Scaling Complexity in Dynamical Systems for Malaria

Robust Analytics for Adaptive Malaria Control

Professor David L Smith, University of Washington, Jan 8, 2025
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https://faculty.washington.edu/smitdave/

ADAPTIVE MALARIA CONTROL

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- Adaptive Vector Control is funded by grant **Spatial Targeting and Adaptive Vector Control for Residual Transmission and Malaria Elimination in Urban African Settings** (R01 AI163398, PI = David L Smith), from US National Institute of Allergies and Infectious Diseases (NIAID).

University of Washington

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Uganda *(RAMP-Uganda, NMCD, DHI)*

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BIMEP *(Bioko Island Malaria Elimination Program)*

Guillermo Garcia, Carlos Guerra, David Galick

Etc.

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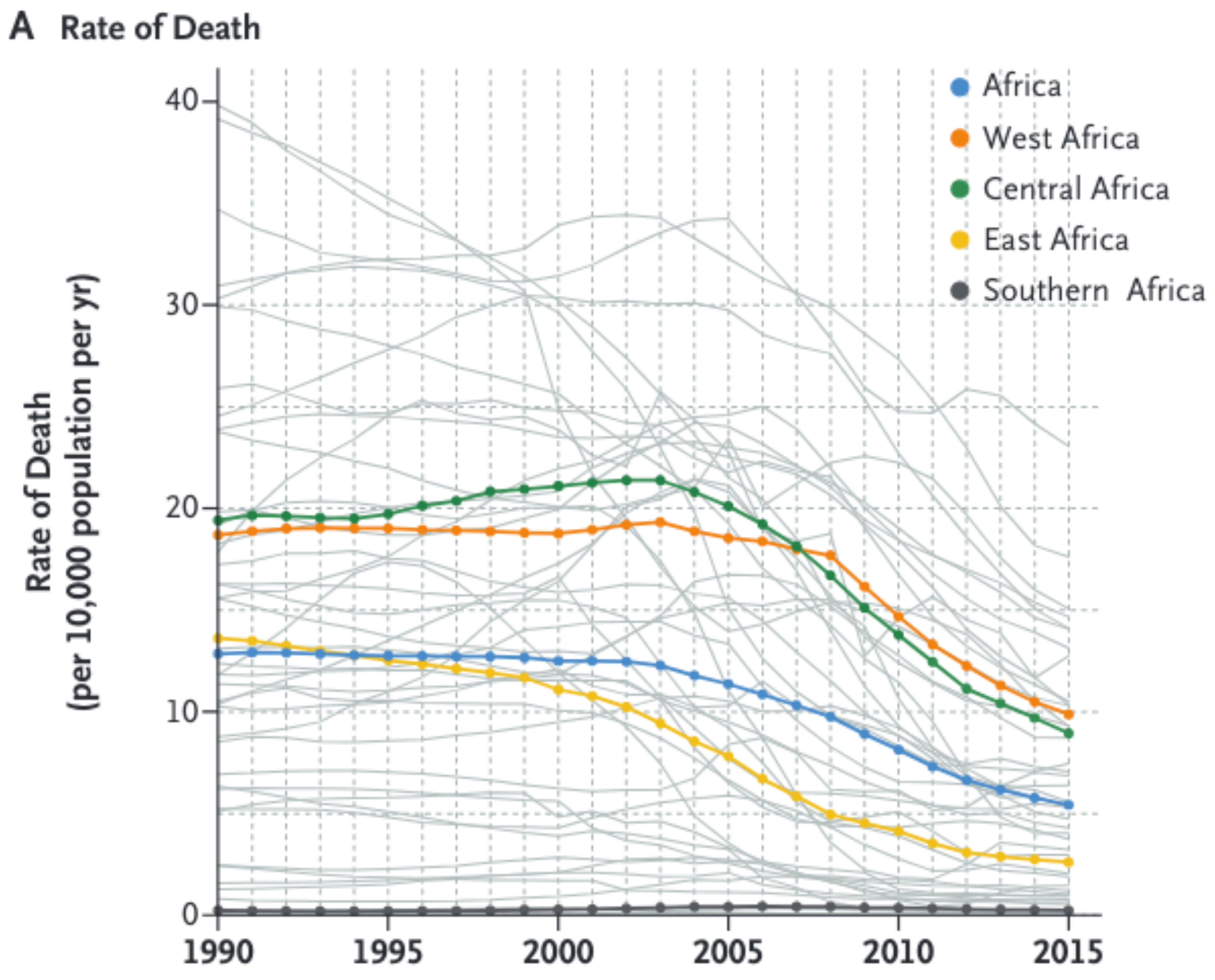
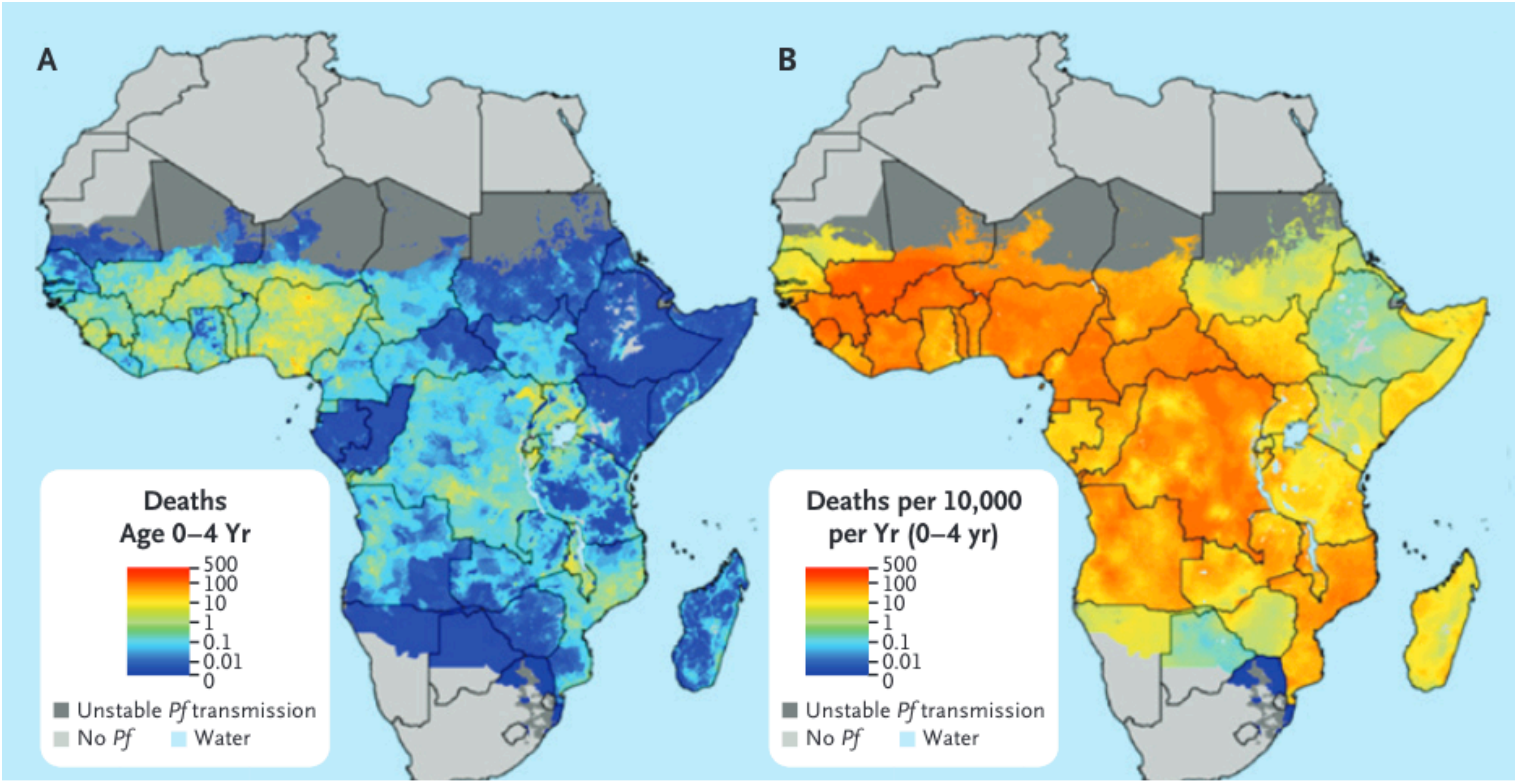
Human malaria can be understood as a set of loosely coupled, managed, complex adaptive systems with multiple interacting agents (*i.e.*, parasites, mosquitoes, humans, & managers), non-linear interactions (*e.g.,* immunity, blood feeding & transmission, mosquito population regulation), and exogenous forcing by weather & malaria control. The systems evolve through evolution of resistance to drugs & insecticides, changing climate, and socio-economic development.

Mapping *Plasmodium falciparum* Mortality in Africa between 1990 and 2015



~631,000 deaths in Africa, 2015



https://www.nejm.org/doi/full/10.1056/NEJMoa1606701

…*malaria is so moulded and altered by local conditions that it becomes a thousand different diseases and epidemiological puzzles. Like chess, it is played with a few pieces, but is capable of an infinite variety of situations*.

Lewis Hackett, 1937

Robust Analytics for Adaptive Malaria Control

Defining malaria analytics

- **Malaria Analytics** → systematic analysis of data for decision support or to develop malaria policy advice
- **Robust Analytics for Malaria Policy (RAMP)**
  - A bespoke inferential system that combines conventional and simulation-based analytics to develop malaria policy advice
  - Advice is ***robust*** in the sense that it would not change if the analysis had been done in a slightly different but reasonable way
  - Robust analytics was designed to characterize, quantify, and propagate uncertainty (ontological, epistemic, & aleatoric) through the analysis including its effects on the policy advice
- **Adaptive Malaria Control** → adaptive management for malaria: iterative, robust analytics with a feedback loop to modify surveillance or conduct studies to reduce uncertainty over time

Scaling Complexity for Malaria Analytics

Mathematics / Scientific Research / Analytics

- **Mathematics** → Formulate new classes of dynamical systems. Critically evaluate equations. Develop new methods or algorithms for computation or analysis. Qualitative analysis. Prove conjectures. Verify model or computational methods. **What can we understand about the dynamical behavior of the equations?**

- **Scientific Research** → Build models to understand malaria or address focused research questions. Prefer simple, analytic models. Analyze models to understand something about malaria. Estimate parameters, measure transmission. Fit models to aggregated data. Model selection & parsimony. Make general conclusions about *how things work* or *what we know.* Identify critical knowledge gaps. How accurate is the model? **What does the model teach us about malaria?**

- **Analytics** → Build models to address policy questions. Fit models to data describing malaria *in situ.* Make recommendations about *what to do now* or *strategic plans* affecting malaria. Identify critical data gaps affecting malaria policy. Is the policy advice robust to uncertainty? **What does the analysis suggest is the best malaria policy?**

Scaling Complexity for Malaria Analytics

What makes a model / framework / analysis good for policy?

- **Timely** → *Nimble*
- **Responsive** → Fit for Purpose; Realistic
- **Accurate** → Models Observational Process; Fitted to Data
- **Useful** → Specific Advice; Output Thresholds, Burden, Avertable Burden, …
- **Accountable** → Replicable; Repeatable; Transparent
- **Thorough** → *Robust Analytics;* Ensemble Analyses
- **Adaptive** → Evolving; *Relevant Details*

Scaling Complexity for Malaria Analytics

What makes a model / framework / analysis good for policy?

Nimble

- Models are integrated into well-organized information systems that include data processing pipelines, algorithms for routine analysis, and up-to-date *malaria intelligence* assessments
- A framework enables model building to rapidly develop simulation-based analyses fit-for-purpose

Relevant Detail

- Pipelines are developed that propagate uncertainty through ensembles of simulation-based policy analyses
- The ensembles are analyzed to identify parameters that affect the policy advice
- If the uncertainty could be narrowed, what would resolve uncertainty about what to do?

Malaria: Dynamical Systems

Ronald Ross
1899-1911

1911

THE PREVENTION OF MALARIA

SOME QUANTITATIVE STUDIES IN EPIDEMIOLOGY.

$$\frac{dz}{dt} = k'z'(p - z) + qz$$

$$\frac{dz'}{dt} = kz(p' - z') + q'z'$$

These studies require to be developed much further; but they will already be useful if they help to suggest a more precise and quantitative consideration of the numerous factors concerned in epidemics. At present medical ideas regarding these factors are generally so nebulous that almost any statements about them pass muster, and often retard or misdirect important preventive measures for years. RONALD ROSS.

