

# Malaria Dynamics within the Mosquito

Olivia Prosper  
Department of Mathematics  
University of Tennessee

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# Acknowledgements



Lauren M. Childs  
Department of Mathematics  
Virginia Tech

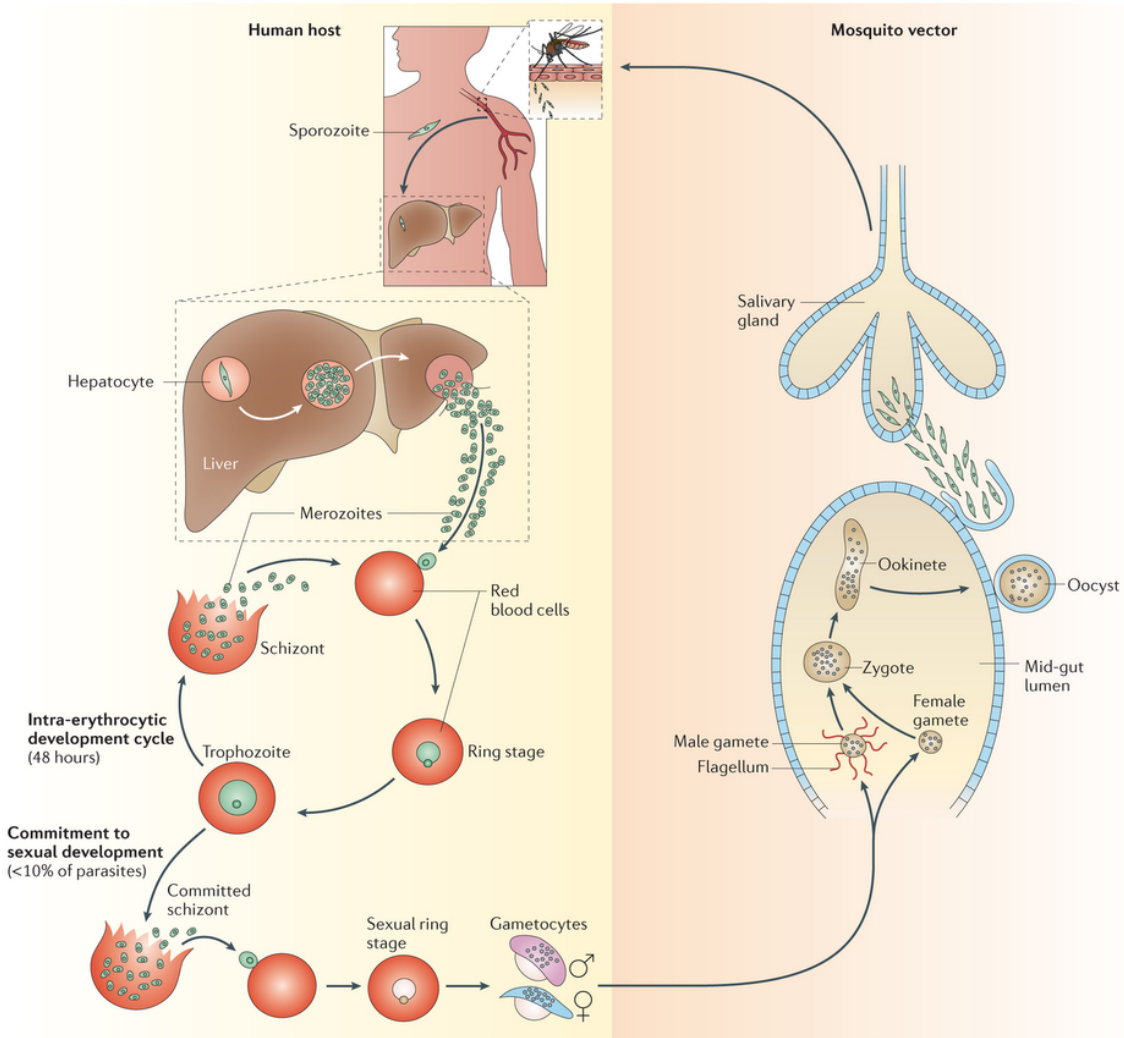
# Outline

- Background
- Biology -> Models
  - Measuring parasite diversity
  - Measuring time to infectiousness

# Malaria Burden

- 228 million new infections in 2018
- 405,000 deaths
- 272,000 in children <5 years of age.
- Greatest mortality caused by *Plasmodium falciparum*

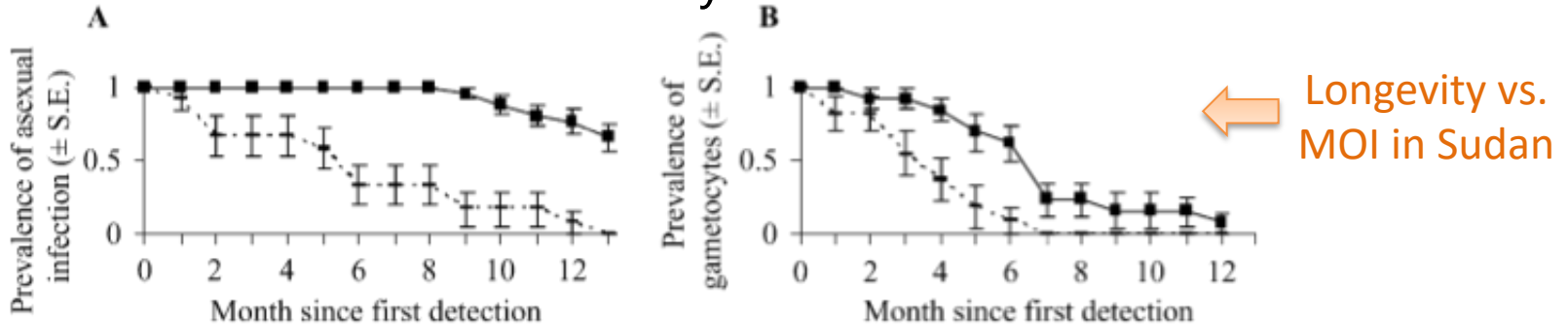
# *P. falciparum* life-cycle



- ❑ Asexual reproduction within vertebrate host
- ❑ Sexual reproduction within female *Anopheles* mosquito

# Why study diversity?

- New strains can evade immune system



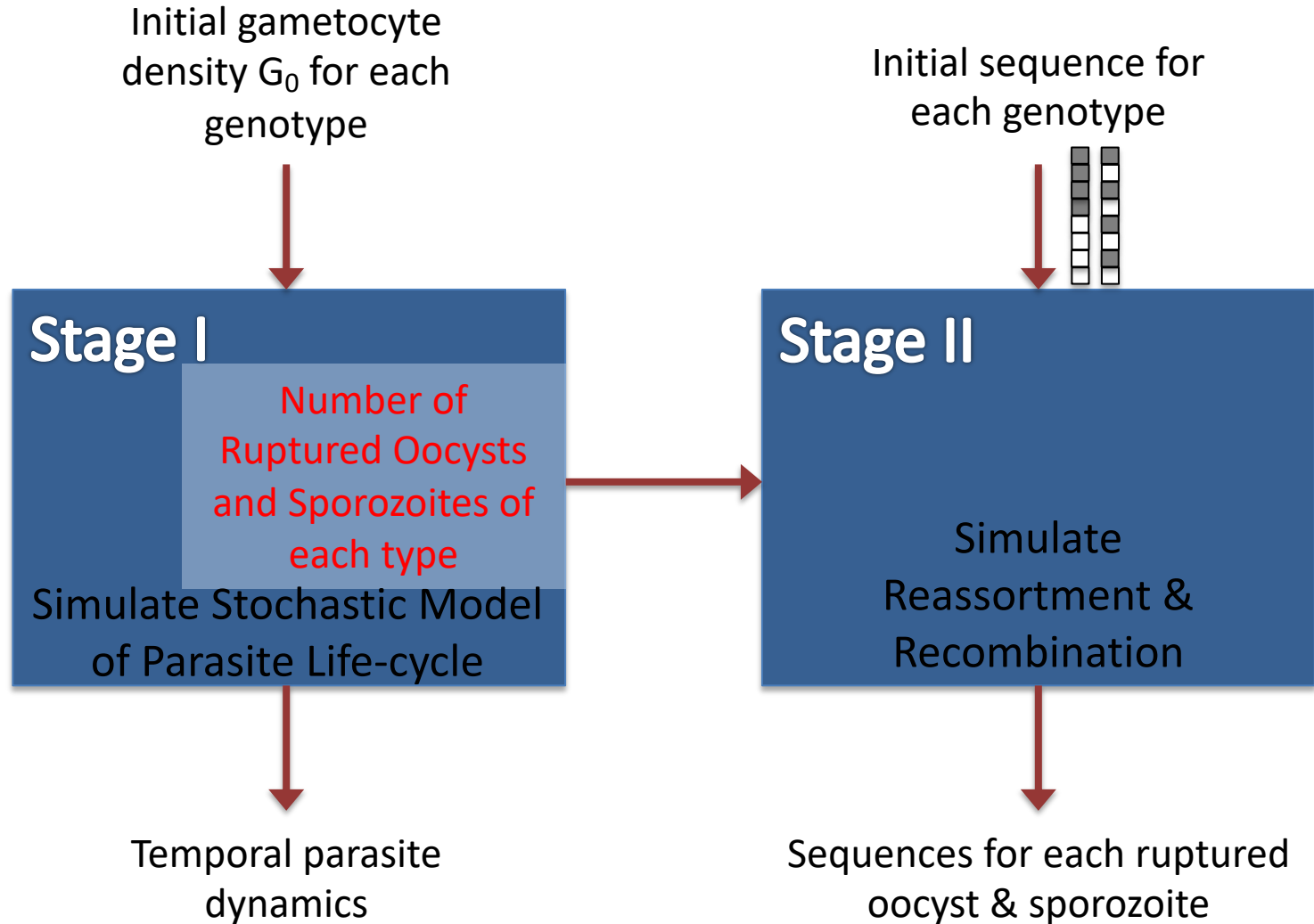
- Challenges drug & vaccine development
  - First-line treatment in malaria endemic countries:
    - Artemisinin-based combination therapies
  - Vaccine Development
    - RTS,S/AS01 (Mosquirix)
- (Potentially) increased infectivity with Multiplicity of Infection (MOI), more severe symptoms

