Mosquito-Borne Diseases: Modeling and Control

From Simple to Complex Models

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Mosquito-Borne Diseases

Mosquitoes are vectors for many of the most important human infections

- Malaria

  Protozoan parasite: *Plasmodium spp.*
  Vector: *Anopheles spp.*

  300 to 500 million clinical cases per year…
  … leading to between one and two and a half million deaths

- Dengue

  Virus (four serotypes)
  Vector: *Aedes aegypti* (and others)

  50 million cases per year, about 1% lead to dengue haemorrhagic fever (DHF)
  Untreated, DHF death rate can be 20%+, but treatment reduces this to 1%.
  (*A. aegypti is also the vector for yellow fever)*

- Yellow fever, West Nile virus, Eastern & Western equine encephalitis, LaCrosse encephalitis, …

Control of Mosquito-Borne Infections

- Reduce vector population:
  - Make environment less mosquito-friendly by draining standing water
    - Malaria ("marsh fever") was a major problem in South-East England before marshlands were drained
  - Use insecticides
    - *Not without problems: e.g. DDT, insecticide resistance*

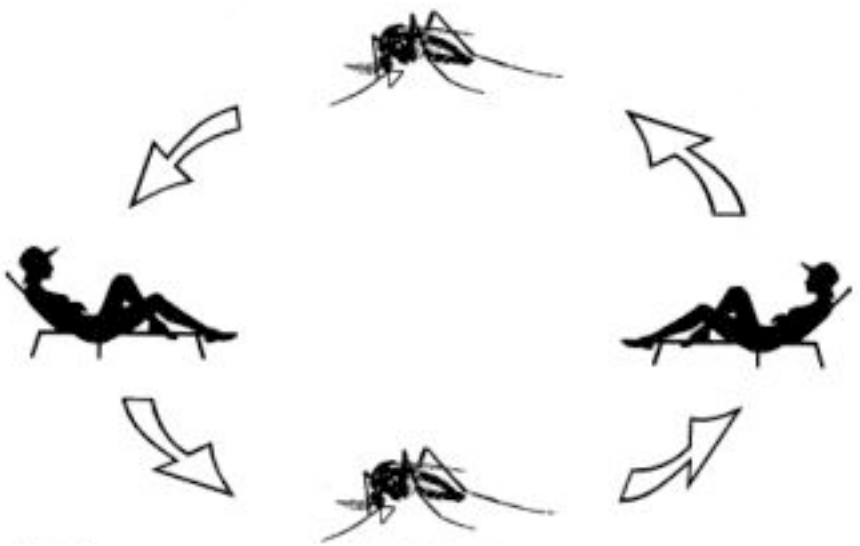
- Prevent mosquitoes biting people
  - Insecticide-laced bed nets
    - *Ineffective against mosquitoes that mainly bite during the day* (e.g. *A. aegypti*)

- Vaccines and drug treatments.
  - Not always available, problems with drugs and drug resistance

Typical Lifecycle of a Mosquito-Borne Infection
(dengue)

Adult female mosquitoes need blood to produce eggs

(Rudyard Kipling: The female of the species is more deadly than the male)

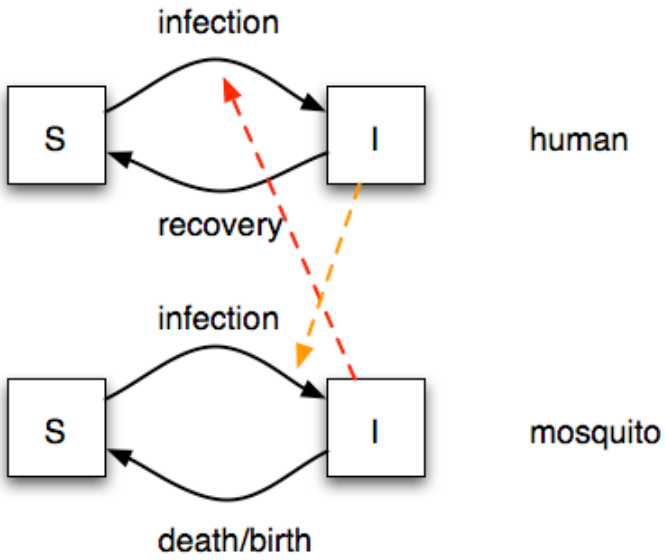


1. Adult female mosquito bites infected person
2. Incubation of virus within mosquito
   extrinsic incubation period ~ 7-14 days
   (temperature dependent)
3. Infectious mosquito bites susceptible person
4. Virus incubates within person
   average intrinsic incubation period ~ 4-5 days
   average human infectious period ~ 4-5 days

   (cycle repeats)

Lifecycle involves the mosquito biting twice at appropriate times

Simplest Model: Ross-Macdonald Model



Assumptions made in this compartmental model:

- Number of mosquitoes, V, is constant
- Mosquitoes are either susceptible or infectious, I

- Constant human population size, H
- Humans are either susceptible or infectious, Y

  this ignores immunity

- Ignore incubation periods

- The rate at which mosquitoes bite humans is **proportional to the number of mosquitoes** but **independent of the number of people**