George Macdonald
1950-1969

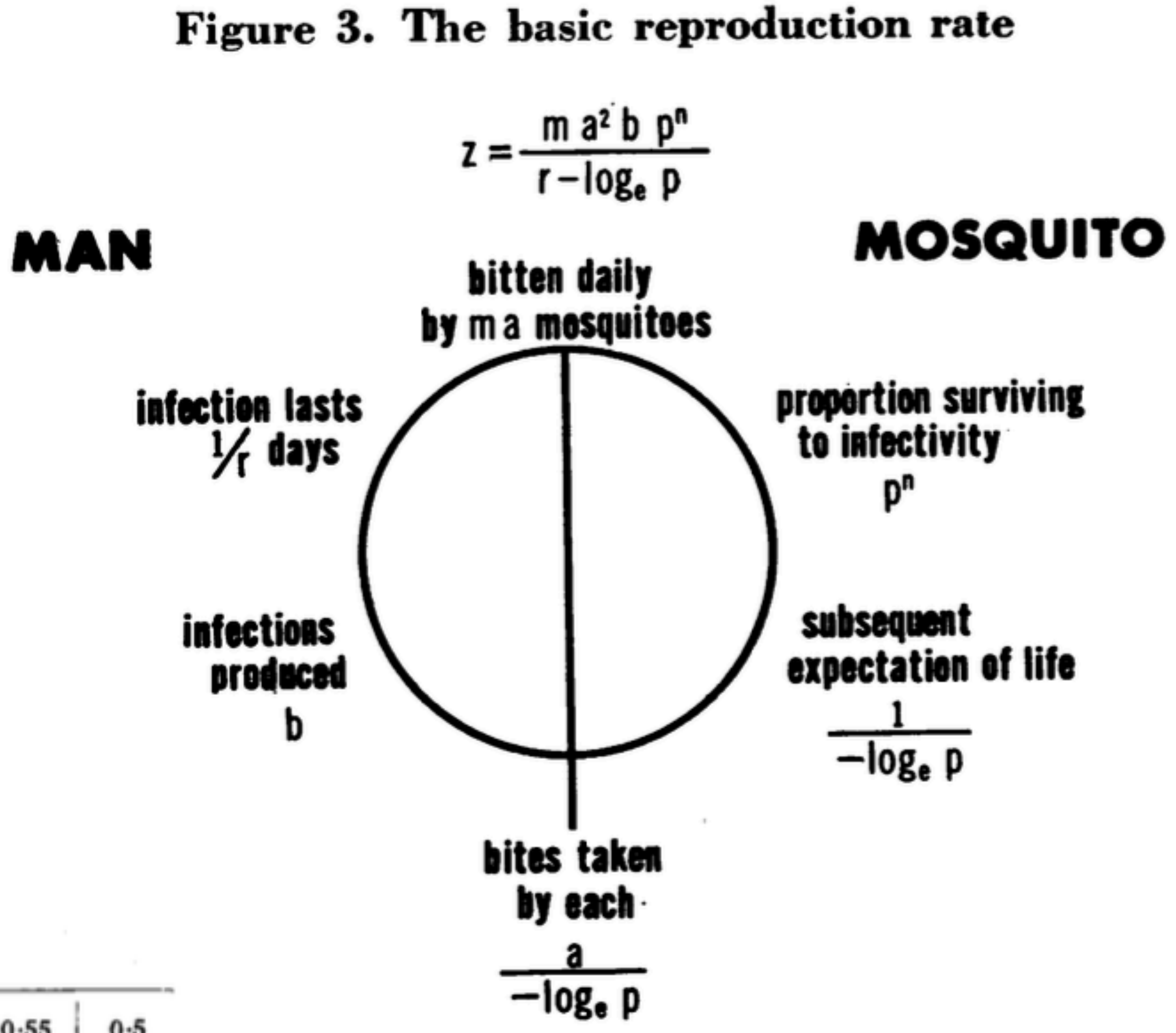


TABLE I

Values of p^n and $-\log_e p$

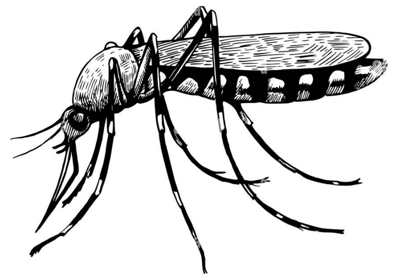
Value of p:—	0·95	0·9	0·85	0·8	0·75	0·7	0·65	0·6	0·55	0·5
p^8	0·6633	0·4304	0·2725	0·1677	0·1002	0·0577	0·0318	0·0168	0·0084	0·0039
p^9	0·6302	0·3875	0·2316	0·1342	0·0751	0·0404	0·0207	0·0101	0·0046	0·0019
p^{10}	0·5987	0·3486	0·1967	0·1075	0·0564	0·0283	0·0135	0·0060	0·0025	0·0010
p^{11}	0·5687	0·3138	0·1673	0·0859	0·0423	0·0198	0·0087	0·0036	0·0014	0·0005
p^{12}	0·5402	0·2823	0·1422	0·0687	0·0317	0·0138	0·0057	0·0022	0·0008	0·0002
p^{13}	0·5134	0·2542	0·1209	0·0550	0·0238	0·0097	0·0037	0·0013	0·0004	0·0001
p^{14}	0·4876	0·2288	0·1028	0·0440	0·0178	0·0068	0·0024	0·0008	0·0002	
p^{15}	0·4632	0·2059	0·0874	0·0352	0·0134	0·0047	0·0016	0·0005	0·0001	
p^{16}	0·4401	0·1853	0·0743	0·0281	0·0102	0·0033	0·0010	0·0003		
p^{17}	0·4181	0·1667	0·0631	0·0225	0·0075	0·0023	0·0007	0·0002		
p^{18}	0·3972	0·1501	0·0536	0·0180	0·0053	0·0016	0·0004	0·0001		
p^{19}	0·3773	0·1351	0·0456	0·0144	0·0042	0·0011	0·0003			
p^{20}	0·3585	0·1215	0·0388	0·0115	0·0032	0·0008	0·0002			
$-\log_e p$	0·0513	0·1054	0·1625	0·2232	0·2877	0·3567	0·4308	0·5108	0·5979	0·6932

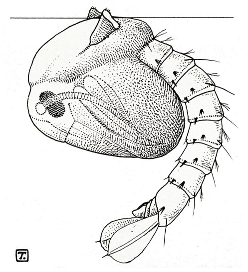
Note : The fact that $-\log_e p$ is a *positive* number must be borne in mind.

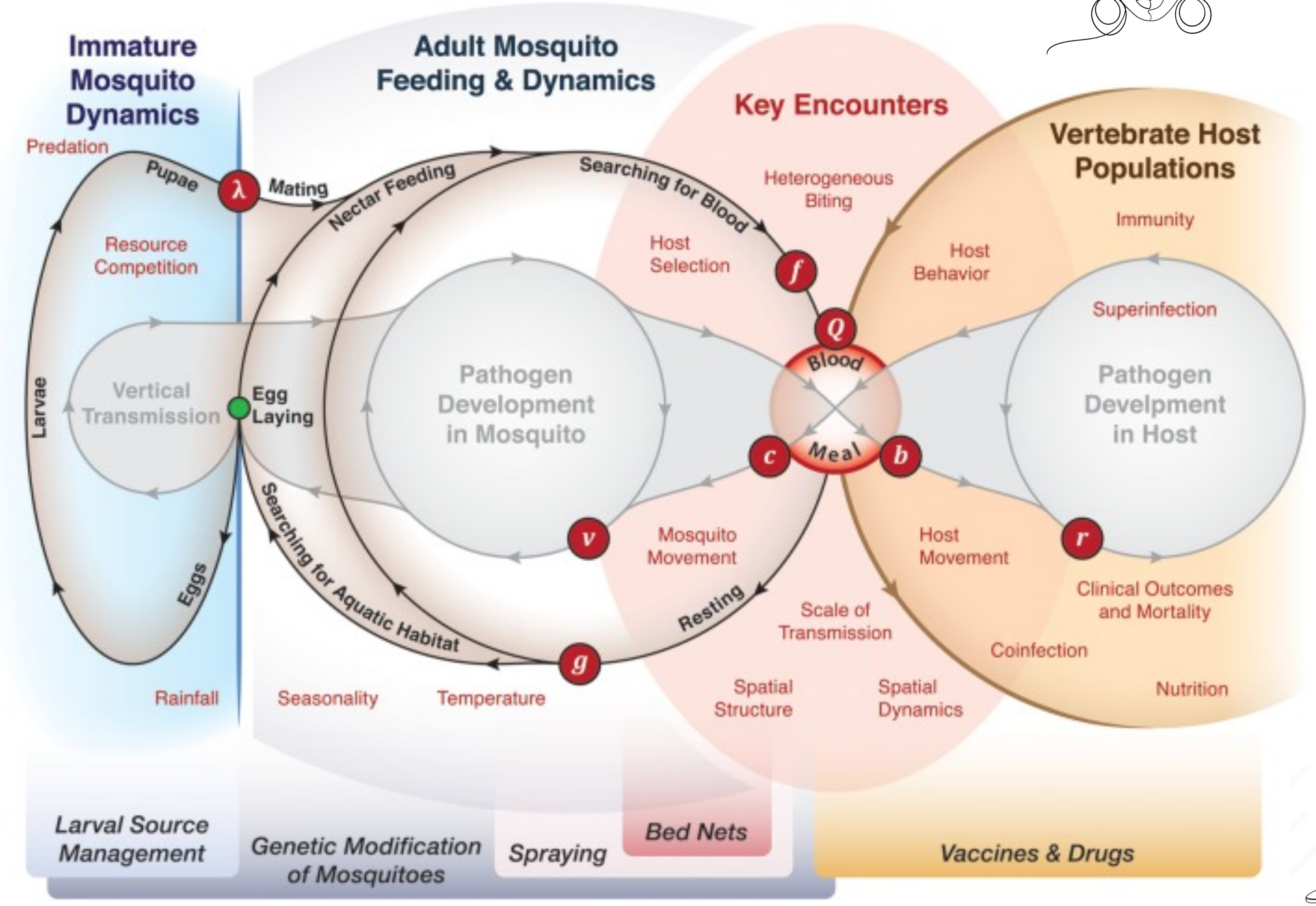
Ross, Macdonald, and a Theory for the Dynamics and Control of Mosquito-Transmitted Pathogens

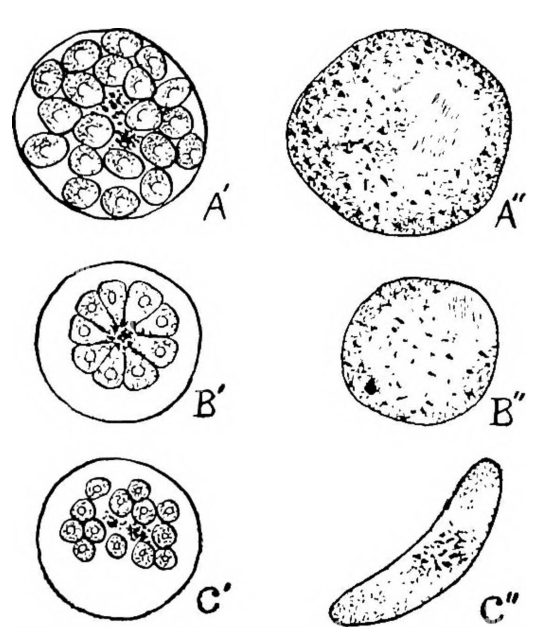
https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1002588