Contributors: Superinfection, Sexual Reproduction, Mutation

# Methods

- Stage I:
  - Model within-vector dynamics of two genotypes
    - Three fitness biases: 0%, 10% and 50%
  - Reproduce variation in parasite numbers across mosquitoes
- Stage II:
  - Simulate mechanisms generating novel sequences
    - Reassortment & Recombination
    - No Mutation
  - Quantify diversity generated

# Model Framework

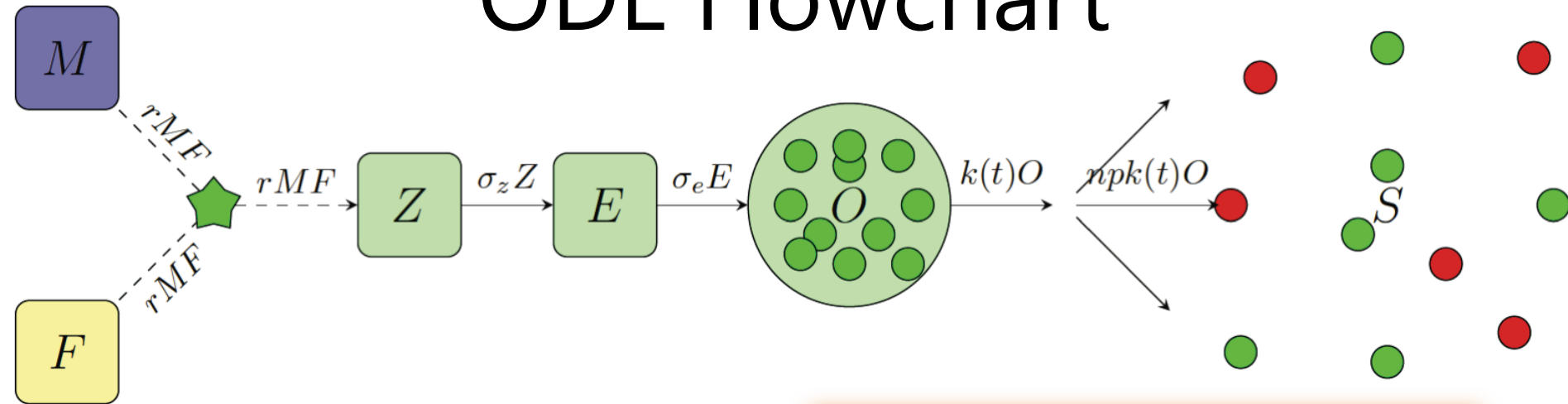




# Stage I: Parasite Life-Cycle Model

- Teboh-Ewungkem, M. I., T. Yuster, and N. H. Newman. *Infectious Disease Modelling Research Progress* (2010): 177-199.
- Teboh-Ewungkem, Miranda I., and Thomas Yuster. *Journal of Theoretical Biology* 264.2 (2010): 273-286.

# ODE Flowchart



State Variable	Description
M	Male Gamete
F	Female Gamete
Z	Zygote
E	Ookinete
O	Oocysts
S	Sporozoites

$$k(t) = \begin{cases} 0, & \text{if } 0 < t < t_0 \\ d, & \text{if } t \geq t_0 \end{cases}$$