(idea is that mosquitoes only need a certain number of blood meals, so as long as there are sufficiently many humans around…)

- Populations are "well-mixed"
- Deterministic (non-random): large population sizes

Simplest Model: Ross-Macdonald Model

$$\dot{Y} = abI\left(\frac{H-Y}{H}\right) - \xi Y$$ Infective humans

$$\dot{I} = ac(V-I)\frac{Y}{H} - \delta I$$ Infective mosquitoes

Parameters:

a mosquito biting rate

b mosquito to human transmission probability, per bite

c human to mosquito transmission probability, per bite

ξ human recovery rate: average duration of human infection, D_H , is $1/\xi$

δ mosquito death rate: average duration of mosquito infection, D_M , is $1/\delta$

- Mosquito biting assumption leads to an asymmetry in the transmission term

- This model was developed for malaria, but is widely used as a generic model for other mosquito-borne infections

Behavior of the Ross-Macdonald Model

- Very simple behavior: infection can invade and persist if the basic reproductive number (R_0) is greater than one

- Basic reproductive number is the average number of secondary infections that result if a single infectious individual is introduced into an entirely susceptible population

$$R_0 = ma^2bcD_HD_M = \left(abD_M\right)\left(macD_H\right) = R_0^{VH}R_0^{HV}$$

# of humans infected by a mosquito

# of mosquitoes infected by a person

m : number of mosquitoes per person

(Notice square of biting rate in R_0 expression)

Control of Infection

$$R_0 = ma^2bcD_H D_M = \left(mabD_M\right)\left(acD_H\right) = R_0^{VH} R_0^{HV}$$

- Infection can invade and persist if R_0 is greater than one
- Aim of control is to reduce R_0 below one:

  shorten duration of infection in human (D_H)
  shorten mosquito lifespan (D_M)
  reduce number of mosquitoes (m)
  reduce biting rate (a)

If you could vaccinate people, you would need to vaccinate $p_c = 1 - 1/R_0$ to achieve control

- herd immunity: don't need to vaccinate everyone, just sufficiently many
- it's more difficult to control an infection with a larger R_0

But the Real World is More Complicated…

What complexities have we ignored?

- Stochasticity
  - random events (e.g. a mosquito might die before biting anyone)
    - Important when numbers of infectives are "low" --- e.g. invasion of infection
- Population structure
  - Populations are not well-mixed or homogeneous, e.g. spatial structure, age structure
- Mosquito biology and behavior
  - Population dynamics of mosquito (perhaps weather-dependent or seasonal)
  - Mosquito biting behavior: mosquitoes prefer some people over others
  - When and where do mosquitoes bite, rest, lay eggs, … ?
    - Important differences between *Aedes* and *Anopheles* mosquitoes
- Details of infections
  - Incubation periods (may be temperature-dependent)
  - Human immunity
  - Malaria: multiple strains of *Plasmodium* parasite, complicated immunity
  - Dengue: four serotypes of virus, interactions between serotypes

Ross-Macdonald compartmental framework can be extended to account for many of these additional complexities…

Accounting for the Extrinsic Incubation Period

It's simple to account for the incubation period within a mosquito if we assume that mosquito death rate is independent of age (constant daily survival prob.)

Just multiply R_0^{VH} (and hence R_0) by P, the probability of surviving EIP:

$$R_0 = ma^2bcD_H D_M P = ma^2bcD_H D_M p_d^n$$

p_d is the daily survival probability, n is the average duration of incubation period

Highly non-linear dependence on p_d led people to focus on shortening adult lifespan

This idea is back in fashion with the development of *Wolbachia* – based control methods

More complex models are needed if one has to account for non-constant survival or temperature-dependence of extrinsic incubation period

Stochastic Model

Deterministic model treats state variables (e.g. number of infectives) as continuously varying quantities, with rates of movement between states

A stochastic formulation reinterprets the rates in terms of probabilities of individuals moving between states, considering state variables to be integers

Event	Transition	Rate at which event occurs	Probability of transition in time interval $[t, t+dt]$
Infection of Host	$Y \to Y+1$	$\alpha I\left(\frac{H-Y}{H}\right)$	$\alpha I\left(\frac{H-Y}{H}\right)dt$
Infection of Vector	$I \to I+1$	$\beta(V-I)\frac{Y}{H}$	$\beta(V-I)\frac{Y}{H}dt$
Recovery of Host	$Y \to Y-1$	ξY	$\xi Y dt$
Death of Vector	$I \to I-1$	δI	$\delta I dt$

Table 1. *Events of the Ross model, their rates and probabilities of occurrence in a time interval of length dt.*

Stochasticity: Invasion Probabilities

Will infection invade following an introduction into some location?