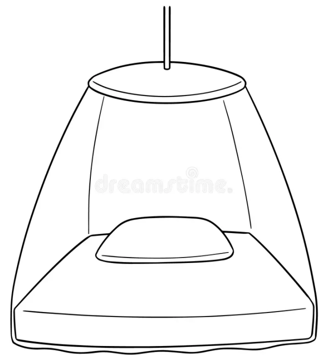
Malaria Theory









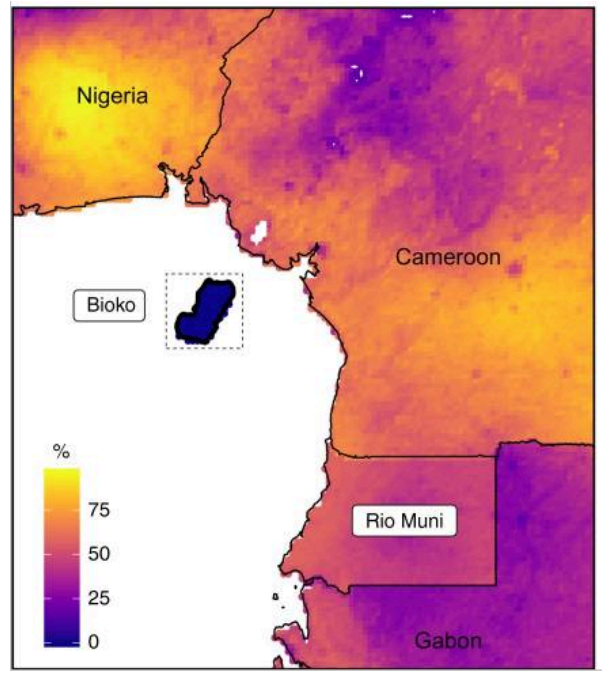


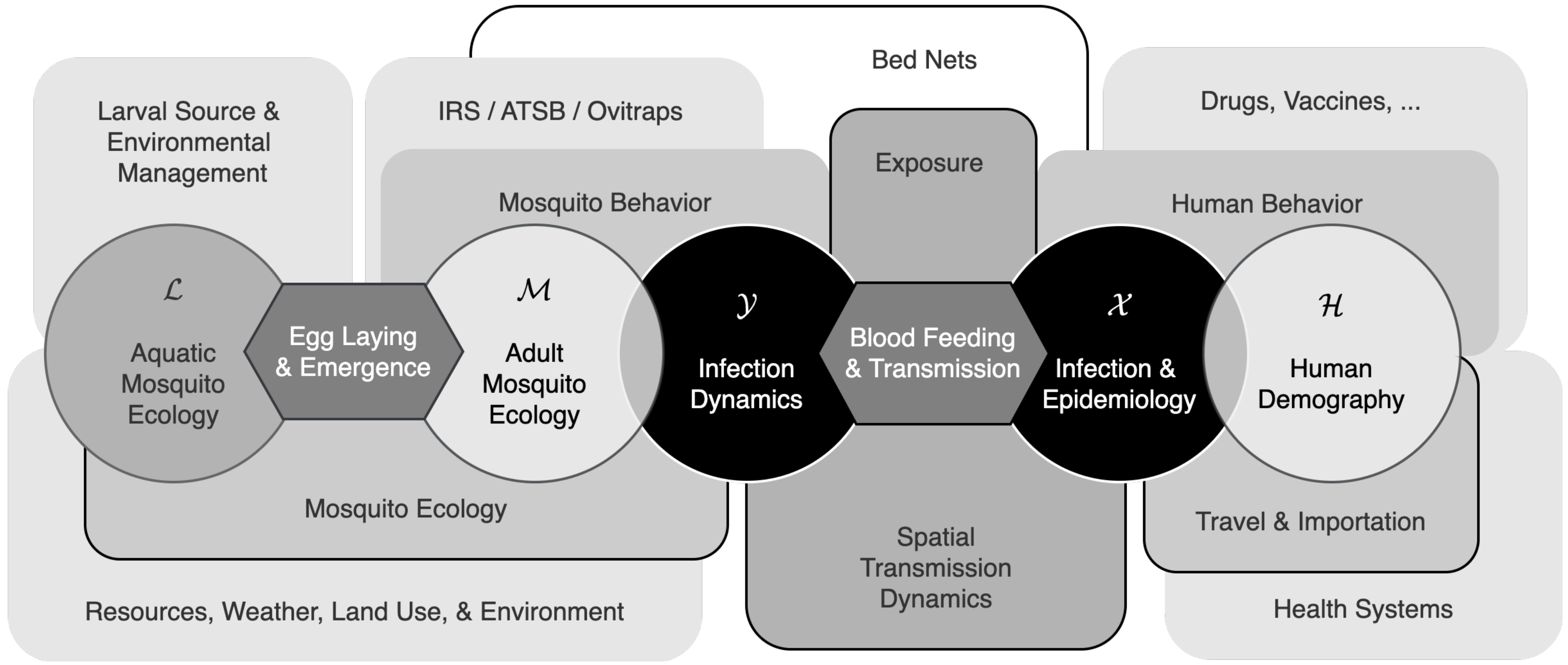
Recasting the theory of mosquito-borne pathogen transmission dynamics and control
https://academic.oup.com/trstmh/article/108/4/185/1924536

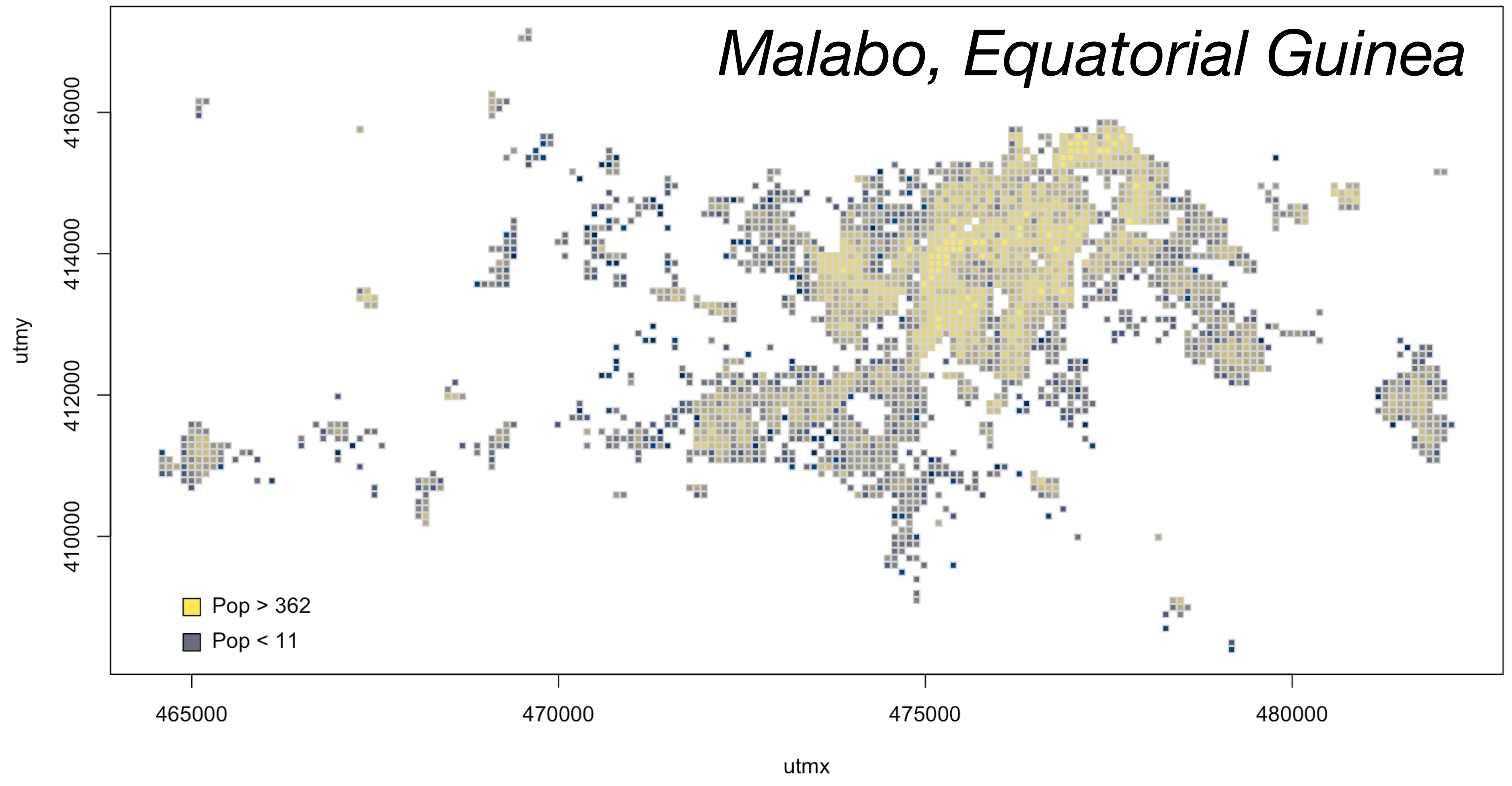
A systematic review of mathematical models of mosquito-borne pathogen transmission: 1970–2010
https://royalsocietypublishing.org/doi/full/10.1098/rsif.2012.0921

A Modular Framework for Malaria Model Building

Scalable Complexity for Malaria Analytics







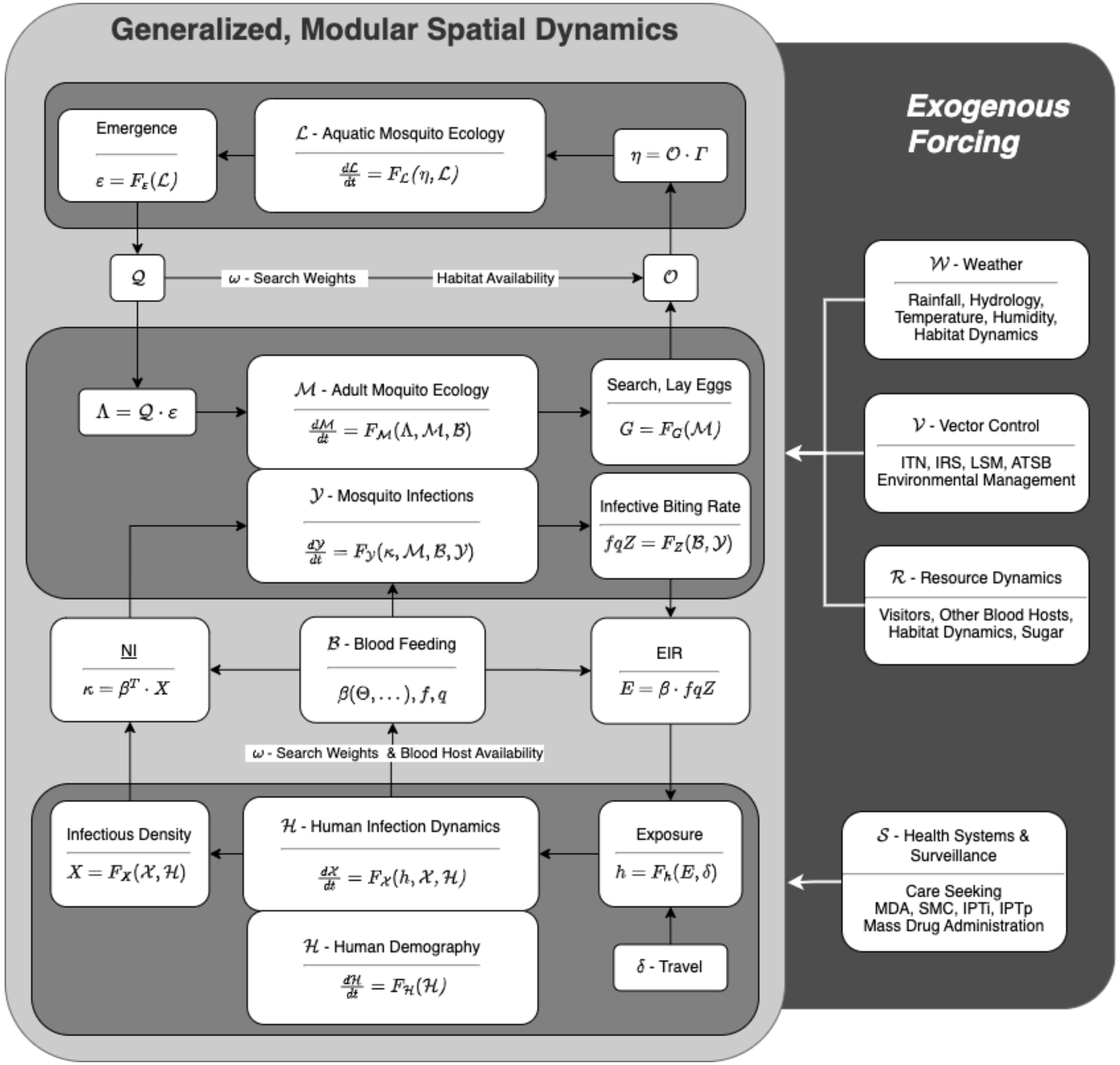
Mosquito Dynamics
Aquatic Ecology

Egg Laying & Emergence

Adult Mosquito
Demography, Behavior, Infection Dynamics

Blood Feeding & Transmission

Humans
Malaria Epidemiology Demography



Environment
Habitat Dynamics, Resource Dynamics, Weather

Malaria Control
Vector Control, Vaccines, Mass Therapy

Health Systems
Primary Healthcare & Surveillance

Spatial dynamics of malaria transmission
https://doi.org/10.1371/journal.pcbi.1010684

Scalable Complexity

Software Design Features

- **Modular**
  - 3 dynamical ***components*** (sub-systems) representing 5 distinct sets of processes
  - rigorous ***interfaces*** for blood feeding and egg laying (patch-based meta-population dynamics)
  - internalize lagged computations for delay differential equations
- **Flexible**
  - arbitrary numbers of human population strata, patches & aquatic habitats
  - multiple vector / host species
  - trivial modules
  - boundary conditions (malaria importation)
- **Extensible**

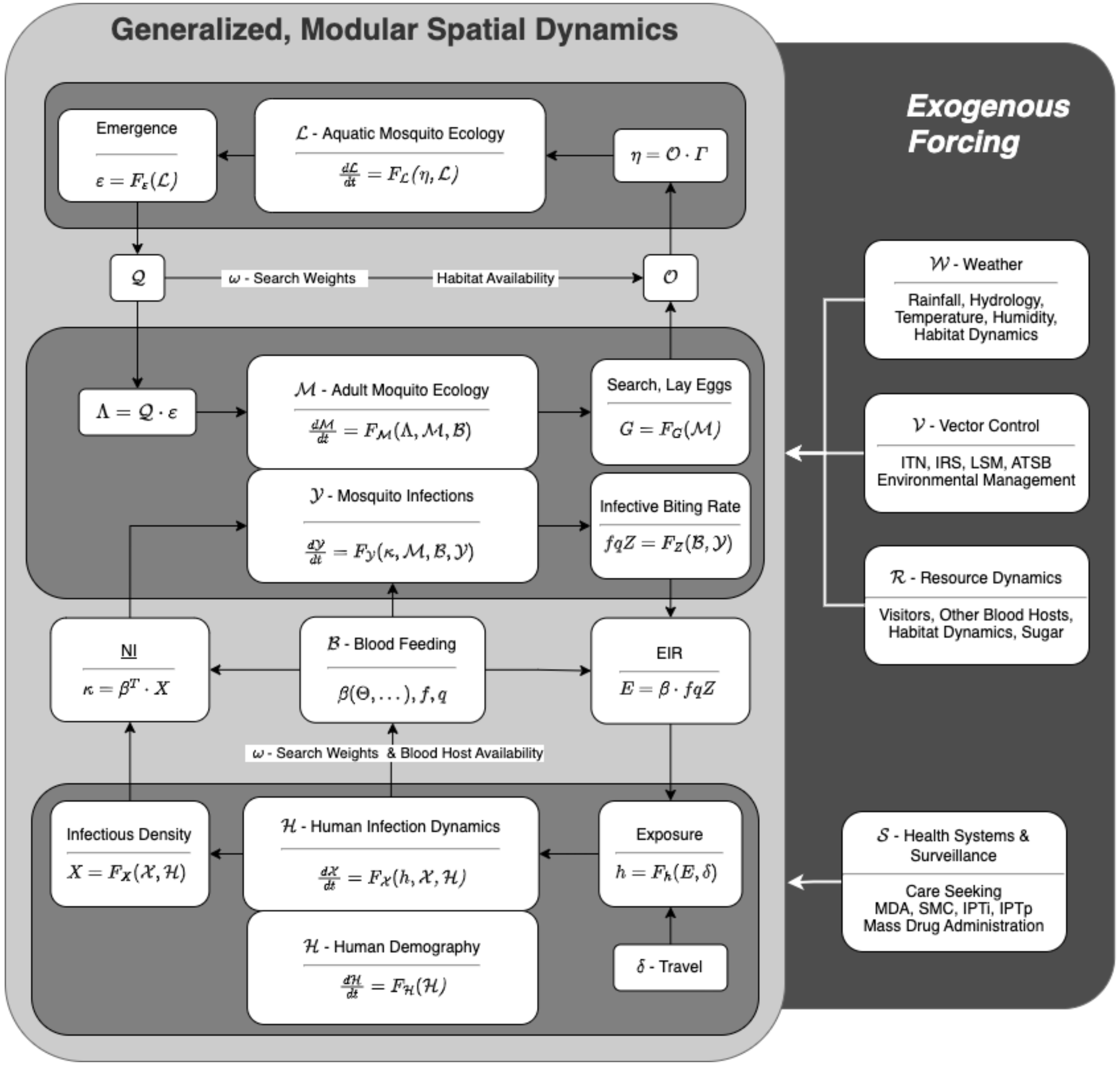
Mosquito Dynamics
Aquatic Ecology

Egg Laying & Emergence

Adult Mosquito
Demography, Behavior,
Infection Dynamics

Blood Feeding & Transmission

Humans
Malaria Epidemiology
Demography



Environment
Habitat Dynamics,
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Spatial dynamics of malaria transmission
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SimBA