$$M' = -aM - rMF$$

$$F' = -bF - rMF$$

$$Z' = rMF - (\sigma_z + \mu_z)Z$$

$$E' = \sigma_z Z - (\sigma_e + \mu_e)E$$

$$O' = \sigma_e E - (k(t) + \mu_o)O$$

$$S' = n_0 p k(t) O.$$

# Single Genotype Stochastic Analog

## Continuous Time Markov Chain

$(M_0, F_0, 0, 0, 0, 0)$

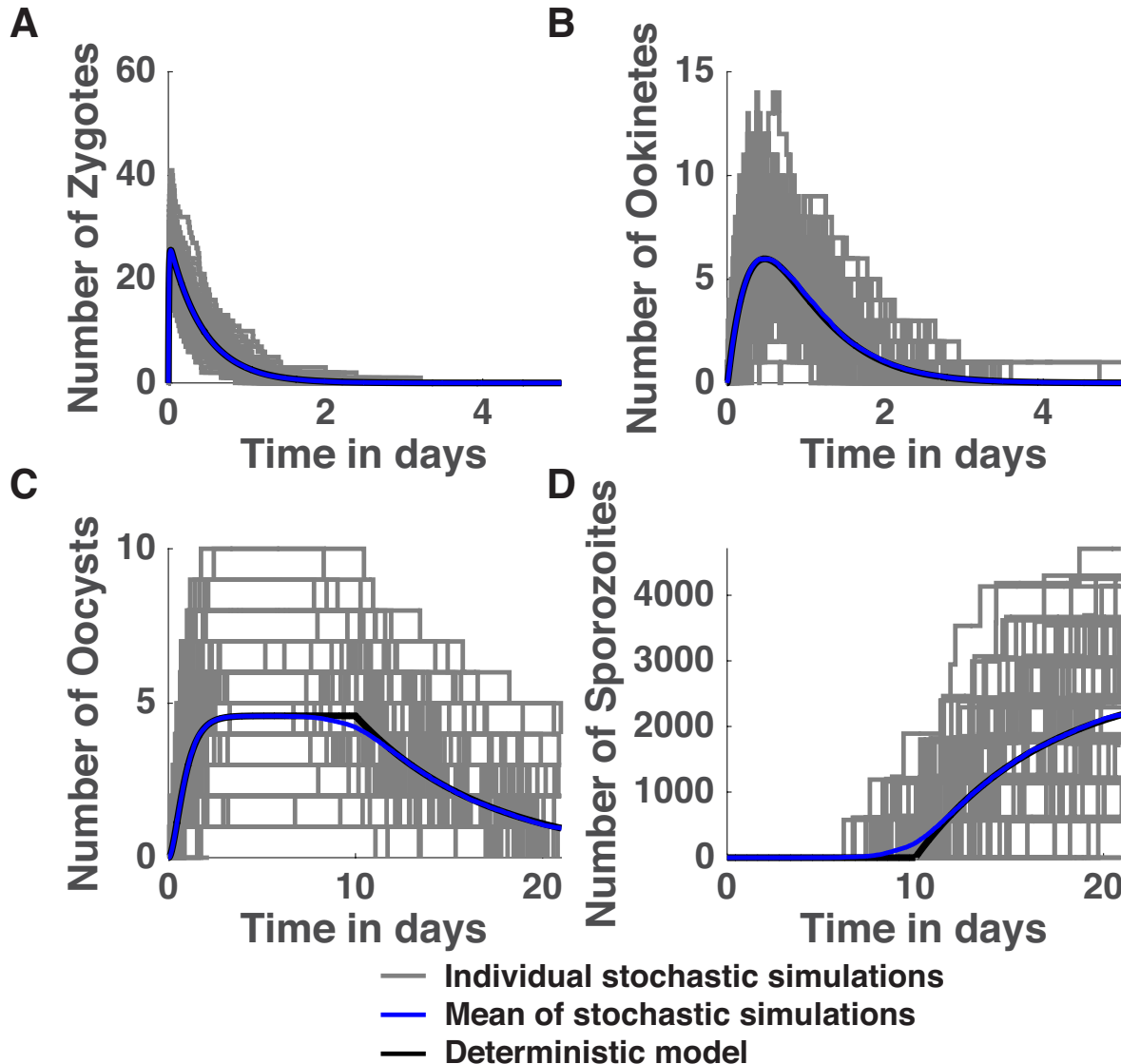
$(M, F, Z, E, O, S)$

Event	Probabilities	Transitions
Death of Male gamete	$aM\Delta t + o(\Delta t)$	$(-1, 0, 0, 0, 0, 0)$
Mating	$rMF\Delta t + o(\Delta t)$	$(-1, -1, 1, 0, 0, 0)$
Death of Female gamete	$bF\Delta t + o(\Delta t)$	$(0, -1, 0, 0, 0, 0)$
Death of Zygote	$\mu_z Z\Delta t + o(\Delta t)$	$(0, 0, -1, 0, 0, 0)$
Zygote to Ookinete progression	$\sigma_z Z\Delta t + o(\Delta t)$	$(0, 0, -1, 1, 0, 0)$
Death of Ookinete	$\mu_e E\Delta t + o(\Delta t)$	$(0, 0, 0, -1, 0, 0)$
Ookinete to Oocyst progression	$\sigma_e E\Delta t + o(\Delta t)$	$(0, 0, 0, -1, 1, 0)$
Death of Oocyst	$\mu_o O\Delta t + o(\Delta t)$	$(0, 0, 0, 0, -1, 0)$
Bursting of Oocyst (sporozoite production)	$k(t)O\Delta t + o(\Delta t)$	$(0, 0, 0, 0, -1, n)$

$$k(t) = d\beta(t)$$

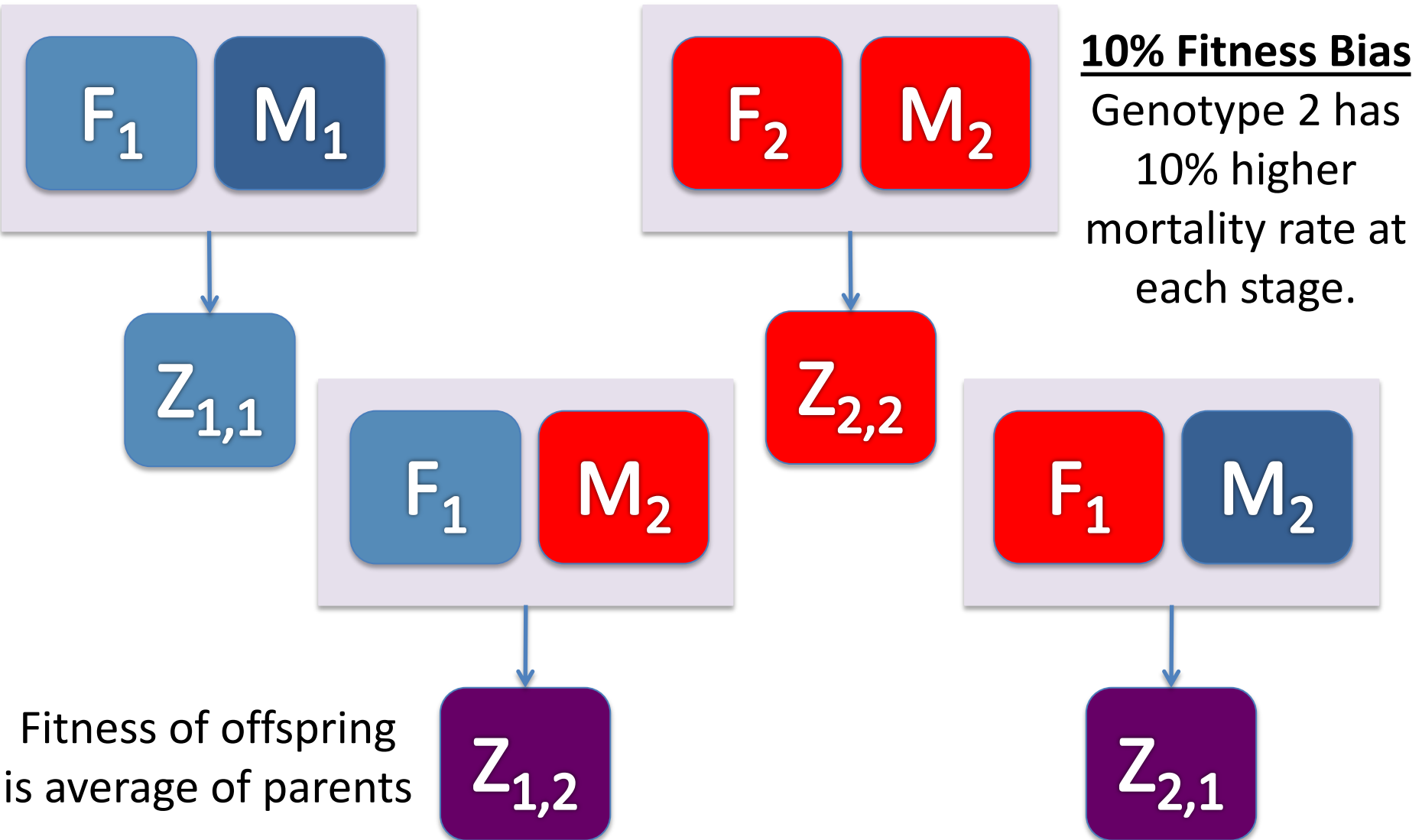
$$\beta(t) = (1 + \exp(t_0 - t))^{-1}$$

# Single Genotype Dynamics



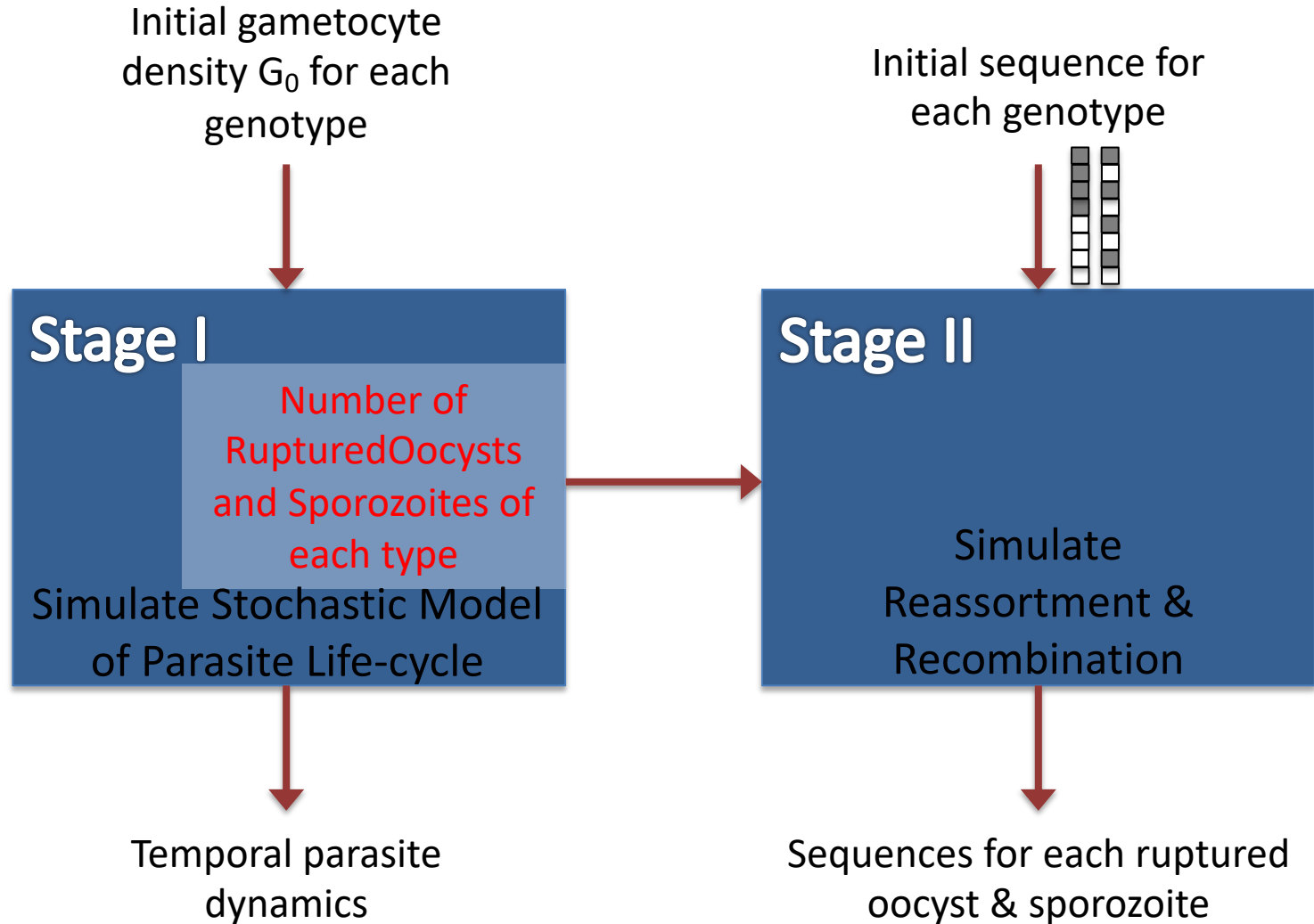
Initial Gemetocyte Density, $G_0$	Sporozoite Prevalence, Day 21
150	62.90
200	82.98
250	92.95
300	97.42
350	99.47
400	99.84
450	99.95