Deterministic model talks about the average number of secondary infections, but there will be a *distribution* about this average

Even if R_0 is greater than one, randomness can lead to breaks in chains of transmission:

minor outbreaks: ones that petered out early on

major outbreaks: didn't die out early on… invasion occurred

Probability of invasion can be obtained using a branching process approximation to the Ross-Macdonald model (Bartlett 1964, Griffiths 1972, Ball 1983)

If R_0 ($=R_0^{HV}R_0^{VH}$) > 1, then major outbreak probabilities are

$$1-\frac{R_0^{HV}+1}{R_0^{HV}(R_0^{VH}+1)}$$ following the introduction of a single infectious mosquito

$$1-\frac{R_0^{VH}+1}{R_0^{VH}(R_0^{HV}+1)}$$ following the introduction of a single infectious person

Stochasticity: Invasion Probabilities

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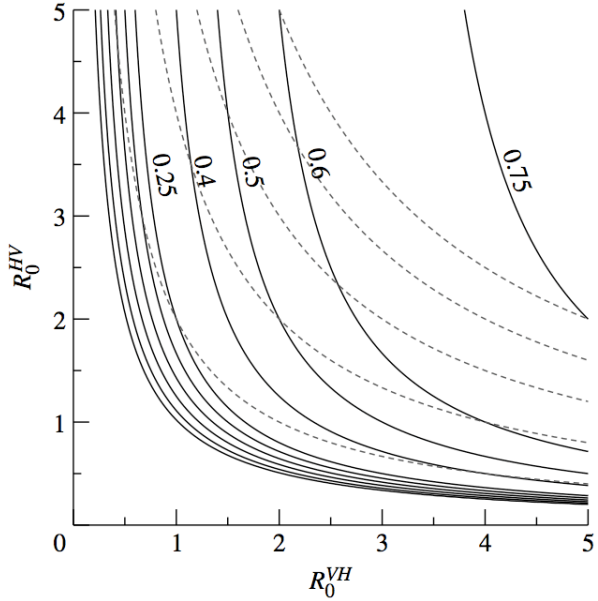
Figure: Invasion probability from one infective mosquito

Contours of equal invasion probability (solid)

Contours of equal overall R_0 (dashed)



Asymmetry in invasion probability:

if $R_0^{HV} \neq R_0^{VH}$, it matters whether an introduction occurs via human or mosquito, even if the overall R_0 is the same

e.g. if R_0^{VH}=5, R_0^{HV}=2

P(outbreak from one mosquito) = 0.75

P(outbreak from one human) = 0.60

Lloyd et al. (2007) J. R. Soc. Interface **4**, 851.

Stochasticity: Variability About Endemic Equilibrium

Deterministic model: if R_0 is greater than one, prevalence of infection approaches a stable equilibrium (the endemic equilibrium)

Stochastic model: randomness causes fluctuations in prevalence about the endemic equilibrium

If fluctuations are large enough, the infection can go extinct, even though $R_0 > 1$

Critical community size: larger population means smaller (relatively) fluctuations, reducing chance of extinction

Quantify the magnitude of these fluctuations by calculating variances of the numbers of infectives

can be achieved by deriving equations for higher order moments, going beyond means

$$\frac{d}{dt}E(Y) = \alpha E(I) + \frac{\alpha}{H}E(YI) - \xi E(Y) \quad (3.17)$$

$$\frac{d}{dt}E(I) = \frac{\beta V}{H}E(Y) - \frac{\beta}{H}E(YI) - \delta E(I) \quad (3.18)$$

$$\frac{d}{dt}E(Y^2) = \alpha E(I) + \xi E(Y) + \frac{\alpha(2H-1)}{H}E(YI) - 2\xi E(Y^2) - \frac{2\alpha}{H}E(Y^2I) \quad (3.19)$$

$$\frac{d}{dt}E(I^2) = \delta E(I) + \frac{\beta V}{H}E(Y) - 2\delta E(I^2) + \frac{\beta(2V-1)}{H}E(YI) - \frac{2\beta}{H}E(YI^2) \quad (3.20)$$

$$\frac{d}{dt}E(YI) = \alpha E(I^2) - (\xi+\delta)E(YI) + \frac{\beta V}{H}E(Y^2) - \frac{\alpha}{H}E(YI^2) - \frac{\beta}{H}E(Y^2I) \quad (3.21)$$

Heterogeneity in Transmission

- Examples of Heterogeneities:
  differences in infectiousness or susceptibility
  differing chances of getting bitten or of biting
  differing productivities of different houses
  mixing patterns of populations (e.g. spatial structure)
- 80/20 "rule" (Woolhouse et al.)
  80% of all transmission is due to 20% of all individuals
- Example: de Benedictis et al. (2003):

DNA profiling of blood meals in *Ae.* aegypti collected in 22 houses in Florida, PR
about 100 residents, field workers and visitors connected to the houses
identified sources of 80% of the blood meals

Feeding non-random ($P=2.4\times10^{-17}$) with a bias towards young adults and males