*Software for **Sim**ulation-**B**ased **A**nalytics*

R packages on GitHub

- **ramp.xds** → e**X**tensible **D**ynamical **S**ystems for malaria and mosquito-borne pathogens: setup & solve autonomous and non-autonomous systems of ordinary & delay differential and difference equations with spatial dynamics, including stochastic difference equations (replaces *exDE & MicroMoB*)

- **ramp.library** → reusable code library of (perhaps slightly modified) published / peer reviewed models, imported as dynamical modules for the major components

- **ramp.control** → reusable code library of algorithms implementing malaria control, including most forms of vector control & mass distribution of therapeutics

- **ramp.forcing** → reusable code library of peer reviewed algorithms implementing exogenous forcing by weather & other factors

- **ramp.work** → algorithms to accomplish specific tasks

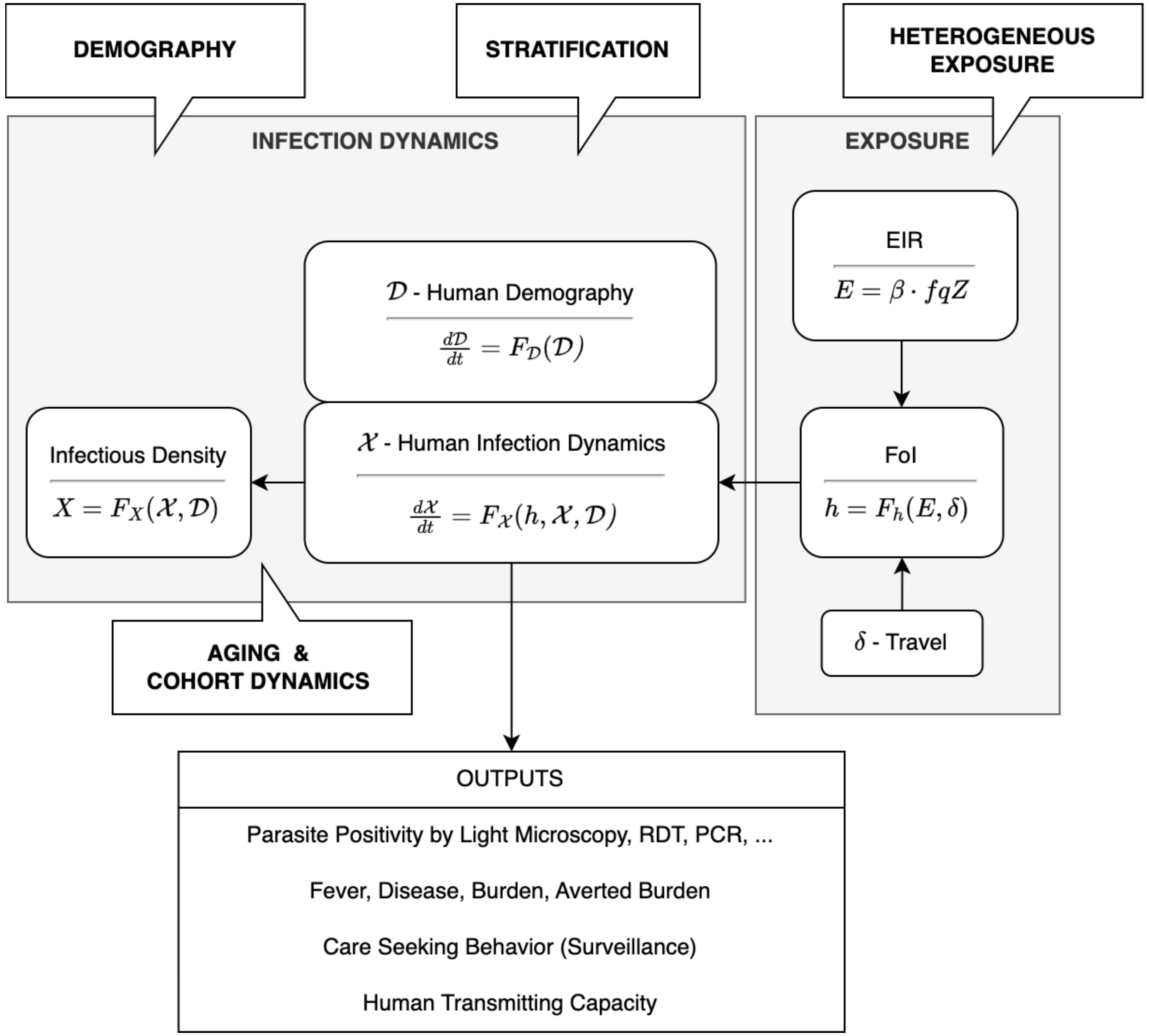
https://faculty.washington.edu/smitdave/simba/index.html

Robust Analytics

Malaria Epidemiology

The Robust Approach

- Exposure
- Dynamics of Infection & Immunity
- Human Demography
    - Births, Deaths, Migration
    - Aging / Cohort Dynamics
- Heterogeneity / Stratification
- **<u>Outputs</u>**
    - Research Metrics
    - Surveillance Metrics
    - Analysis

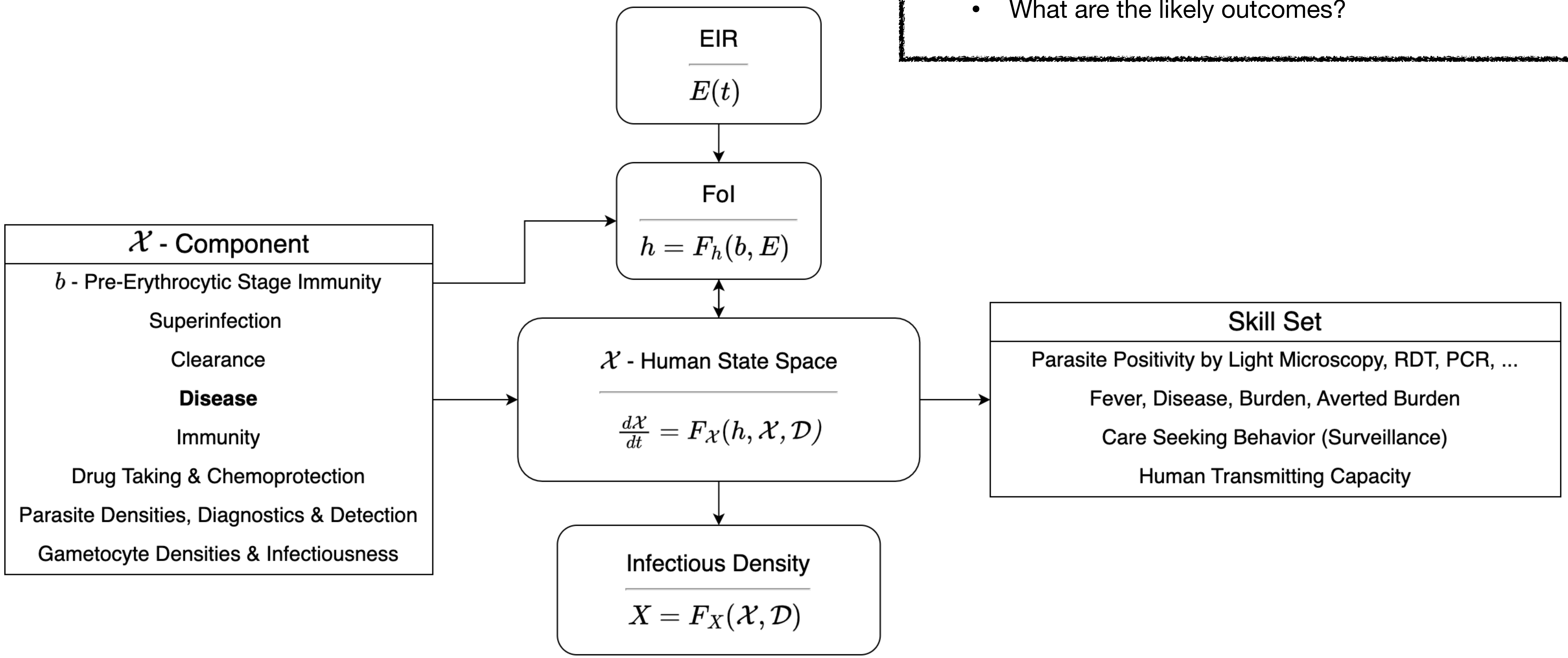


Malaria Epidemiology

Dynamics of Infection & Immunity

Given my current ***state*** and my history of exposure and infection…

- How would my state change over time without exposure?
- How would my state change upon exposure?
- What are the likely outcomes?