# Extension to two genotypes



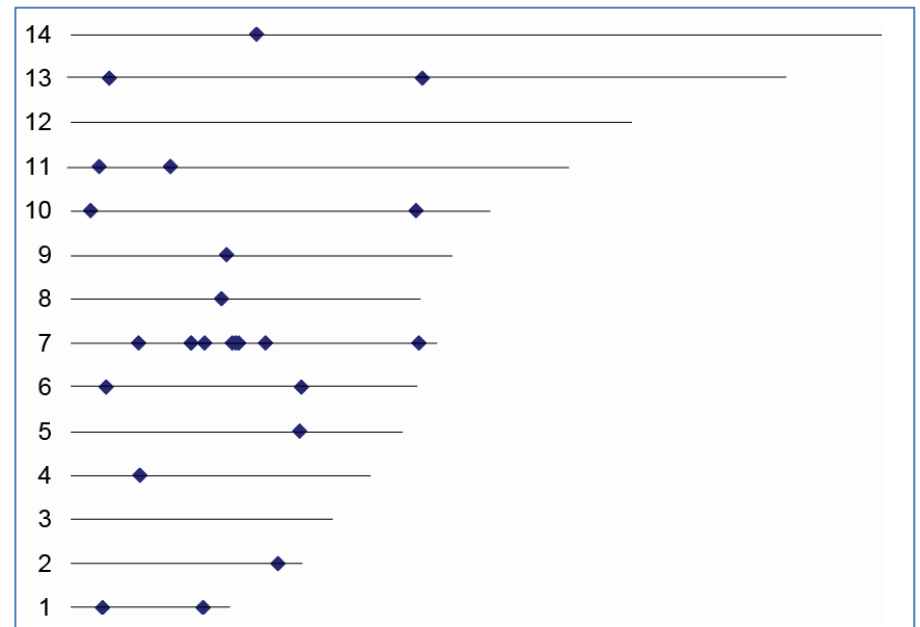
# Model Framework: Stage II

# Model Framework



# Barcode Characterization

- Distinguishes between genetically different *P. falciparum* parasites.
- Sequence of 24 Single Nucleotide Polymorphisms (SNPs),  
2 Alleles

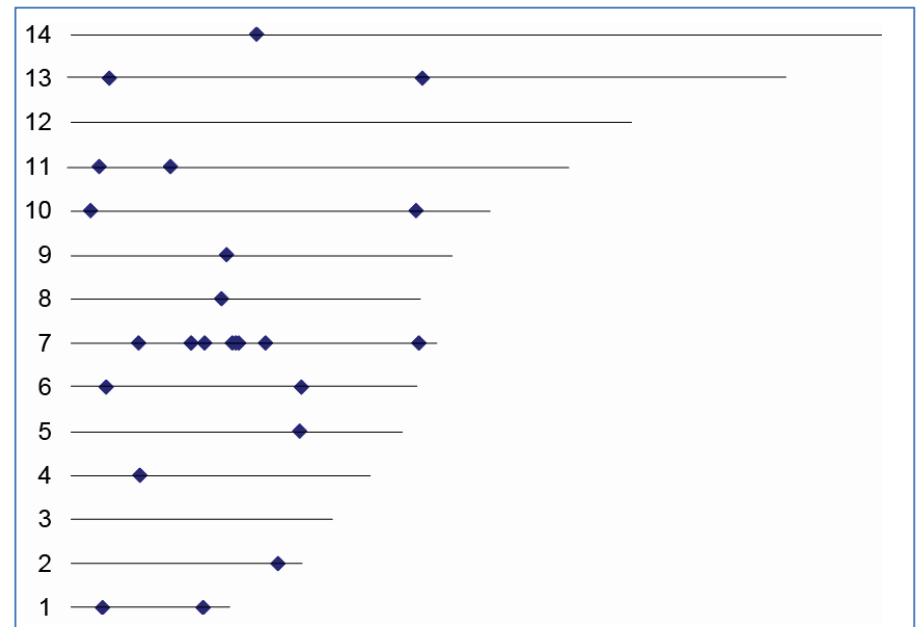


Daniels, Rachel, et al. "A general SNP-based molecular barcode for Plasmodium falciparum identification and tracking." *Malaria Journal* 7.1 (2008): 1.

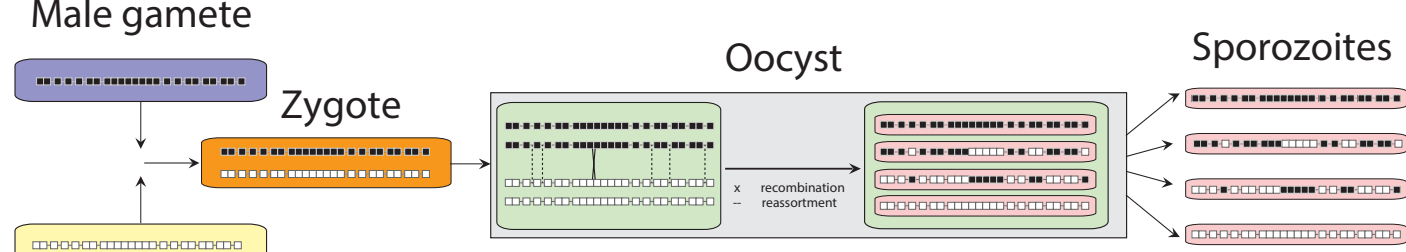


# Barcode SNP Locations

SNP	Chromosome	Position
1	1	130573
2	1	539044
3	2	842803
4	4	282592
5	5	931601
6	6	145472
7	6	937750
8	7	277104
9	7	490877
10	7	545046
11	7	657939
12	7	671839
13	7	683772
14	7	792356
15	7	1415182
16	8	613716
17	9	634010
18	10	82376
19	10	1403751
20	11	117114
21	11	406215
22	13	158614
23	13	1429265
24	14	755729