Three people accounted for 56% of the meals

Modeling Heterogeneity

Multi group (multi-type) model, with *n* mosquito groups and *m* human groups

e.g. spatial location, susceptibility, biting preference

Simplest version: an individual's type is fixed

e.g. don't model permanent migration from one location to another

$$\dot{Y}_j = \left(\sum_{i=1}^{n} a_{ij} b_{ij} I_i\right) \frac{H_j - Y_j}{H_j} - \xi_j Y_j$$

$$\dot{I}_l = \left(\sum_{i=1}^{m} a_{li} c_{il} \frac{Y_i}{H_i}\right) (V_l - I_l) - \delta_l I_l$$

a_{ij} rate at which a mosquito of type *i* bites humans of type *j*

values depend on the relative sizes of the human groups and mosquito biting preferences

b_{ij} transmission probability from mosquito type *i* to human type *j*

c_{ij} transmission probability from human type *i* to mosquito type *j*

ξ_j , δ_j recovery rate of type *j* person, death rate of type *j* mosquito

Impact of Heterogeneity

- Measure heterogeneity by CV = (standard deviation)/(mean) (e.g. of biting preferences)

- Heterogeneity often increases R_0, and by a factor that reflects the degree of heterogeneity

  R_0 is multiplied by $1 + CV^2$

  High degree of heterogeneity means that CV^2 is much larger than one and that the naïve value of R_0 (ignoring heterogeneity) can be a severe underestimate

  In the setting of malaria in Africa, Dave Smith and colleagues obtained a wide range of estimates of R_0 (IQR: 30-815).

- Increase in R_0 due to heterogeneity facilitates disease invasion/persistence, but prevalence is lower than in homogeneous situation

- Reduction in prevalence and/or eradication is more difficult using uniform control measures, but targeted control can be highly beneficial IF you can identify and reach the relevant subpopulation

  Florida, PR example: those three people contributed enormously to transmission

Heterogeneity in Transmission

Dave Smith's malaria work highlights the implications of extreme heterogeneity for control in that setting:

"very substantial reductions in rate of infectious bites will be necessary to achieve modest reductions in the prevalence of malaria throughout Africa."

"Reducing annual number of infectious bites from from 200 to 100 and then to 50 would reduce prevalence by 4% and then an additional 5%

… effort required to reduce the disease burden in Africa would be enormous."

and the potential importance of targeted control:

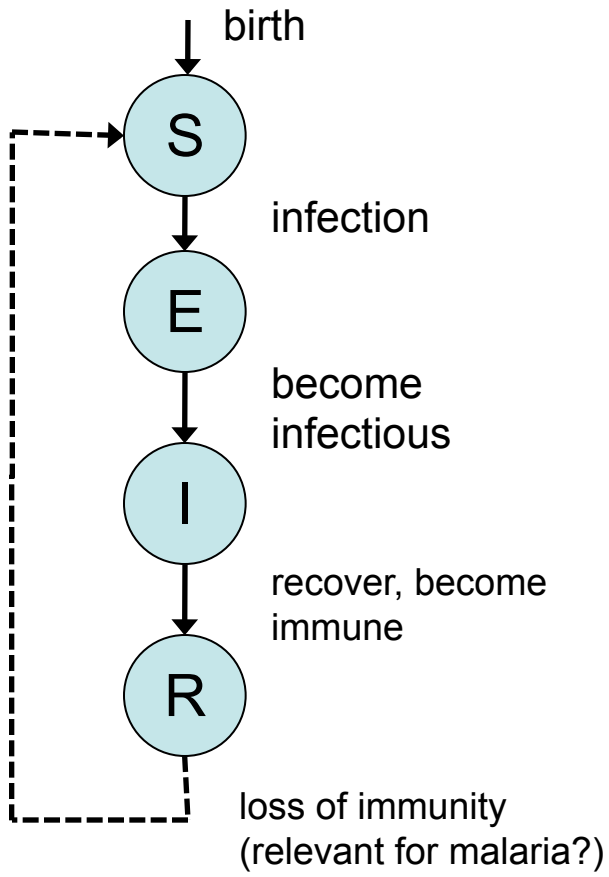
With perfect targeting, removing those individuals who are bitten most often, 20% coverage achieves control when R_0 is 50, 50% coverage succeeds when R_0 is 2000.

(Compared to 98% and 99.95% coverage IF these R_0 values were applicable in a homogeneous biting situation.)

Modeling Human Incubation Period, Immunity, and Demography

Add additional human disease compartments to the model…

… easily done, at the cost of increasing the dimension of the system
(number of state variables/differential equations)