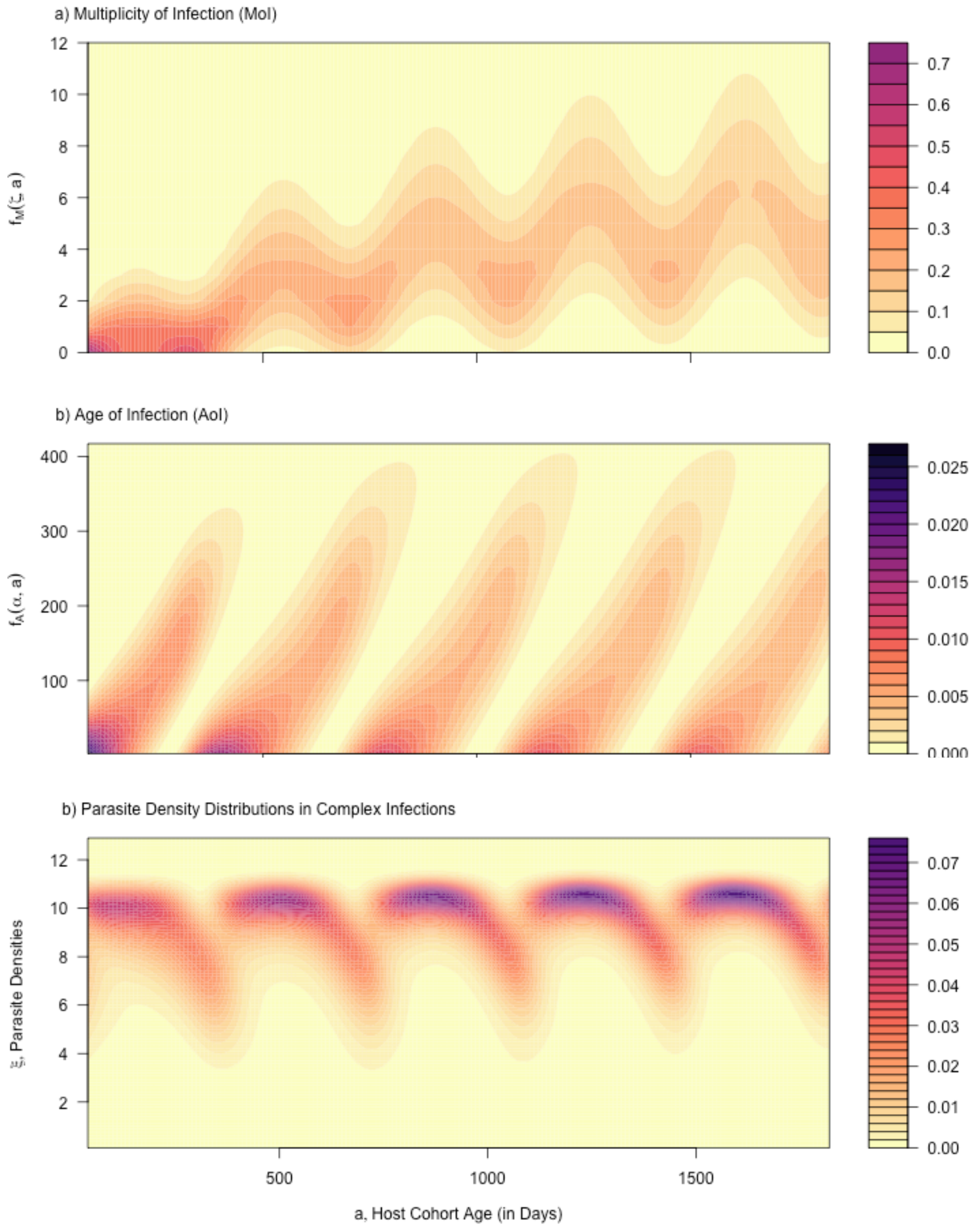


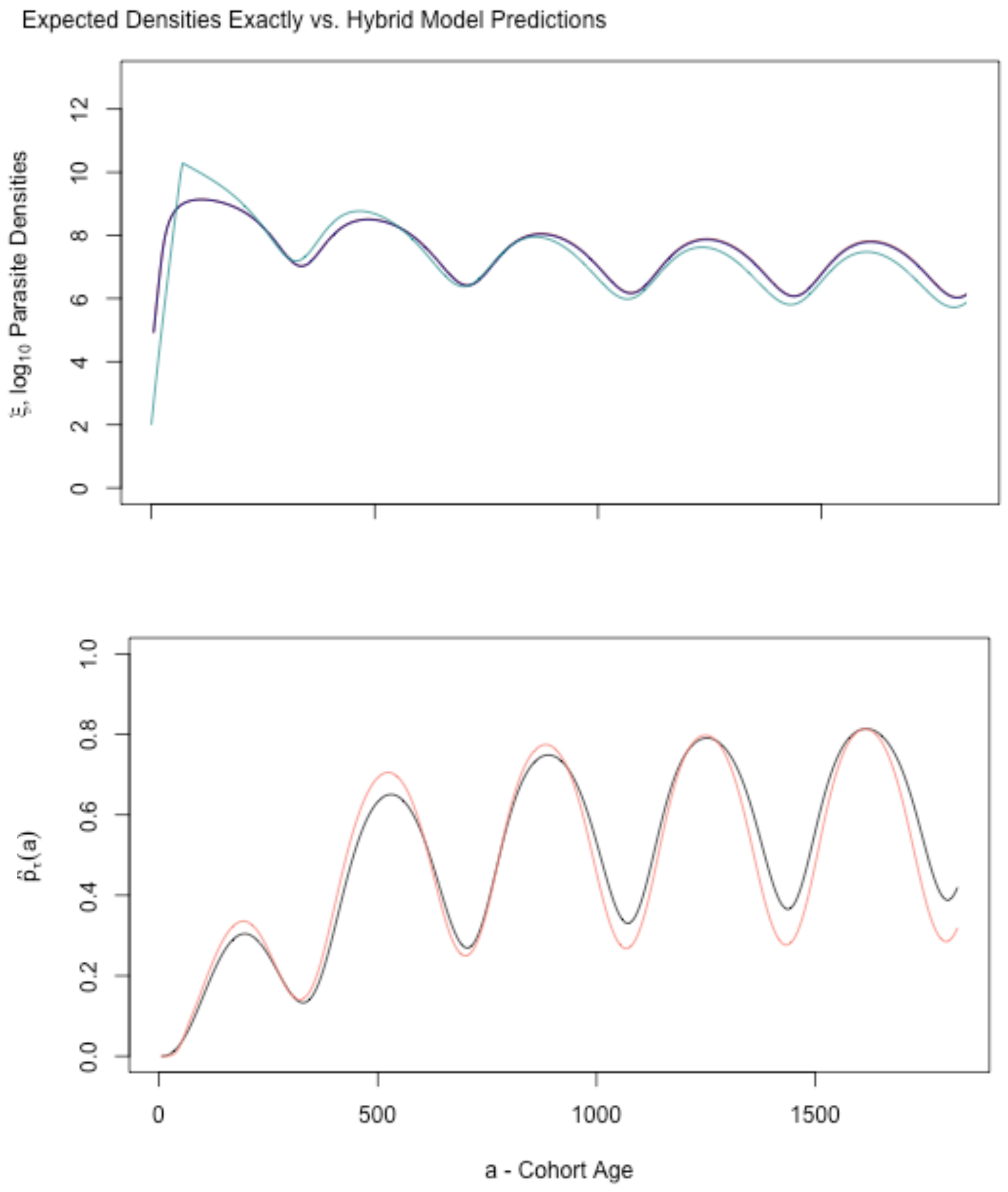
Malaria Epidemiology

Deep Dive: `ramp.falciparum`

$$E[P_\tau(a)] = \int_0^b \xi f_P(\xi; a, \tau | h) d\xi \approx F_\mu(x_\tau(a))$$
$$E[B_\tau(a)] = \int_0^b \xi f_B(\xi; a, \tau | h) d\xi \approx F_\mu(y_\tau(a))$$

$$\frac{dm}{da} = h - rm$$
$$\frac{dx}{da} = 1 - x\frac{h}{m}$$
$$\frac{dy}{da} = 1 - y\frac{h}{p} + \phi(r, m)x$$





PhD Thesis:

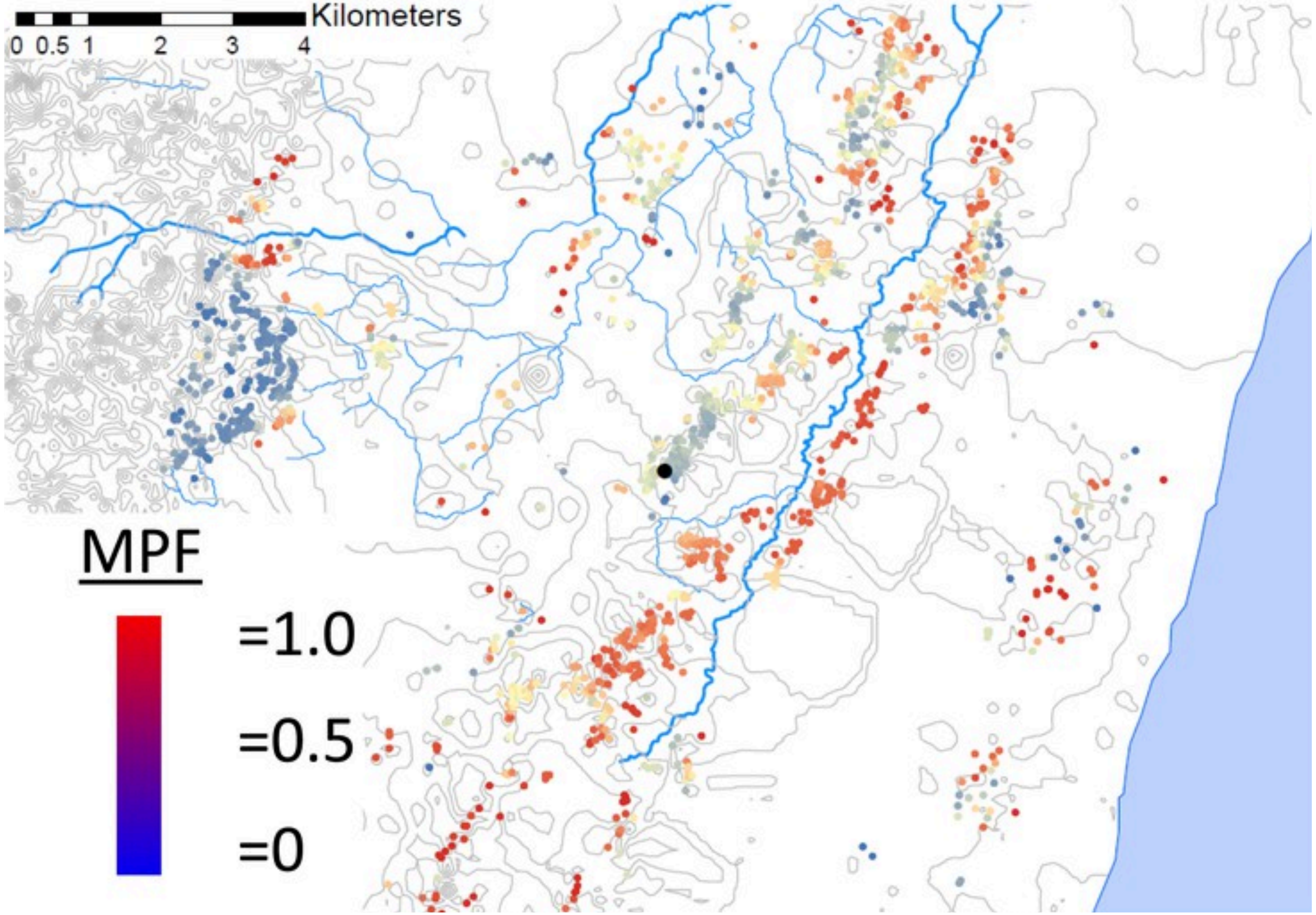
John M. Henry

GitHub R Package

`ramp.falciparum`

https://dd-harp.github.io/ramp.falciparum/

Malaria Positive Fraction (MPF): among all hospital visits from 2003-2011 in which febrile patients from each homestead tested positive for malaria



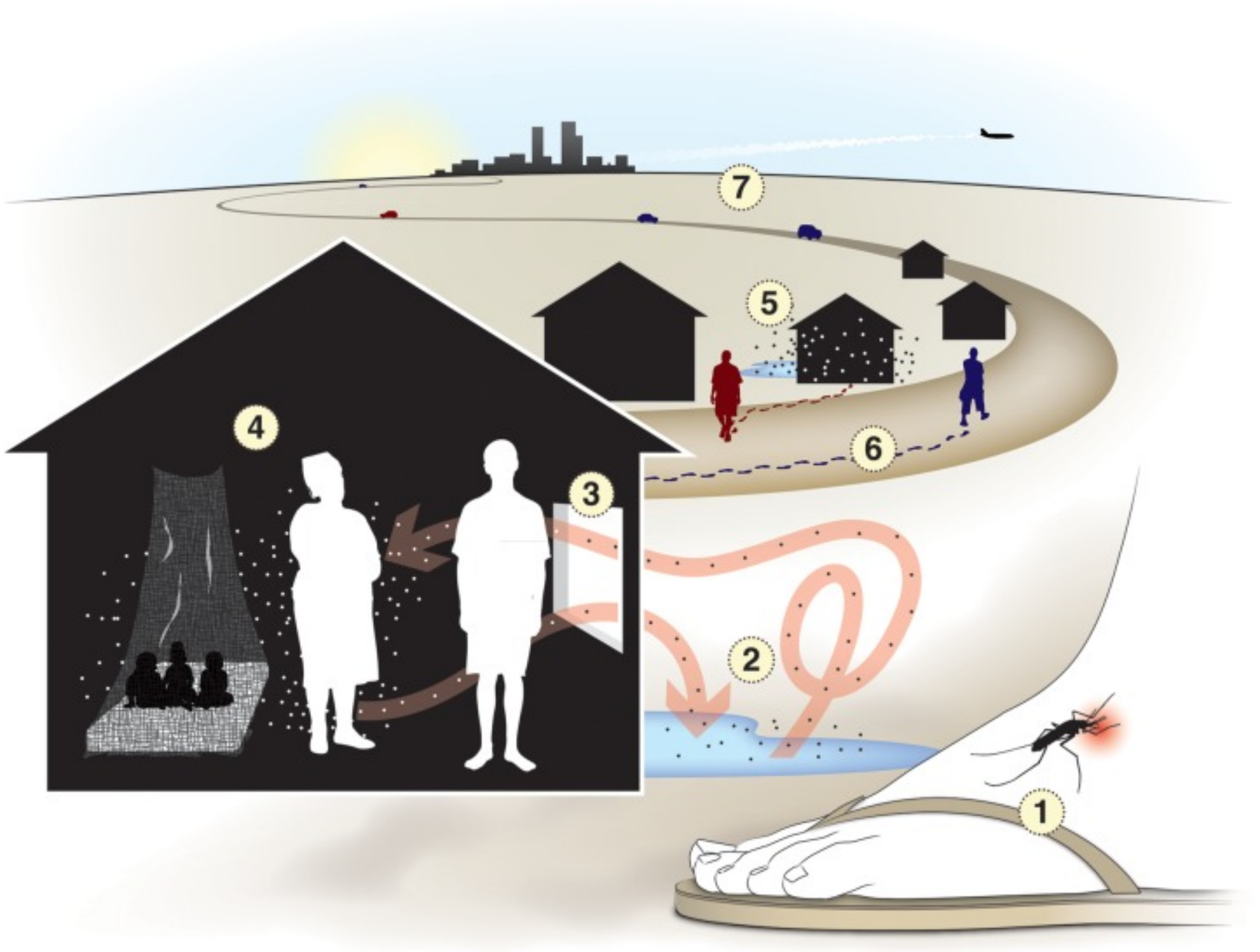
A micro-epidemiological analysis of febrile malaria in Coastal Kenya showing hotspots within hotspots