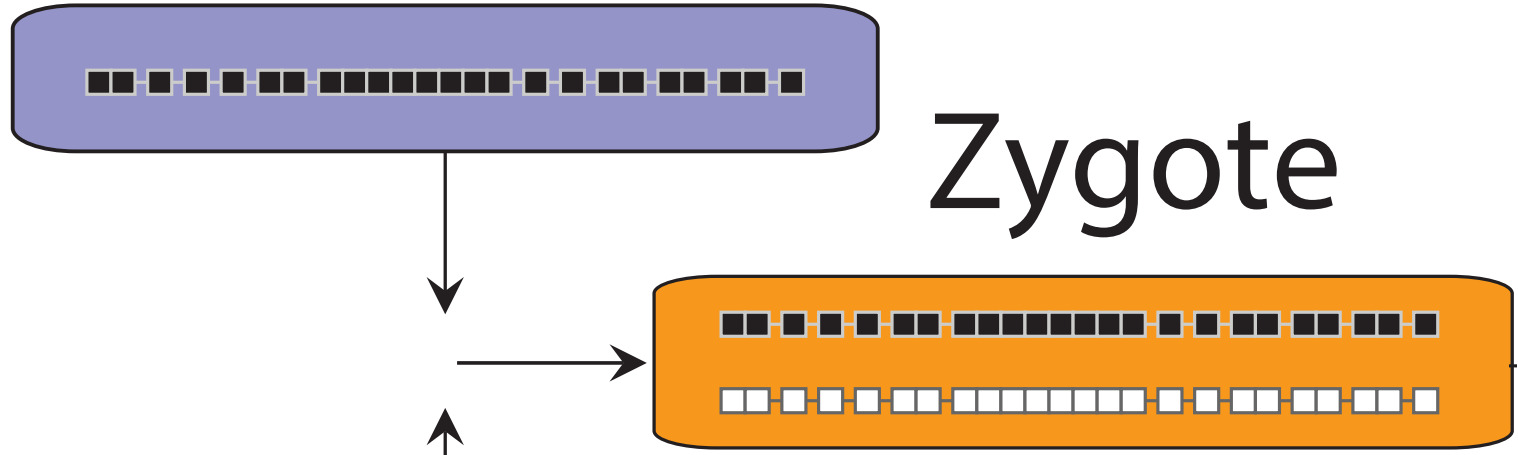






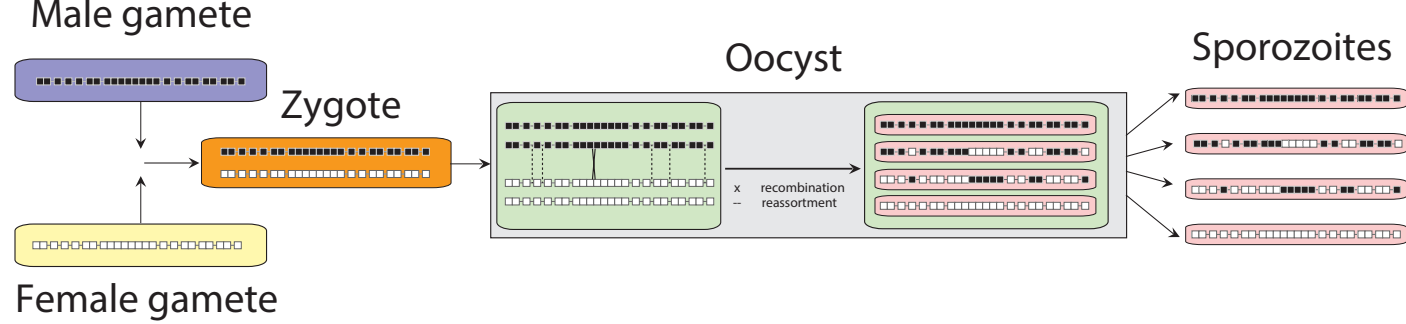
Male gamete

# Male gamete

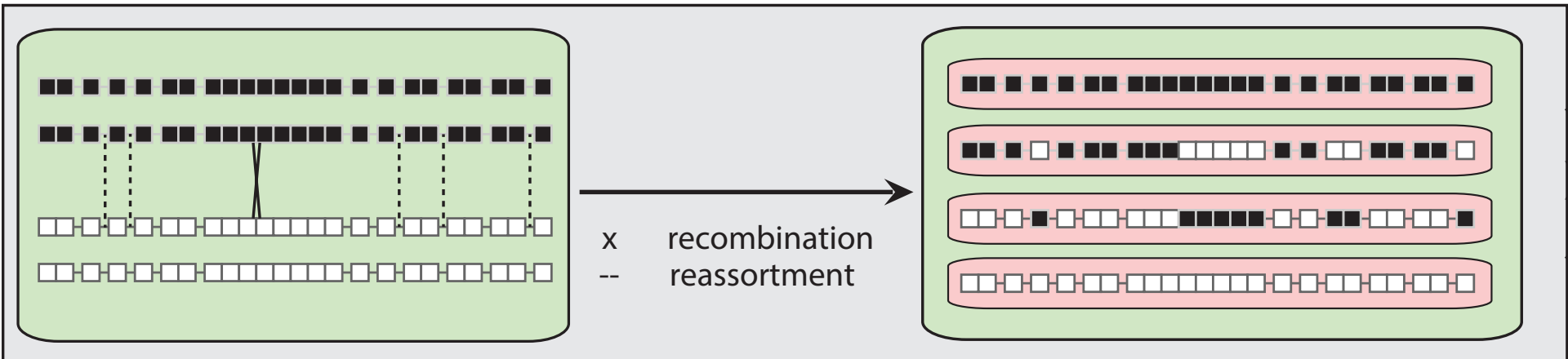


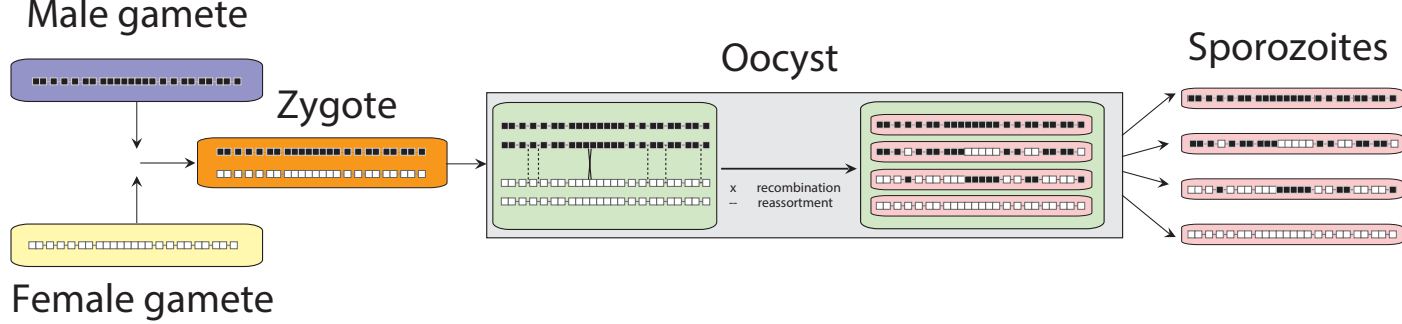
Female gamete

# Female gamete

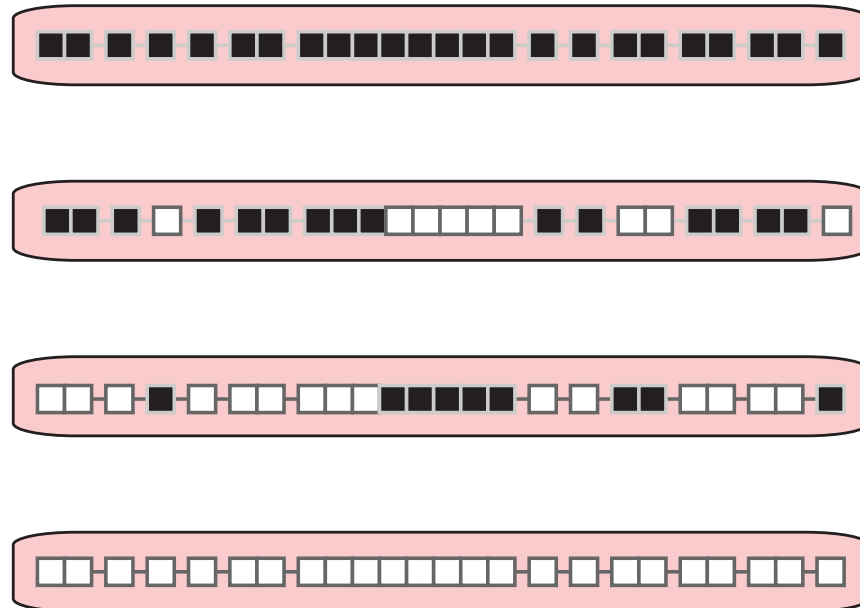


# Oocyst



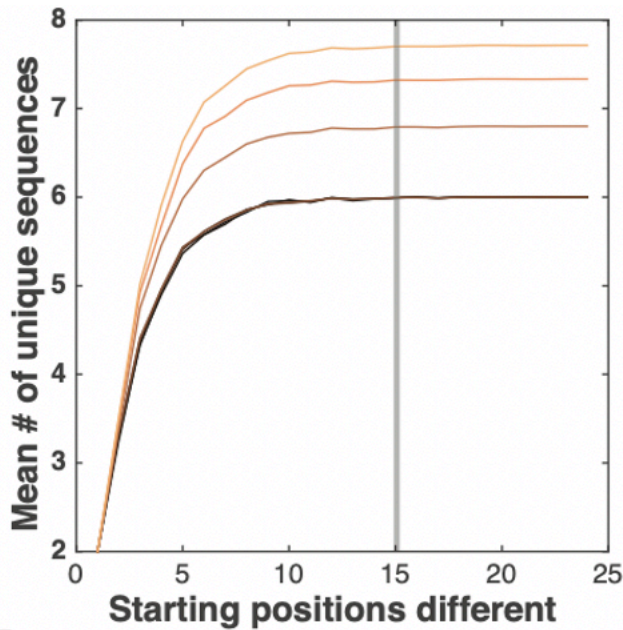