Dengue: Multiple serotypes

- Four serotypes of dengue
- Recovery confers permanent immunity to that serotype, but only temporary immunity to other serotypes

  little to no long-term cross-immunity

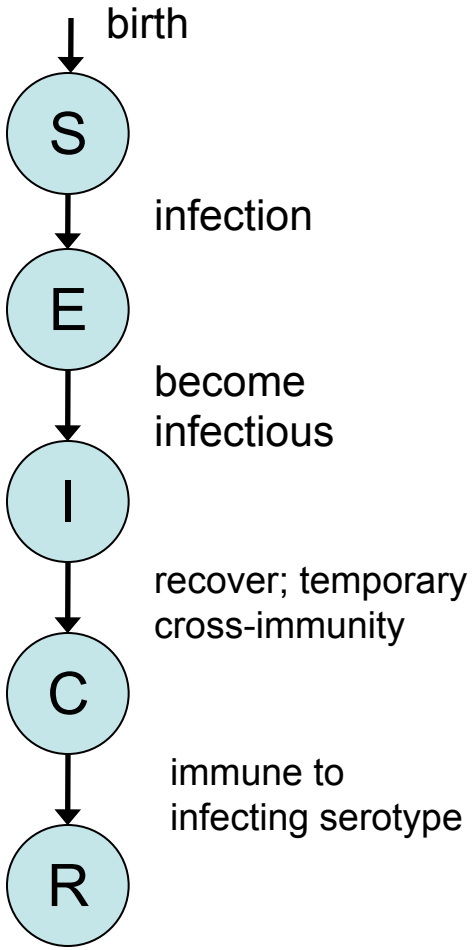
- Immune enhancement: immune response to one serotype *enhances* future infections, can increase likelihood of severe disease

Dengue: Multiple serotypes increases complexity

Example from Krisztian Magori, based on model of Wearing & Rohani

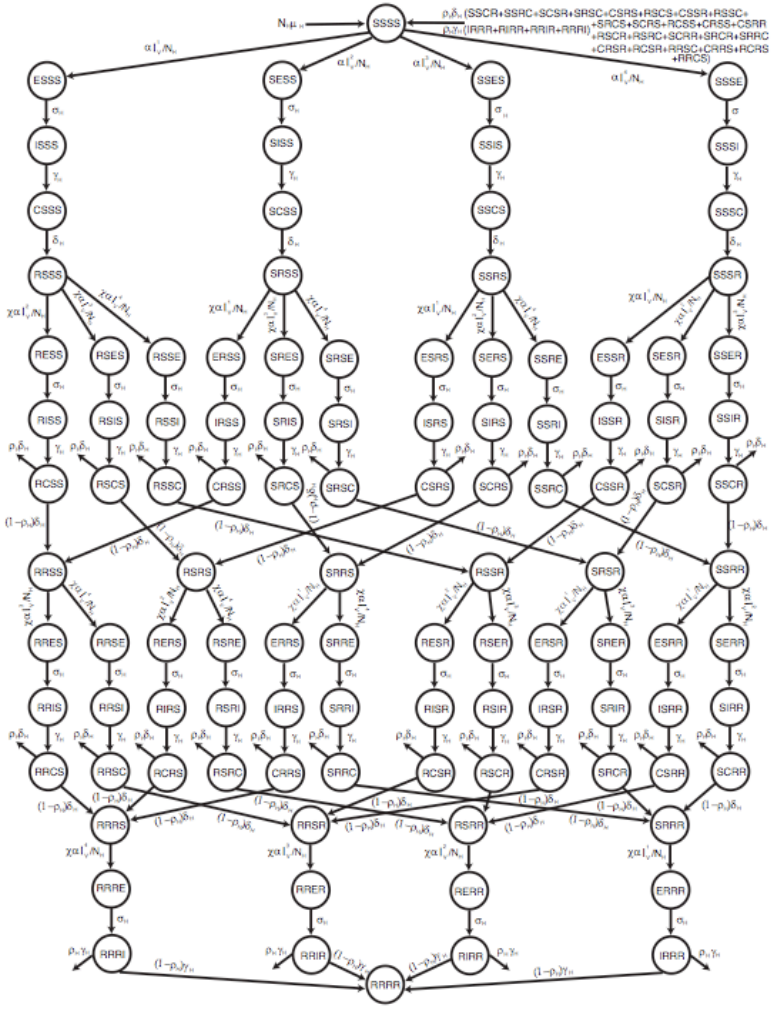
Model accounts for
- latency (E)
- temporary cross-immunity (C)
- permanent immunity (R)

Single serotype model has 5 human compartments



Dengue: Multiple serotypes increases complexity

Figure 1: Flow diagram for the hosts



Example from Krisztian Magori, based on model of Wearing & Rohani

Each serotype modeled as SEICR Susceptible, Exposed, Infectious, temporarily Cross-immune, Refractory

Single serotype model has 5 human compartments

Four serotype model has 108 human compartments

Mosquito Population Dynamics

One possibility: model number of mosquitoes using logistic growth model

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right)$$

K carrying capacity of the environment

Seasonality could be modeled by making K a function of time, or by varying the mosquito birth rate

changing numbers of mosquitoes means that transmission potential varies over the course of a year

Other complexities: model immature (larvae and pupae) and adult mosquitoes separately

A Different Modeling Approach…

We can continue bolting additional components on to the Ross-Macdonald framework in this way, but an alternative is to adopt a radically different approach…

Move from compartmental models, which describe the system at the level of the population…

… to something more akin to an individual-based model, tracking individual mosquitoes or cohorts of mosquitoes and individual people