https://doi.org/10.7554/eLife.02130

Transmission Dynamics

The Robust Approach

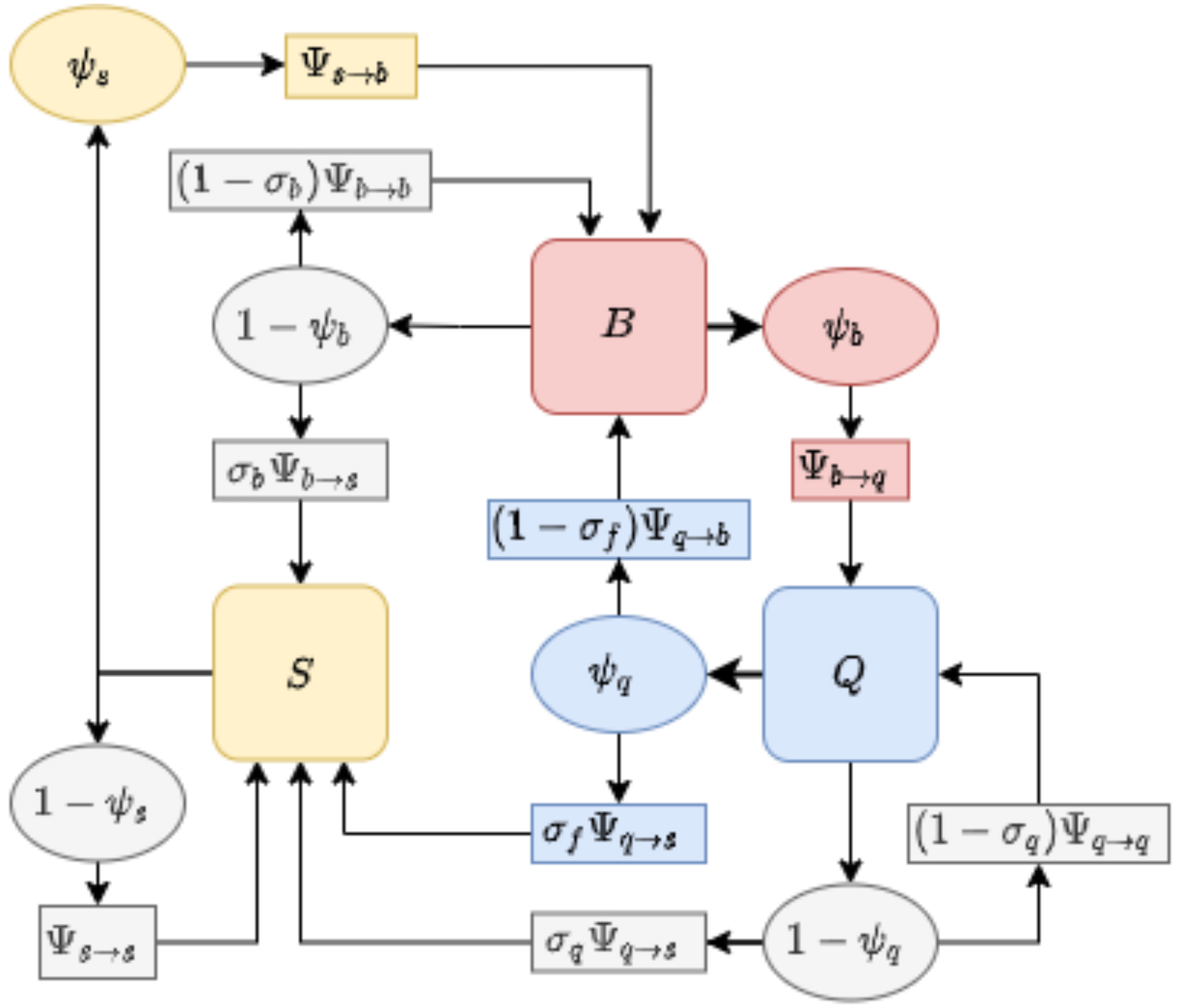
- How far do mosquitoes move?
- What spatial scales are appropriate for modeling transmission?
- What, if anything, is a malaria population?
- What, if anything, is a focus?
- Is all malaria transmission focal?



Mosquito Ecology

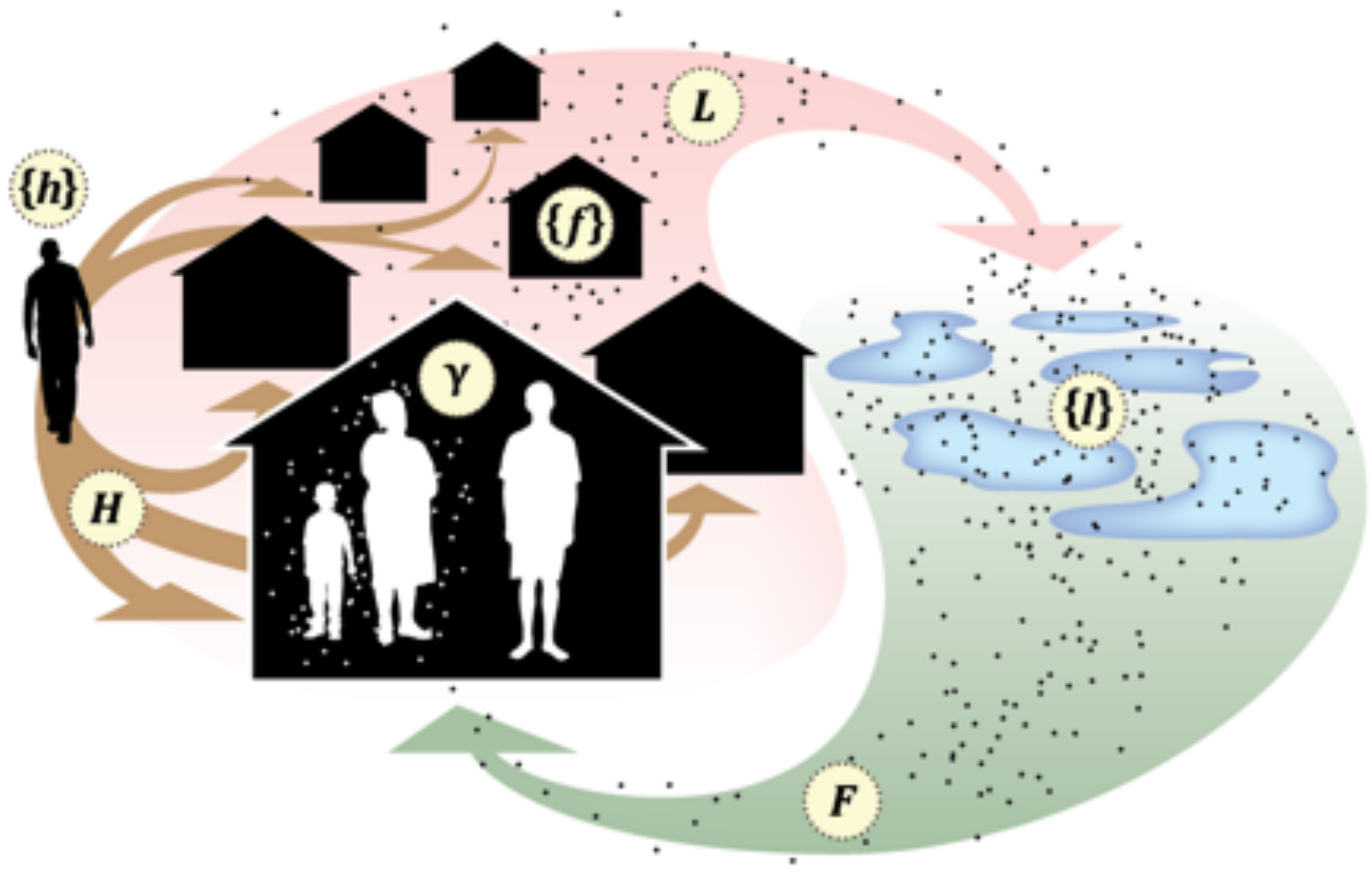
The Robust Approach

Mosquito Behavioral State Models



Microsimulation

Transmission dynamics on point sets



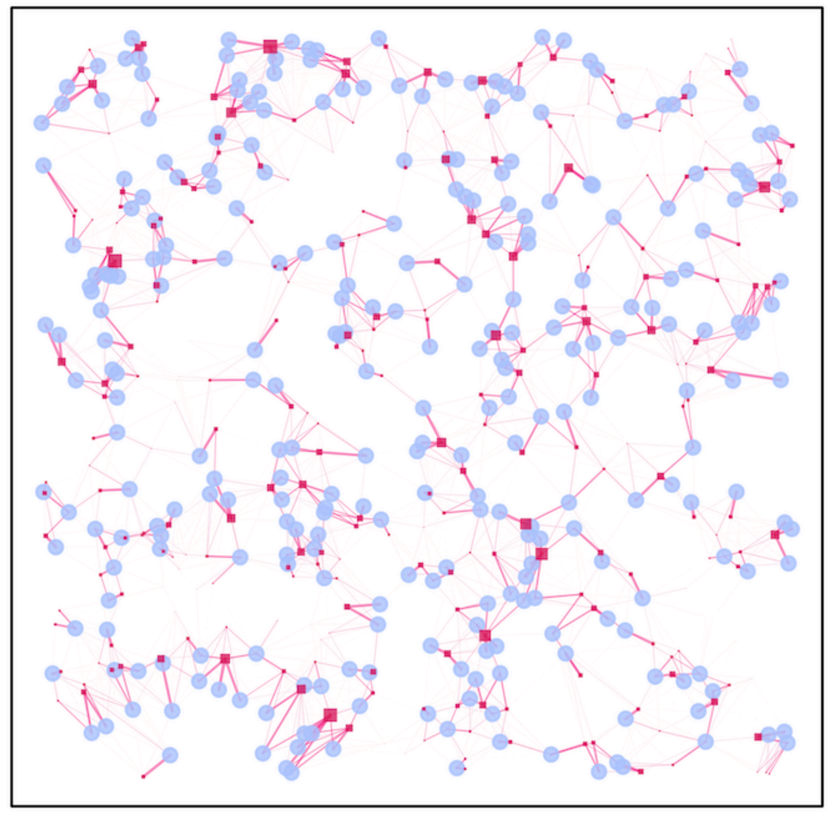
Heterogeneity, Mixing, and the Spatial Scales of Mosquito-Borne Pathogen Transmission

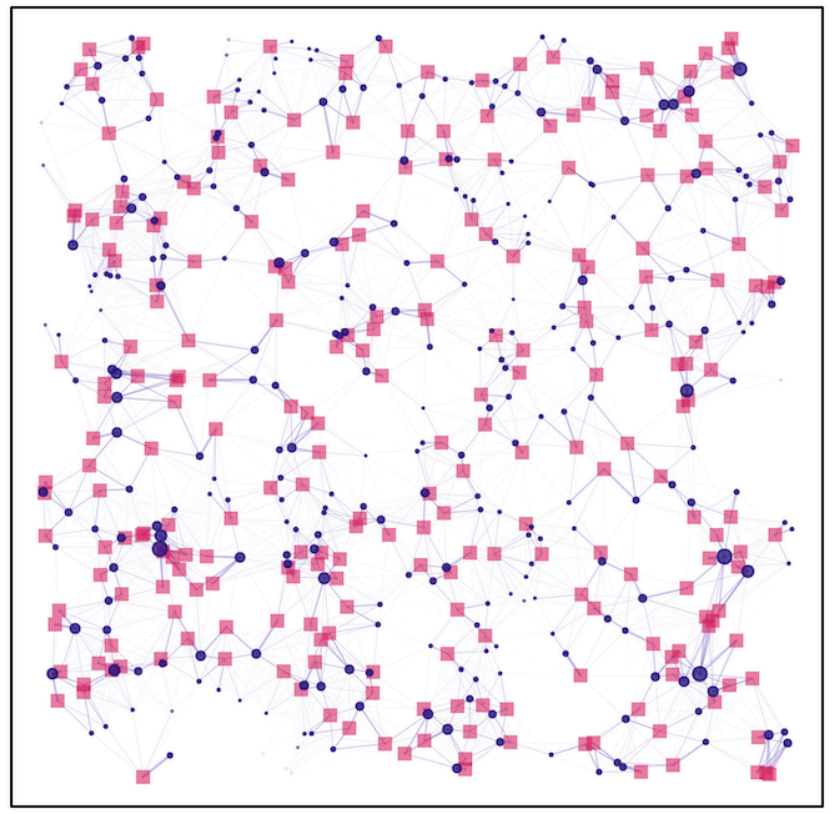
https://doi.org/10.1371/journal.pcbi.1003327

Mosquito Ecology

Deep Dive: `ramp.micro`

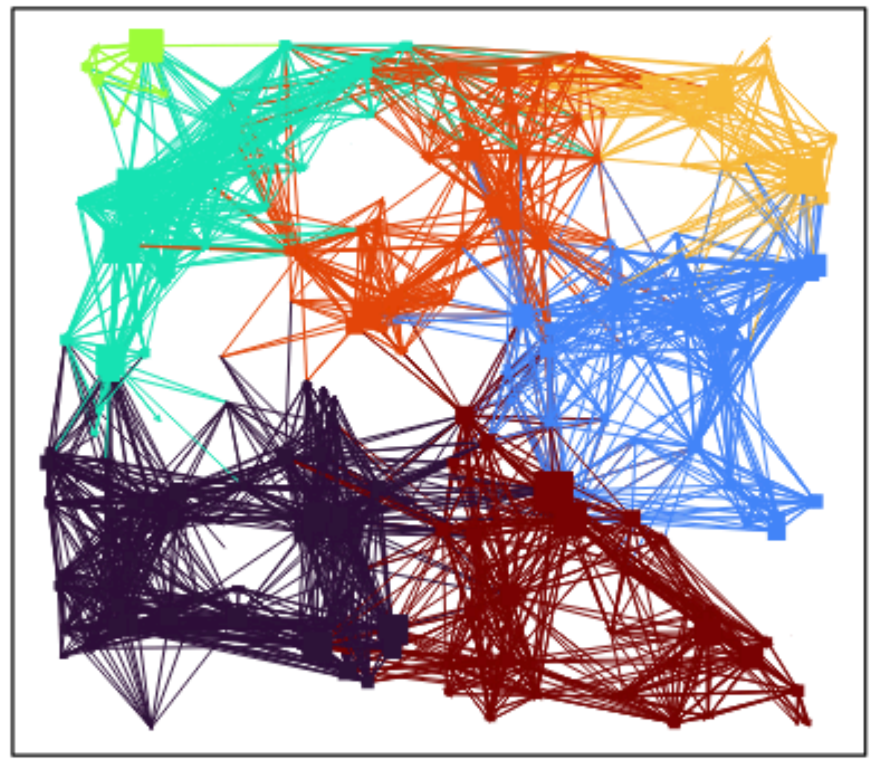
Dispersal while Searching for Blood Hosts