# Sporozoites



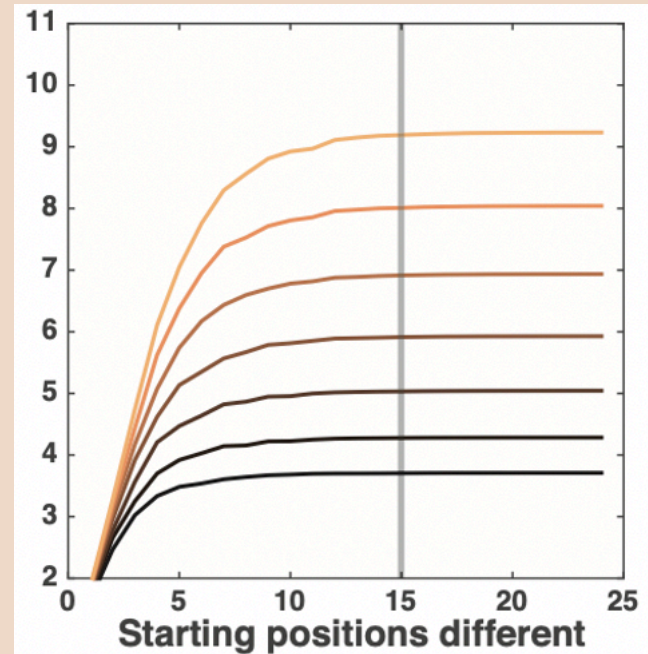
# Results: Sequence Diversity Model

# Number of Unique Sequences

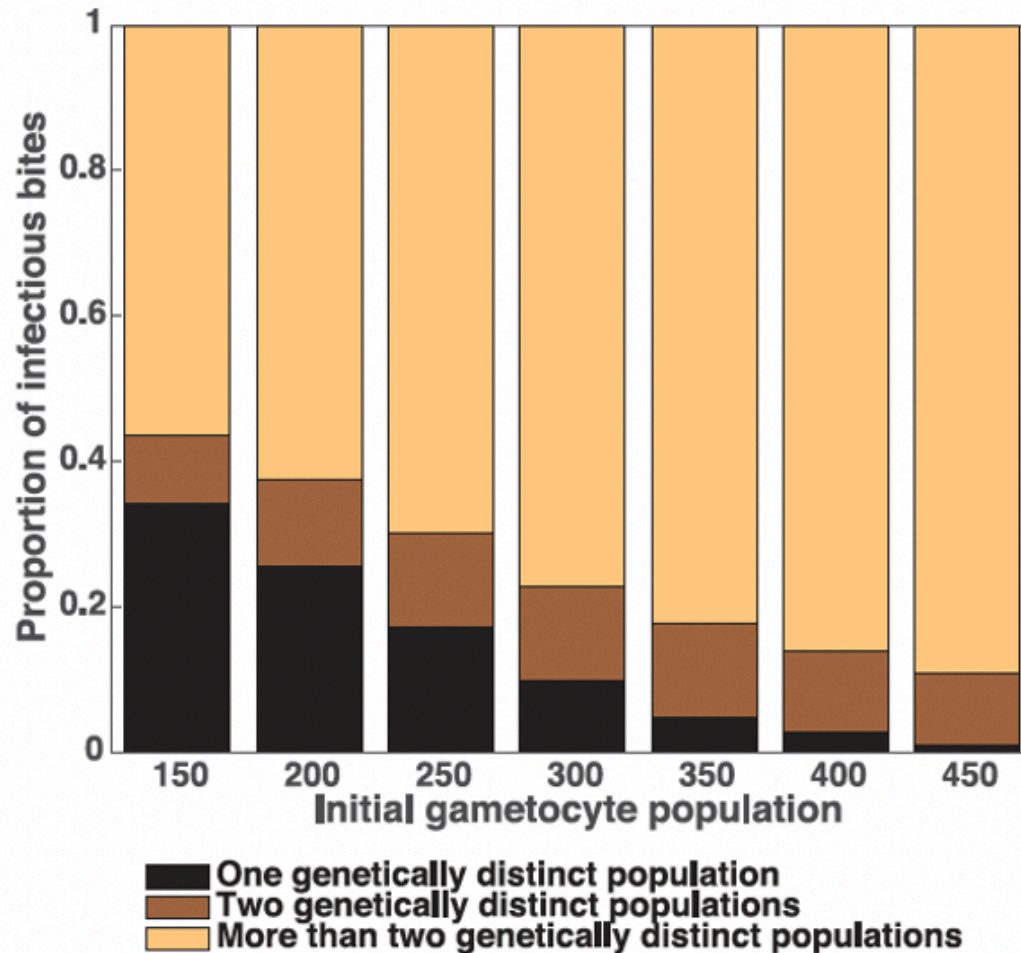


Deterministic Life-cycle model

Stochastic Life-cycle model



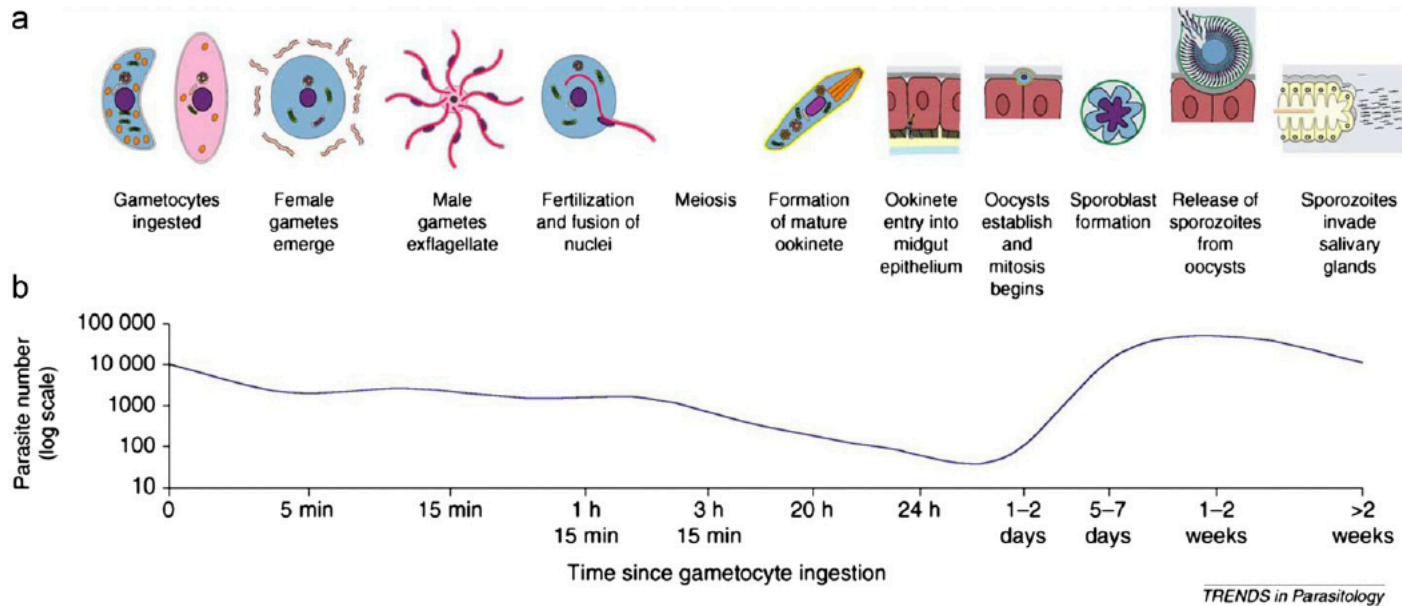
# Onward transmission: how complex is the infection?