Complex Model for Mosquito Populations: Skeeter Buster

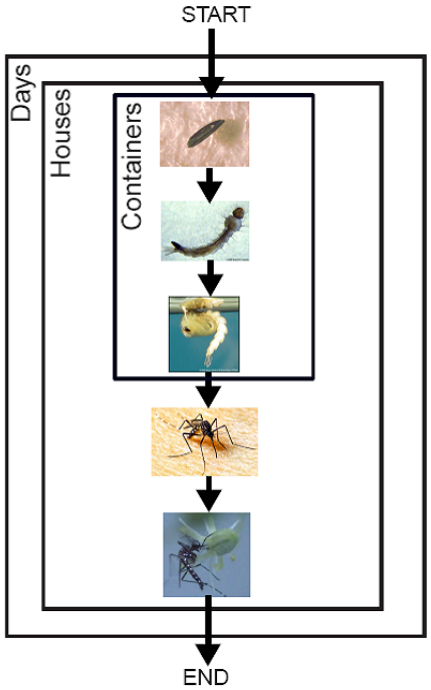
General characteristics:

- Species-specific
- Cohort and stage based
  eggs, larvae, pupae, adults
- Detailed biology
  larval and pupal development
  track weights of cohorts
- Weather-dependent (temperature and rainfall)
- Spatially explicit: includes individual containers in which mosquitoes lay their eggs, and the houses in which containers are found

  adult mosquitoes move between houses

- Stochastic

Based on an earlier complex model, CIMSiM (Focks *et al.*, 1993)



Skeeter Buster: Details

- Daily timestep
- Each container's water level and food content are tracked
  - water gain (rain, human filling), loss (evaporation, human emptying)
  - nutrient input (falling from vegetation, dead pupae), output (consumption)
- Water level important for egg laying and egg development (dessication)
- Larvae compete for food: density dependence
- Enzyme kinetics-based equations model growth and development of immatures
- Female adult weights and gonotrophic cycle are tracked
  - Female mosquitoes bite when they need blood for egg production
- Mating between males and females, depends on sizes
  - larval and pupal development
  - track weights of cohorts
- Movement of adults: typically short-range, occasional long range
  Occasional movement of containers, possibly taking eggs with them
- Fertilization of females? One-time deal, or multiple matings? Sperm choice?

Overlaying Epidemiology on Skeeter Buster

SBEED overlays epidemiology on Skeeter Buster, following the way that DenSIM (Focks et al., 1995) builds epidemiology on top of CIMSiM

- Epidemiological model, takes output of the mosquito model (Skeeter Buster/CIMSiM) as its input
- Individual-based description of the human population
  Includes virus titer within individuals, and its development, and movement of people
- Female mosquito weight and egg production rate affects biting frequency
- Temperature and human virus titer influences extrinsic incubation period and transmission probability