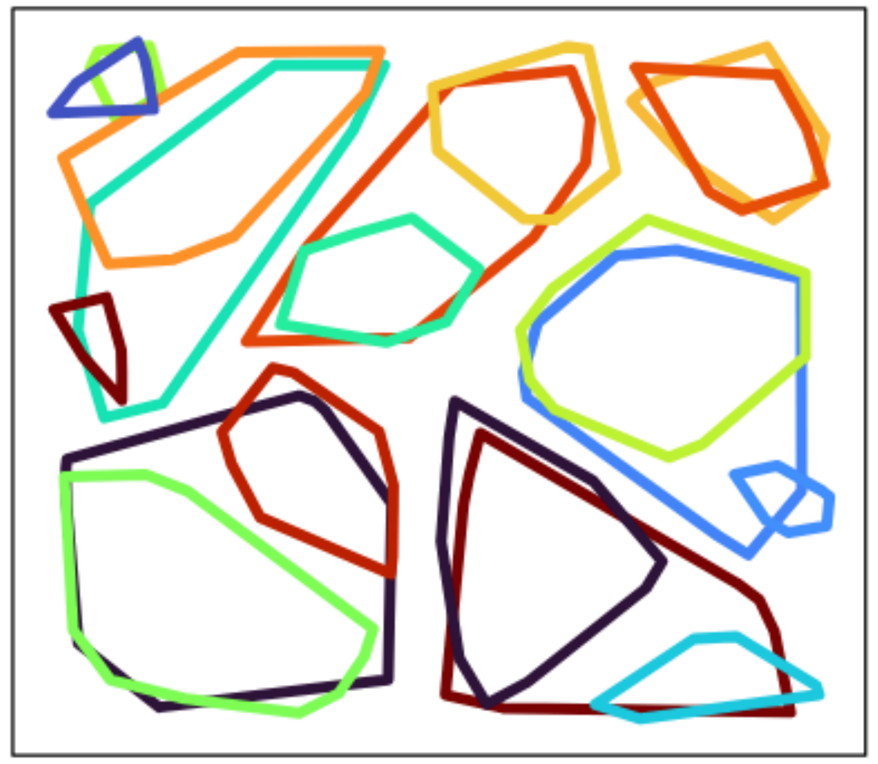


Dispersal while Searching for Aquatic Habitats

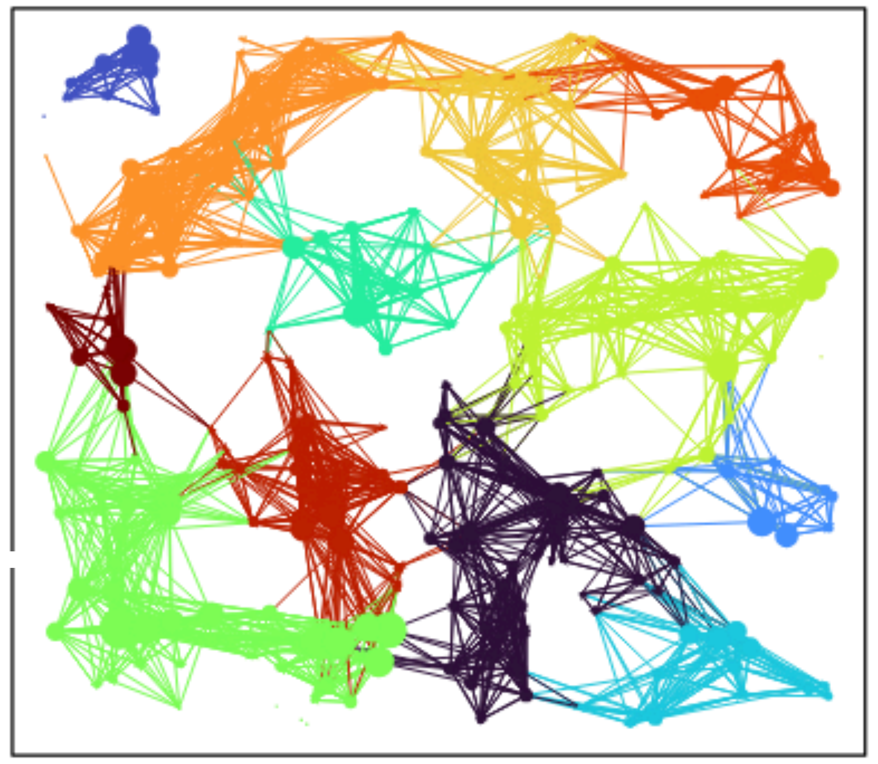
Potential Parasite Dispersal, Population



Convex Hulls



Lifetime Egg Dispersal, Population



MGSurvE: A framework to optimize trap placement for genetic surveillance of mosquito populations

https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1012046

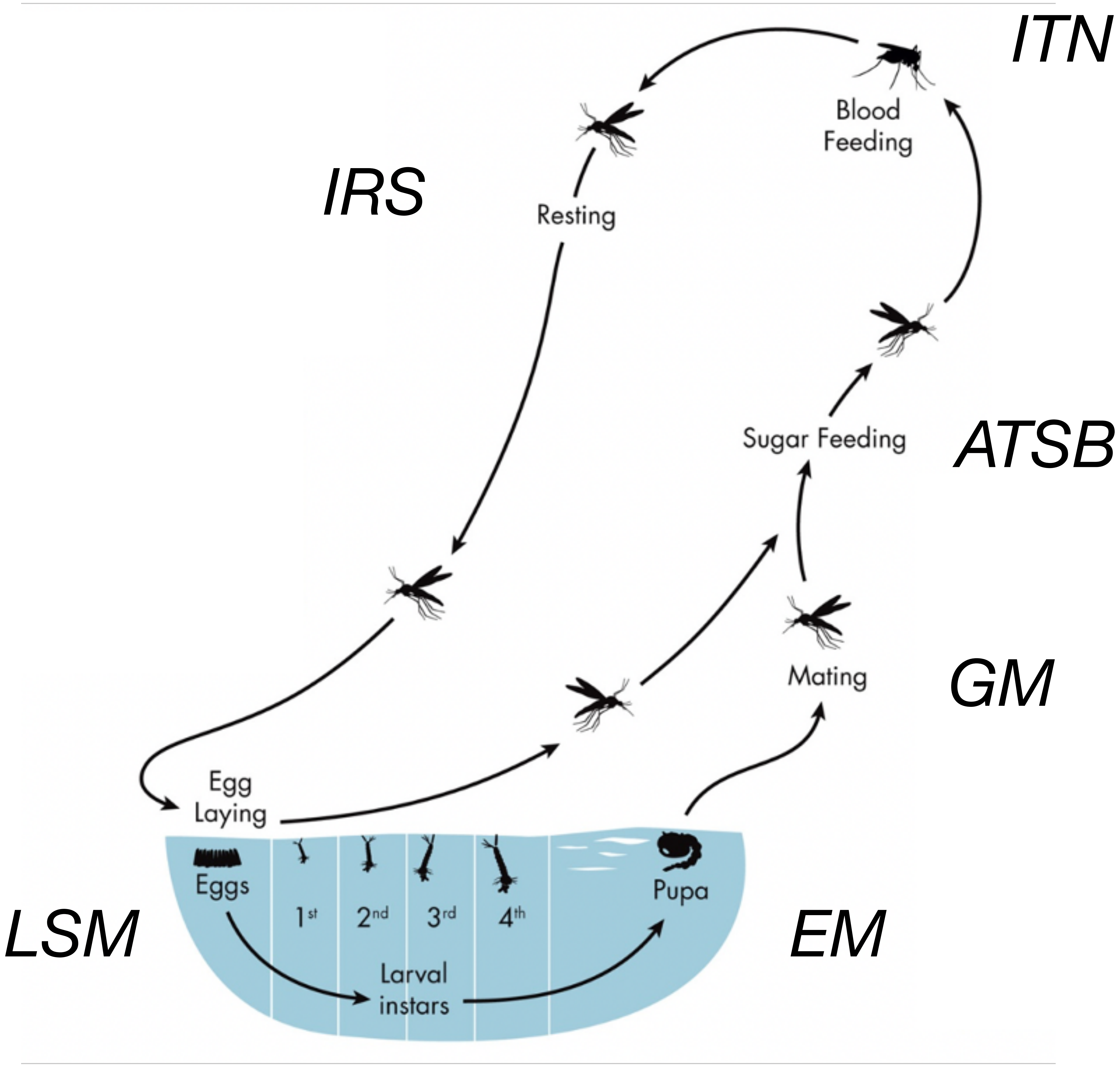
GitHub R Package

`ramp.micro`

Mosquito Ecology & Vector Control

The Robust Approach

- Indoor Residual Spraying (IRS)
- Insecticide Treated Bed Nets (ITN)
- Attractive Toxic Sugar Baits (ATSB)
- Larval Source Management (LSM)
- Environmental Management (EM)
- Genetic Modification (GM)



RAMP for Adaptive Malaria Control

Summary

- **Scalable Complexity:** We developed a mathematical framework for model building that is modular, flexible, & extensible, making it possible to build, solve, and analyze model ensembles for policy analysis at various levels of complexity, including highly realistic models.
  - Spatial dynamics
  - Malaria as a changing baseline that has been modified by control
  - Built-in computation of threshold criteria and other metrics of interest
- We implemented the framework in the **SimBA** software suite, including a growing code library
- **Nimble:** These tools substantially lowered the human costs of building, solving, analyzing, and developing policy advice using mathematical models for malaria
- **Relevant Details:** These systems make it possible to develop and compare dynamical systems models for malaria *in situ* and through analysis and comparisons of models and data, to identify important details affecting decisions or policies
- We are using the model to develop simulation-based analytics and **Adaptive Malaria Control** in Uganda and Equatorial Guinea

The Team

University of Washington: John M. Henry, Sean L. Wu, Dianna Hergott, Austin R. Carter, Daniel T Citron

Uganda: John Rek, Doreen Mbabazi Ssebuliba, Juliet Nakakawa Nsumba, Jaffer Okiring, Meddy Rutayisire, Thomas Eganyu, Jimmy Opigo, Paul Mbaka

Bioko Island Malaria Elimination Program: Guillermo Garcia, Carlos Guerra, David Galick

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ACKNOWLEDGEMENTS

- The Uganda project was supported by a grant from the Bill and Melinda Gates Foundation, **Modeling for Adaptive Malaria Control** (INV 030600, PI = David L Smith, University of Washington).
- Adaptive Vector Control for Bioko Island is funded by grant **Spatial Targeting and Adaptive Vector Control for Residual Transmission and Malaria Elimination in Urban African Settings** (R01 AI163398, PI = David L Smith), from US National Institute of Allergies and Infectious Diseases (NIAID).
- Development of adaptive vector control was supported through a collaboration with the **Bioko Island Malaria Elimination Program**
- Development of adaptive malaria control e was supported through a collaboration with Uganda's **National Malaria Control Division** and **Department of Health Information** in the Uganda Ministry of Health
- Development of this software benefited from funding and collaboration with the NIAID grant **Program for Resistance, Immunology, Surveillance & Modeling of Malaria in Uganda** (PRISM) (2U19AI089674, PIs = Grant Dorsey, University of California San Francisco; and Moses Kamya, Infectious Diseases Research Collaboration), which was part of the **International Centers of Excellence in Malaria Research** (ICEMR) program.
- Funding to develop models of West Nile Virus to support Harris County Public Health was funded by the NSF as part of a project, Computing the Biome (PI = Janos Sztipanovits). The project was part of the Convergence Accelerator program of the National Science Foundation, Directorate for Technology, Innovation, and Partnerships (TIP) (NSF 2040688 and NSF 2040688, PI=Janos Sztipanovits, Vanderbilt University).
- We acknowledge the important formative role played by the mosquito working groups of **RAPIDD** (Research and Policy for Infectious Disease Dynamics), which was sponsored by the Fogarty International Center, NIH, and the Department of Homeland Security. The mosquito working groups were led by Professor Thomas Scott. RAPIDD was led by F. Ellis McKenzie.