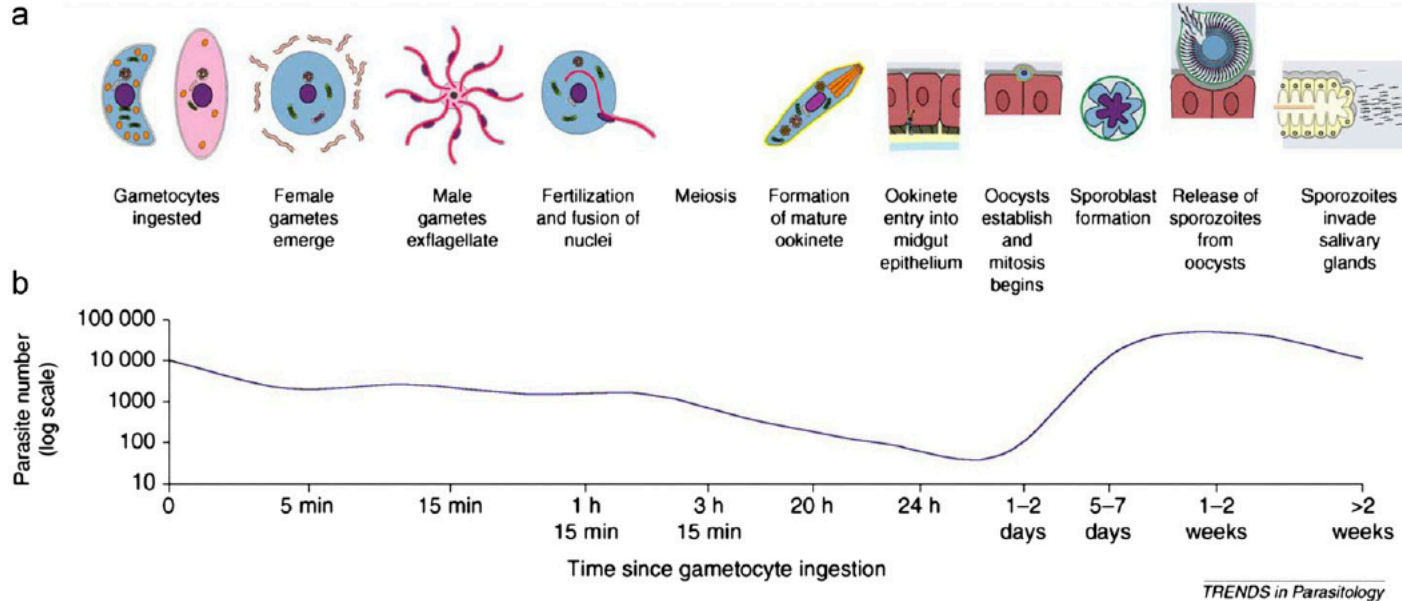


# Measuring time to infectiousness

- EIP: Extrinsic Incubation Period
- Period between infection and infectiousness
- Gametocytes to release of sporozoites

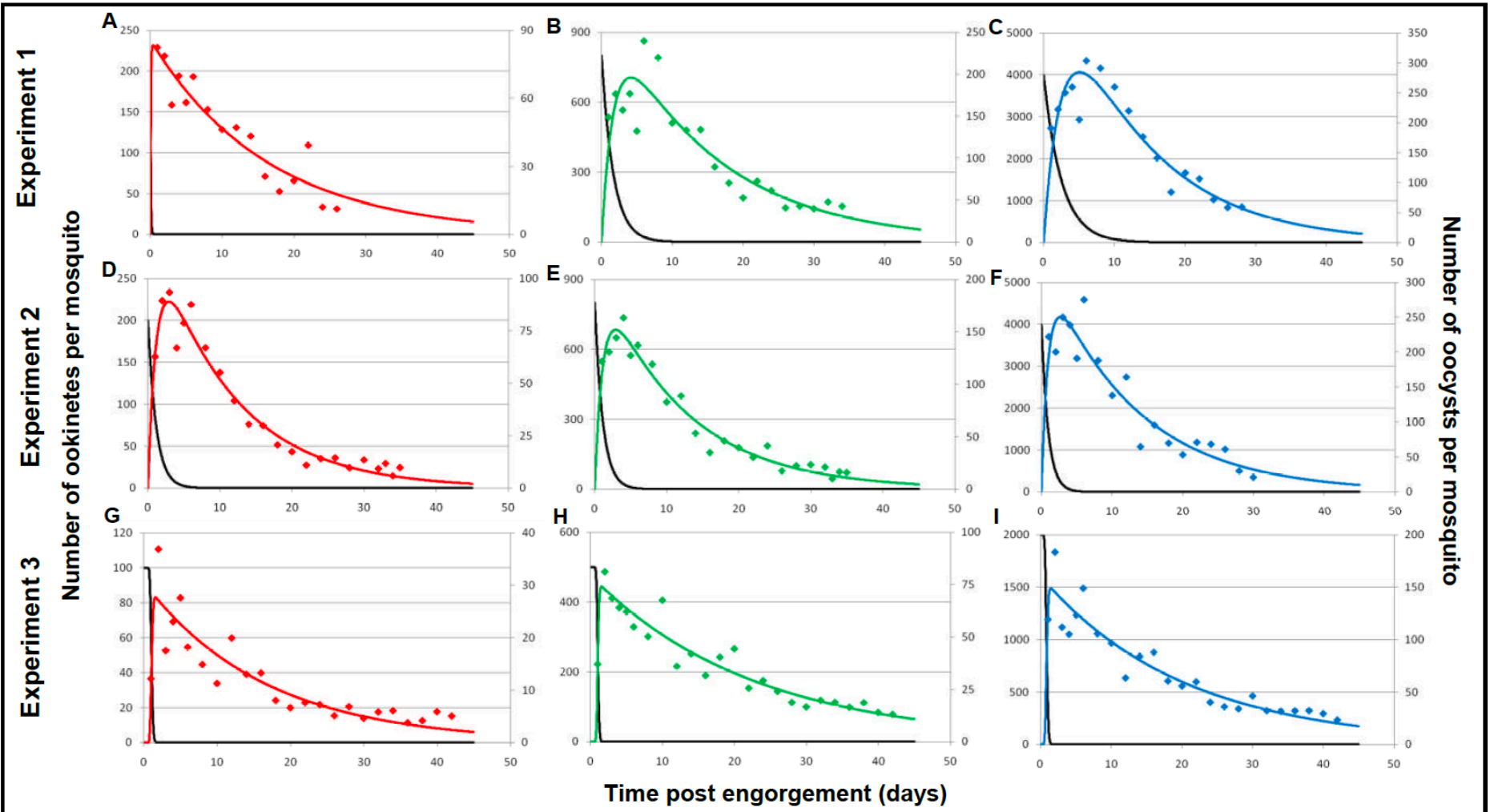


# Controlled Experiments



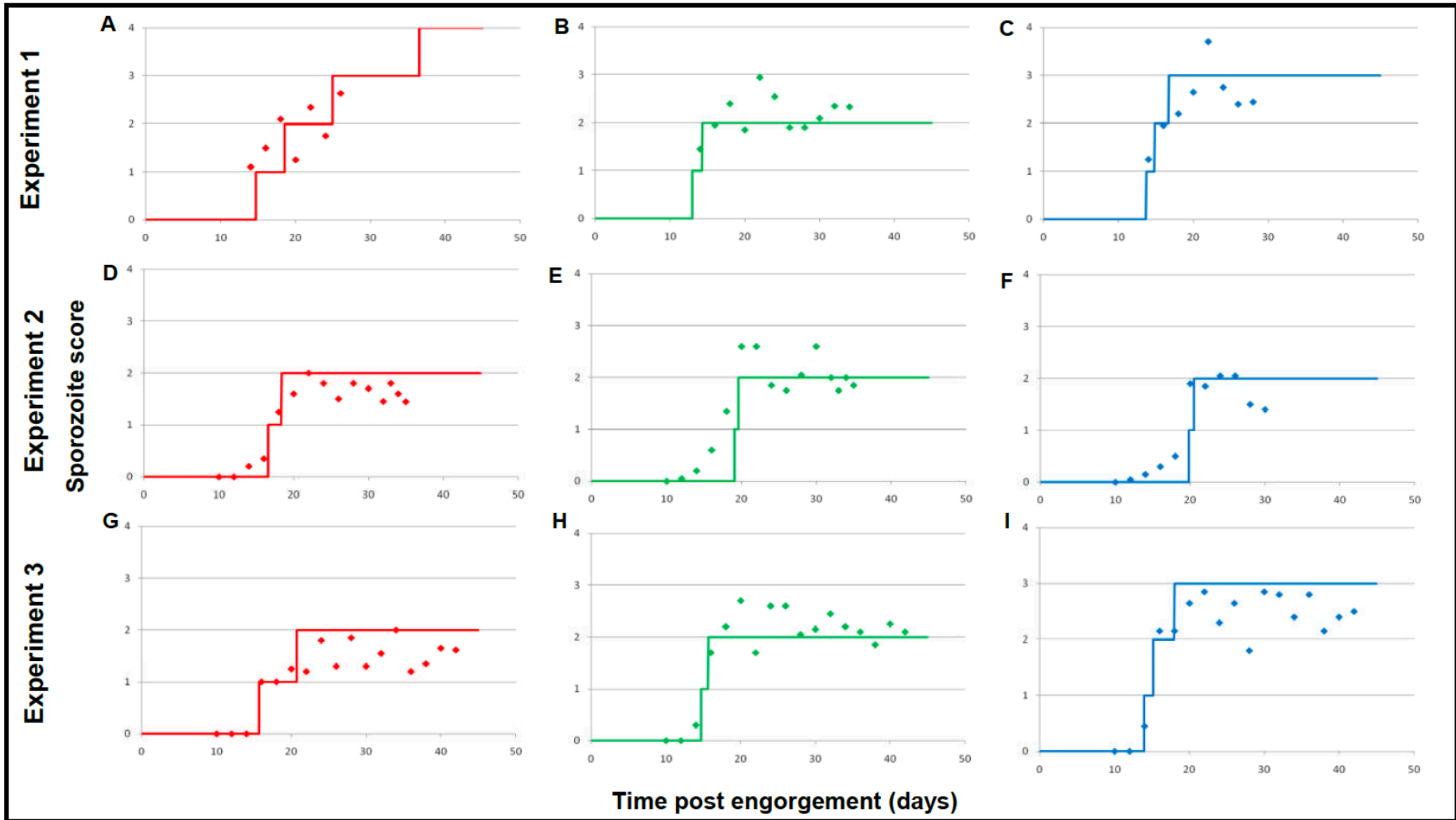
- Introduced ookinetes per microliter
- Measured oocyst number over time
- Recorded sporozoite score over time

# Oocyst Count



**Figure 6.14 – Ookinete to oocyst model results.** Black lines indicate model output ookinete density with time (left-hand axis); coloured lines represent model output oocyst density with time (right-hand axis). Markers represent mean oocyst density raw data. Ookinete density fed per  $\mu$ l of blood: **A** 100: **B** 400: **C** 2000: **D** 100: **E** 400: **F** 2000: **G** 50: **H** 250: **I** 1000.

