosquitoes. A problem that we'll have to deal with sooner or later is that exposure risk differs among humans over space and time. While this might seem like an odd thing to introduce so early, we will have to tackle the topic sometime. The discussion of [Heterogeneous Biting], in the previous chapter, showed that heterogeneity plays an important in understanding transmission and thresholds. This discussion of heterogeneous exposure (*i.e.*, looking at heterogeneous biting from the human side) is a good way of introducing some of the core concepts that are built into the framework:

- [Heterogeneous Biting] is one way of getting around a conundrum. In models with homogeneous biting, the relationship between *average* mosquito density and the prevalence of infection would lead us to make quantitative predictions about the likely effects of vector control.

- We discuss two different kinds of heterogeneous exposure: frailty, and environmental heterogeneity. In a nutshell, frailty multiplies the mean hazard rate for a sub-population by some amount k. Environmental heterogeneity does not affect the mean, but it changes the distribution of the mean.

- We introduce the idea that we can deal with frailties in human populations by segmenting the population into strata.

- We set the stage for a new model of mosquito **blood feeding** that we introduce in the next chapter.

- In a chapter on Approximation, we use these models to discuss the problem of model-based inference.

6.1 Overview

Some reasons heterogeneous exposure to malaria have been documented in hundreds of studies. This is an overview.

6.1.1 Age

- Port, Boreham
- Carnevale

6.1.2 Location

6.1.3 House Type

6.1.4 Activities

6.2 Frailty

In general, we define frailty as a multiplicative factor on the FoI. If the average FoI in the population is h, then the FoI in a stratum is hk. The size of the stratum, p_k, is constrained such that:

$$\int_0^\infty k\, p_k\, dk = 1$$

With this constraint, the mean FoI in the population is h.

Continuous distributions are difficult to extend, but we can stratify a population to accomplish some of the same effects.

6.3 Environmental Heterogeneity

Chapter 7

Blood Feeding

7.1 Availability and Blood Feeding Rates

7.2 Host Selection

Part III

Mosquito Ecology

Chapter 8

Mosquitoes

An overview of mosquito ecology,

Chapter 9

Behavioral State Models

Chapter 10

Aquatic Ecology

Chapter 11

Mosquito Microecology

Modeling mosquito population dynamics on point sets.

Chapter 12

Mosquito Dispersal

Chapter 13

Mosquito Ecology

13.1 Population Dynamics

Chapter 14

Vector Competence

Chapter 15

Measuring Mosquitoes

Part IV

The Framework

Chapter 16

Spatial Dynamics

Chapter 17

Temporal Dynamics

Chapter 18

Stratification

Part V

Epidemiology

Chapter 19

Malaria Infection

In the following sections, we walk through several models for the dynamics of malaria infection and immunity in humans. We cover infection and detection, immunity, infectiousness, disease, drug taking, and cohort dynamics.

19.1 Overview

19.2 Multiplicity of Infection (MoI)

19.3 Age of Infection (AoI)

19.4 Stage of Infection (SoI)

Chapter 20

Malaria Immunity

Exposure *vs.* age.

20.1 The Garki Model

20.2 Stage-Structured Immunity

20.3 Strain Specific Immunity

20.4 Memory Tracking

20.5 Age *vs.* Prevalence

Chapter 21

Detecting Parasites

21.1 Parasite Densities and Detection

21.2 Light Microscopy

21.3 Biomarkers and RDTs

21.4 PCR

Chapter 22

Gametocytes and Infectiousness

22.1 Gametocytemia

22.2 Anti-Gametocyte Immunity

Chapter 23

Fever and Severe Disease

23.1 Fever

23.2 Anemia

23.3 Severe Disease

Chapter 24

Care Seeking

Chapter 25

Drug Taking

25.1 Curing Infections

25.2 Chemoprotection

25.3 Adherance

25.4 Treatment Rates

Chapter 26

Cohorts and Demography

We need a way of incorporating age into our models.

26.1 Boxcar Models

26.2 Delay

26.3 Migration

Chapter 27

Human Mobility

Chapter 28

Malaria Epidemiology

28.1 Age of the Youngest Infection

Part VI

Humans

Chapter 29

Human Behaviors and Ecology

Chapter 30

Human Travel and Malaria Importation

Chapter 31

Pharmaceutical Interventions

31.1 SMC

31.2 MDA

31.3 Drugs

31.4 Vaccines

Part VII

Malaria Control

Chapter 32

Vector Control

Towards a theory of vector control.

Chapter 33

Insecticide-Treated Bednets

Chapter 34

Indoor Residual Spraying

Chapter 35

Larval Source Management

Chapter 36

Attractive Toxic Sugar Baits

Chapter 37

Spatial Control

Chapter 38

Integrated Vector Control

Chapter 39

Pharmaceutical Interventions

39.1 SMC

39.2 MDA

39.3 Drugs

39.4 Vaccines

Chapter 40

Microsimulation

Chapter 41

Spatial Concepts and Connectivity

Part VIII

Estimation

Chapter 42

Approximation

In this chapter, we use some of the simple models we've developed to introduce some basic ideas.

- Because it is easy for models of heterogeneous exposure, we introduce a *model to model distance metric* for models that makes it possible to rigorously measure the distance between two models.
- Using distance metrics, we use model-model comparison to show how models approximate each another. Informally, we compare this to a one way *model to data distance metric* that can be used to compare how far two models are from some data set. We imagine an unobserved real world, and we show how information bout the real world is transferred through data.

42.1 The Distance between Two Models

42.2 The Distance from Models to Data

Chapter 43

Exposure and Infection

The relationships between the annual *Pf*EIR, the *Pf*FoI, and the *Pf*PR are among the most important in malaria. A few studies analyzed the data [17,18]. The first paper I wrote on the topic, in 2005, suggested an important role for heterogeneous biting [19]. At the time, we were thinking mainly about frailty. After some correspondence, we took a closer look at the relationship between the *Pf*EIR and the *Pf*FoI [20], which helped us rule out immunity. With some data in hand, we took a closer look at heterogeneous exposure [21], which drew our attention to environmental heterogeneity. Meanwhile, we developed the age-standardization algorithms for the Malaria Atlas Project [22]. As we grappled with the data from Bioko Island, it became clear that malaria importation could be an important factor [23]. None of this considered either seasonality or drug taking and chemo-protection.

The *Pf*PR to *Pf*EIR converstion algorthims defined in 43.3 are among the most important for policy.

43.1 Data

43.1.1 EIR vs. PR

We have revisited the relationship one more time, but we do it in two steps. First, we take another look at the EIR-PR and EIR-FoI data, with a focus on *house effects*

43.1.2 EIR vs. FoI

43.1.3 Chemoprotection

43.2 Models

Second, we re-evaluate the many sources of variability, and how each one works across the spectrum of transmission:

- Age: What is the age of the population being examined?
- Drug Taking and Chemoprotection: What is the distribution of drug-taking rates and habits in the population?
- Pre-erythrocytic Immunity
- Heterogeneous Exposure
  - seasonality: how much does seasonality affect the probability of detection?
  - Frailty (Section 6.2)
    - age
    - other
  - Environmental Heterogeneity (Section 6.3)
- Travel Exposure and Malaria Importation
- Immunity
  - maternal protection
  - detection

43.3 $Pf\mathrm{PR} \rightarrow Pf\mathrm{EIR}$

Chapter 44

Model Libraries

Part IX

Supplements

Chapter 45

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If you want a PDF and can't find it at the link provided, let us know and we can help you find a copy.

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