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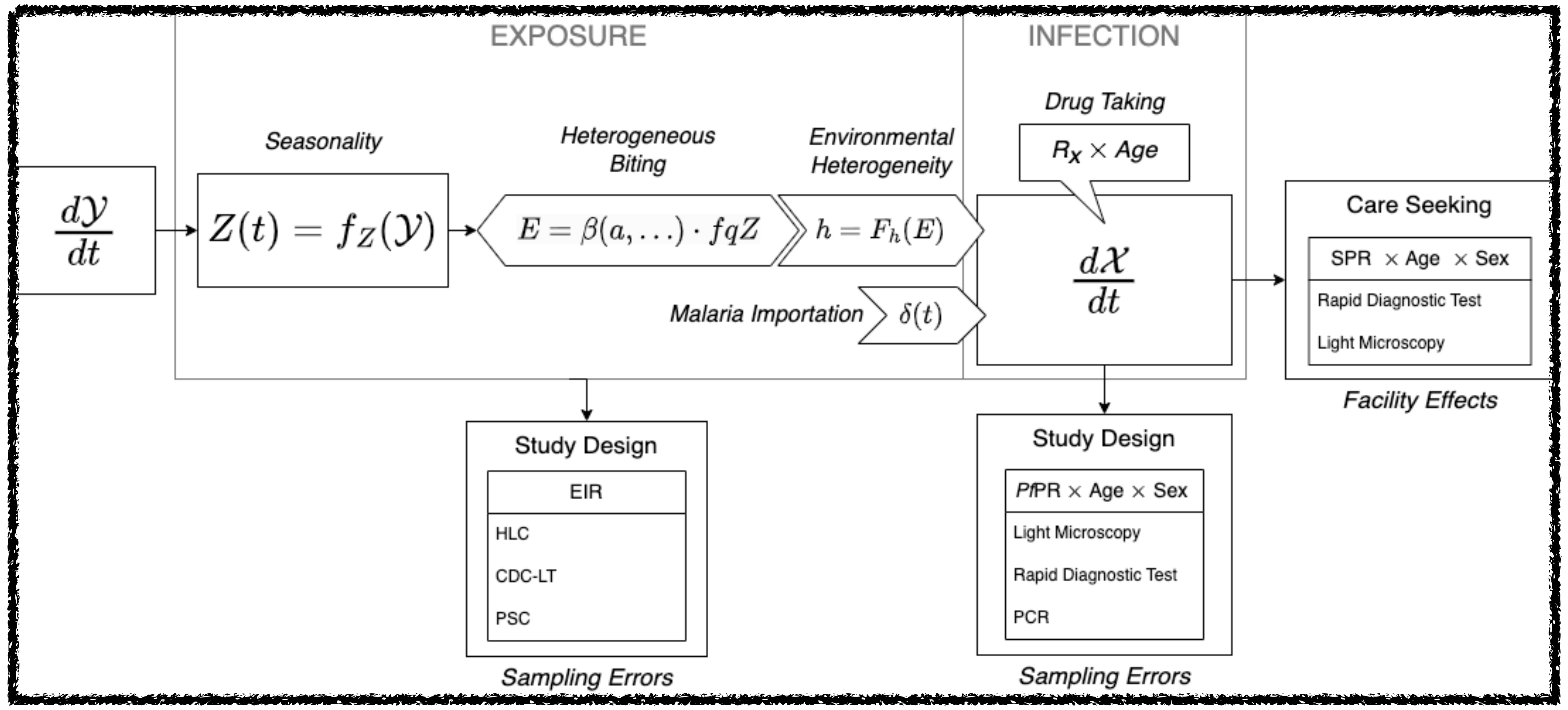
Malaria Epidemiology
Exposure

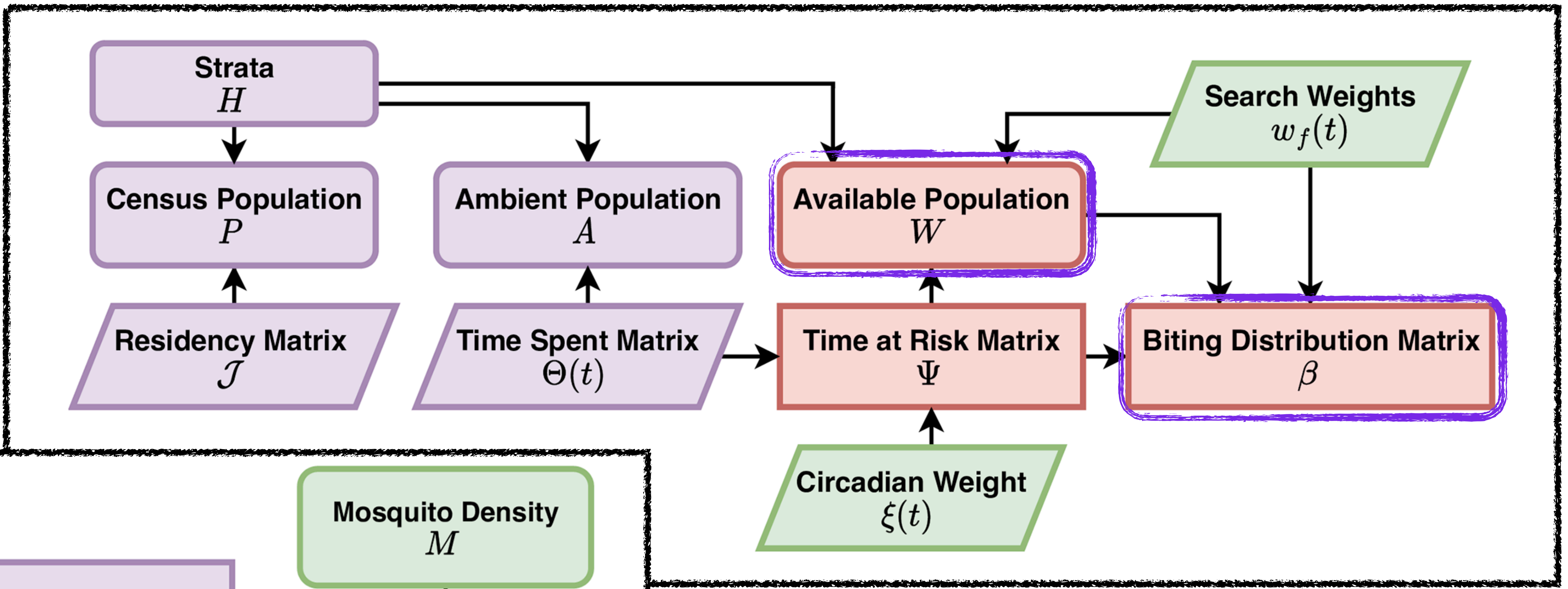
- Time Spent → Biting Distribution Matrix (β)
- Travel / Malaria Importation
- **<u>Heterogeneous Exposure</u>**
  - **Search Weights** → Heterogeneous Biting (*i.e.* frailty / relative biting rates)
    - Age
    - Location / Behavior
    - Attraction
  - $F_h(E)$ → Environmental Heterogeneity (*e.g.* gamma / negative binomial hazards)

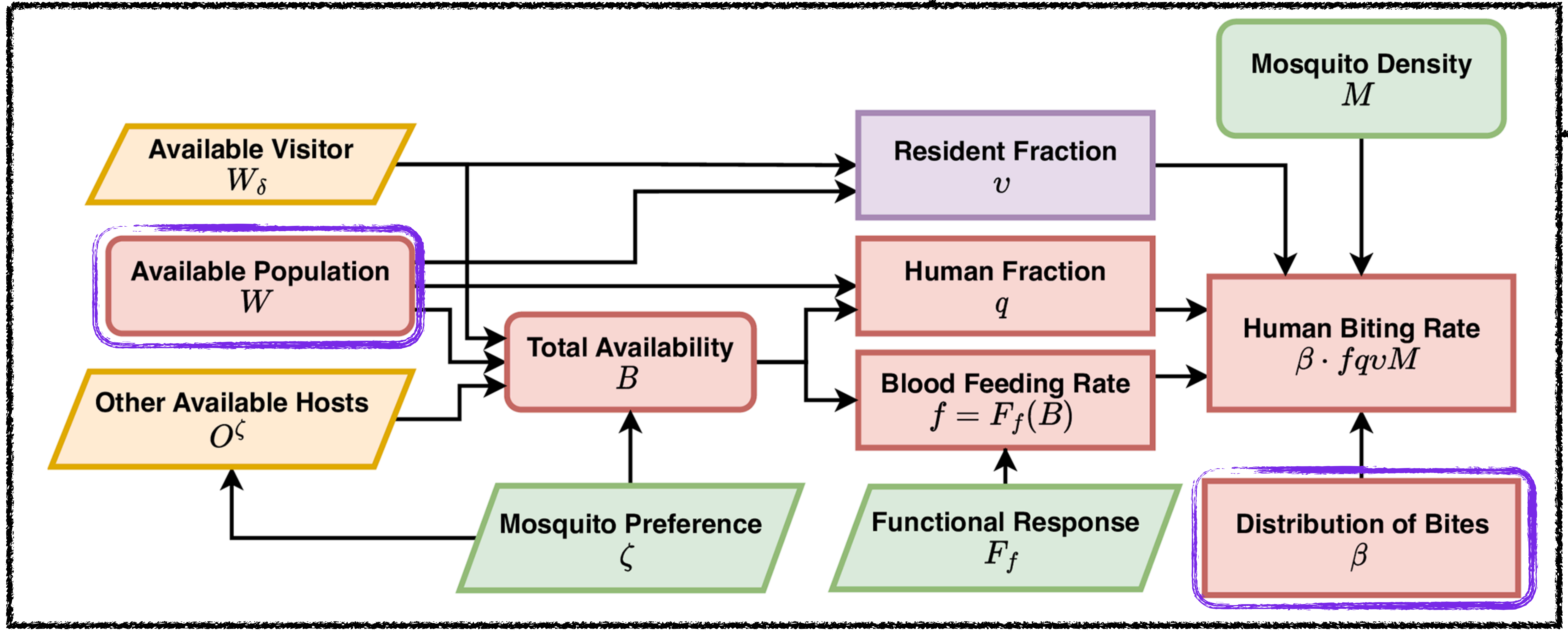


Blood Feeding & Transmission

Blood Feeding Rates and Habits. The Biting Distribution Matrix (β)

Humans Spend Time



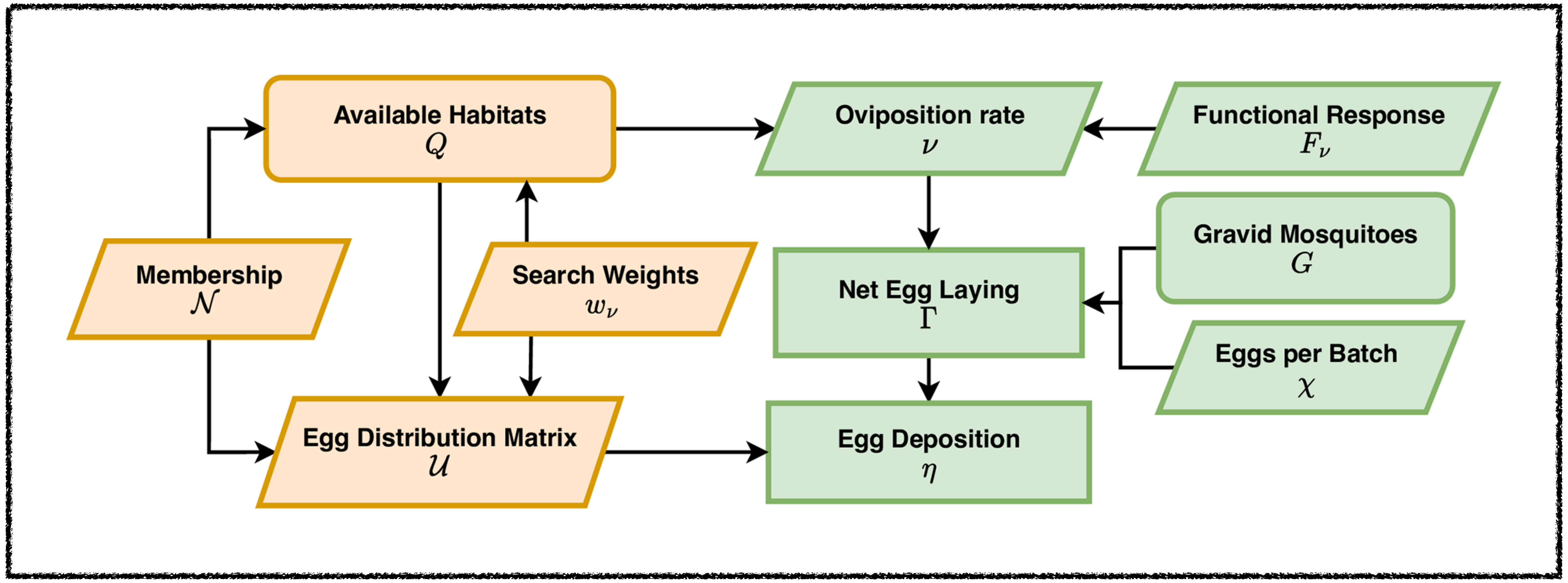


Mosquitoes Search for Blood Hosts

Spatial dynamics of malaria transmission
https://doi.org/10.1371/journal.pcbi.1010684

Egg Laying & Emergence

- Aquatic habitats are located in patches (an arbitrary number)
- Eggs laid by adults in the patch are distributed among aquatic habitats in that patch
- Egg laying, blood feeding, and emigration can not occur if the resource is unavailable



Spatial dynamics of malaria transmission

https://doi.org/10.1371/journal.pcbi.1010684

Malaria Epidemiology

Heterogeneity / Stratification

- **Epidemiological Heterogeneity**
  - Age / Cumulative Exposure
  - Drug Taking
  - Exposure → Housing Quality, Time Spent, Travel, Heterogeneous Biting, …
- **Malaria Control**
  - Access to Healthcare / Drug Taking
  - ITN Ownership / Use
  - Vaccinated