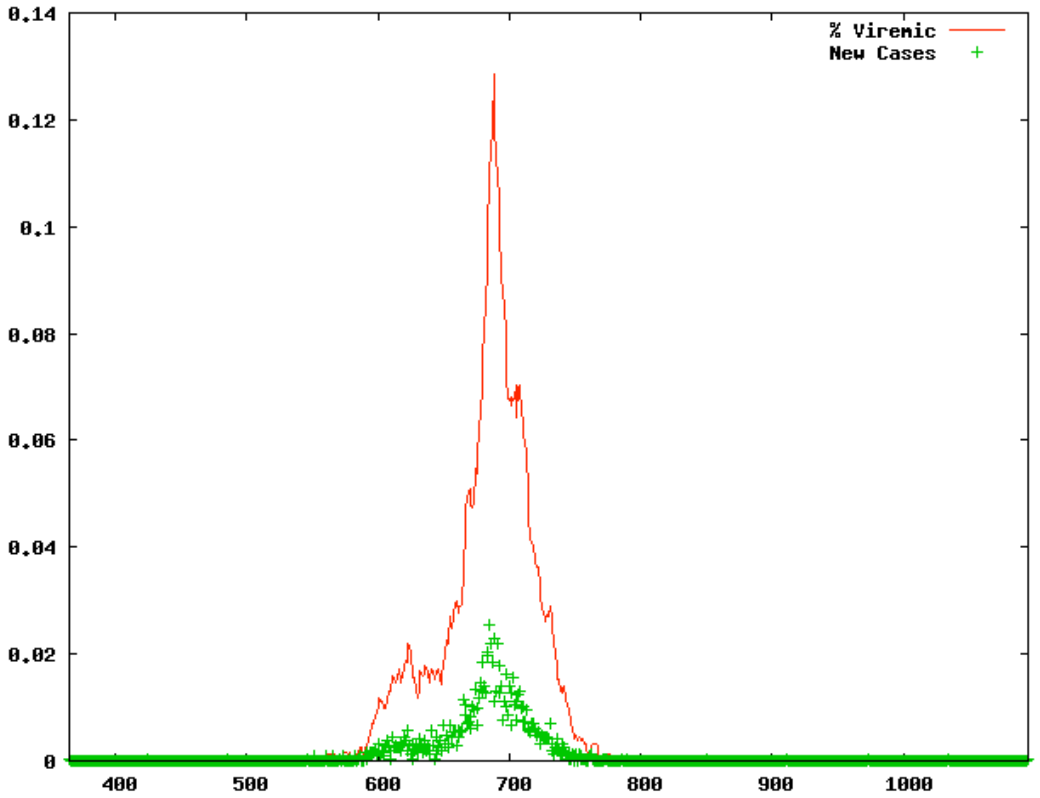
Sample Simulation Results

- Outbreak simulation for
  a single serotype of dengue

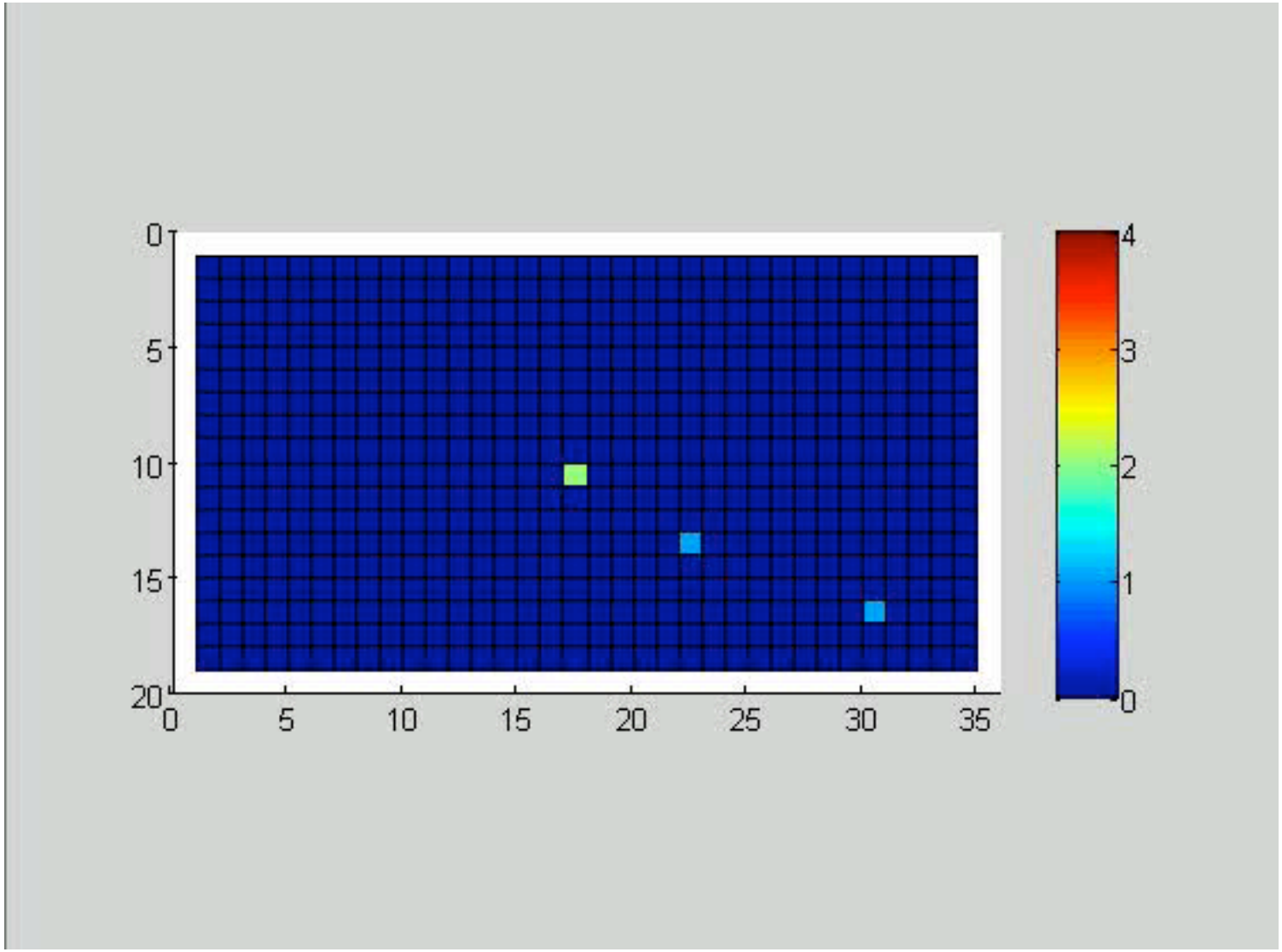
  based on Iquitos, Peru setup

  612 houses, with
  four people per house

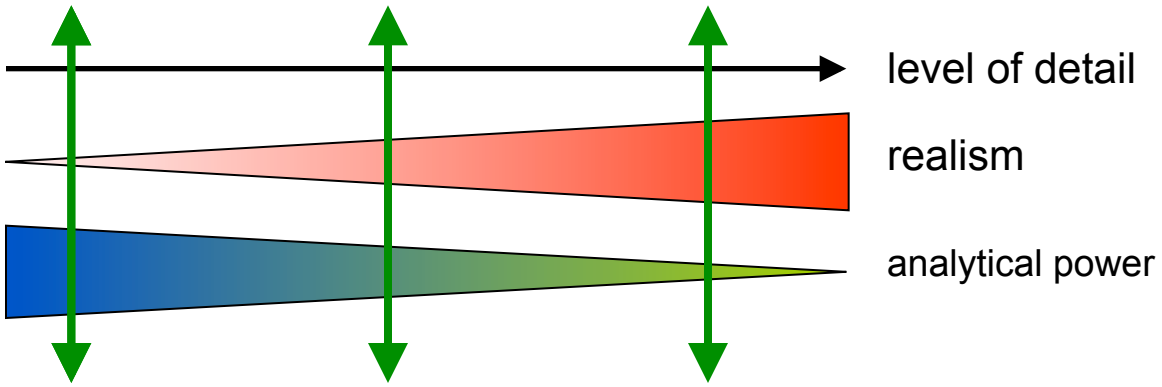
  graph:
  fraction of population vs time (days)



Sample Simulation Results



Simple and Complex Models



Simple models

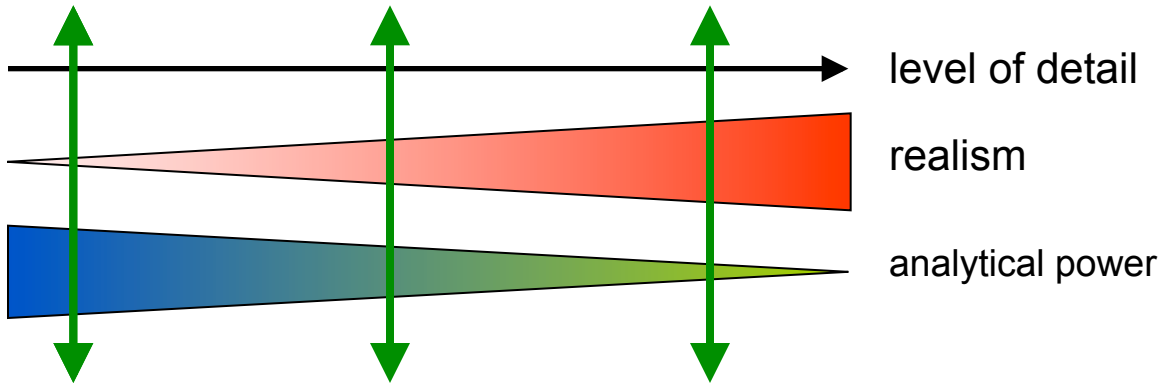
no structure
well-mixed
deterministic

Intermediate complexity

age structure
spatial structure
stochasticity
…

Detailed, biology-rich model of Aedes aegypti : Skeeter Buster

Simple and Complex Models: Pros and Cons



Simple models

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…

Detailed, biology-rich model of Aedes aegypti : Skeeter Buster

✓ Easy to analyze and simulate
gain general insights and understanding

✓ Few parameters
don't need detailed information on the system

✗ Highly simplistic
unlikely to be realistic

✗ Difficult to analyze and simulate
unlikely to yield general insights or understanding

✗ Many parameters: need to have very detailed information on the system

✓/✗ Very specific to a given situation

✓ Has the *potential* to be more realistic provided that we have enough information to parameterize

✗ Easy to be seduced by its apparent realism

Other Thoughts and Observations…

Can we measure model parameters?

Transmission parameters are notoriously difficult to measure directly, values are typically estimated by fitting models to data

what happens if you don't use the correct model?

Is the model formulated in the most useful way?

Transmission models are typically formulated in terms of infectious individuals, but our epidemiological data typically tell us about symptomatic individuals.

In some instances (e.g. dengue), large numbers of cases go unreported, worse still: most incidence data tells us about *severe* infections

Has the model been validated?

If we estimated parameters from a data set, can we consider the model's ability to fit that data a true validation?

Other Thoughts and Observations…

All of these complexities… which ones matter and how can we tell?

Depends on what questions we want to ask

How much do we know about the system?

Surprising number of gaps in our knowledge of the biology

Sensitivity and uncertainty analyses can reveal which processes and/or parameters are more or less important

Can use a complex model as a research tool, to help figure out what we need to know and to help design experiments

Do the predictions of the complex model agree with those made by simpler models?

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IT'S TOO NICE FOR THEM

"*Hubris seems to be the chief vice of the model builder without, and even with, field experience. It induces justified scepticism and is counter-productive. It serves only to convince the determinedly non-numerate public health worker that models are a seductive alternative to understanding*" (Bradley, 1982).

"*... and perhaps none will fully understand the behaviour of the whole system as it operates within the economic, social and political constraints of a given society. This may explain some of the difficulties of predicting with sufficient accuracy the likely consequences of any chosen strategy of intervention. And if one cannot predict the consequences of a given strategy, one had no rational basis for choosing between the available alternatives.*" (Bailey, 1982).

Quotes from Smith *et al.* (2008) Towards a comprehensive simulation model of malaria epidemiology and control. *Parasitology* **135**, 1507-1516.