# Sporozoite Score



**Figure 6.16 – Oocyst to sporozoite density model results.** Lines indicate model output sporozoite score with time. Markers represent mean sporozoite score experimental data. Oocyst density fed per  $\mu\text{l}$  of blood: **A** 100; **B** 400; **C** 2000; **D** 100; **E** 400; **F** 2000; **G** 50; **H** 250; **I** 1000.

# Previous Models

Multiple ookinete stages

Multiple oocyst stages

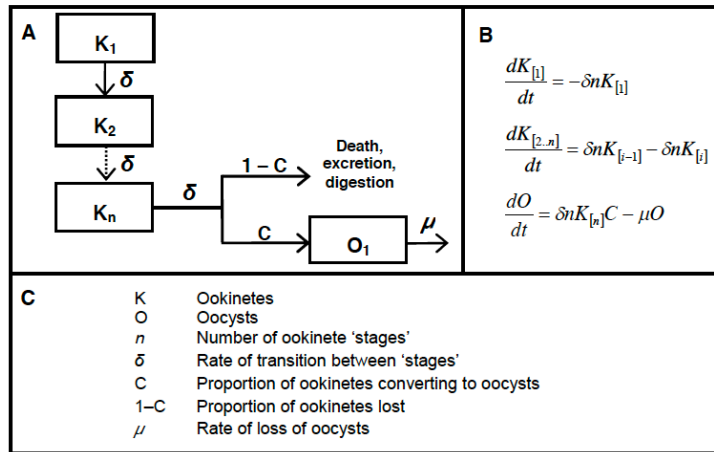


Figure 6.13 – Ookinete to oocyst model. A Summary of model structure. B Model equations. C Parameter and variable definitions.

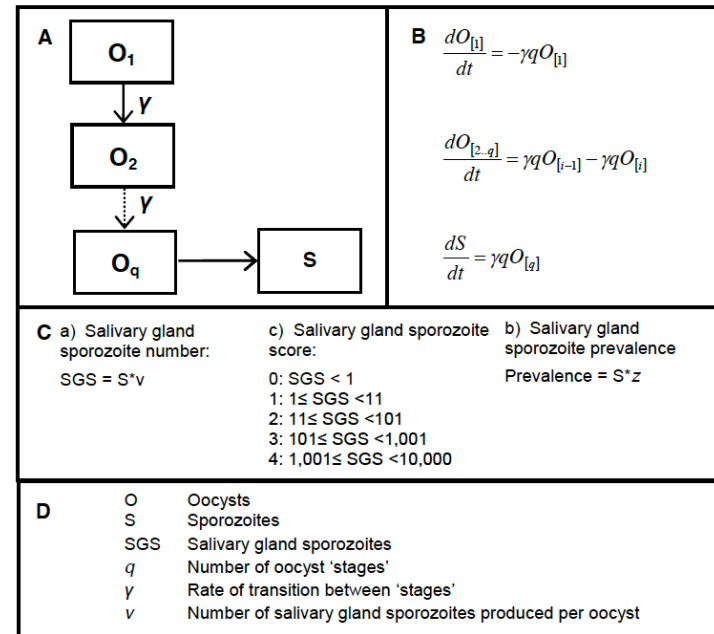
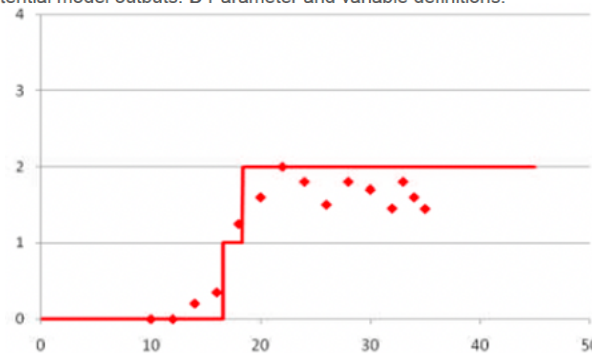
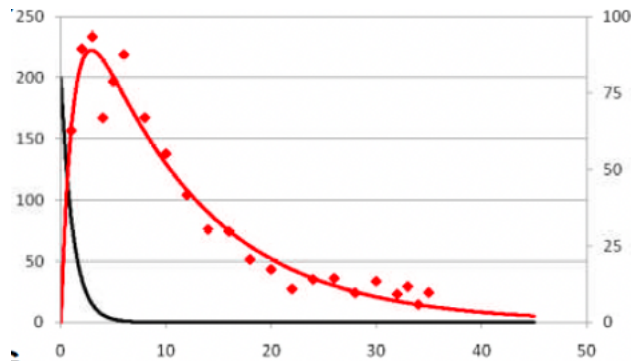
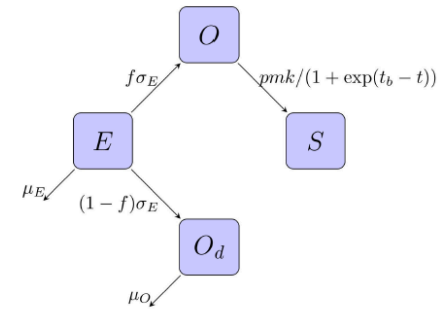
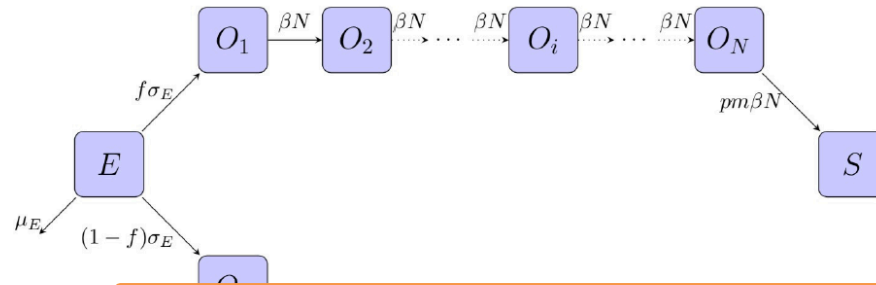
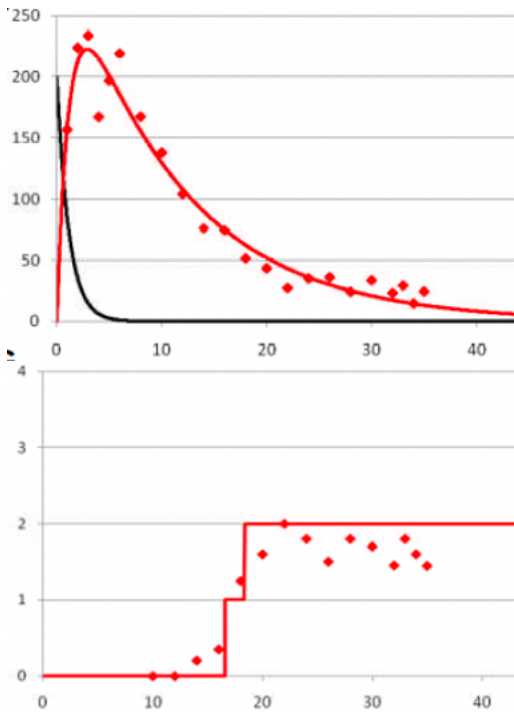


Figure 6.15 – Oocyst to sporozoite models. A Summary of model structure, beginning with  $O_1$ , oocyst density 10 days post-engorgement. B Model equations. C Potential model outputs. D Parameter and variable definitions.



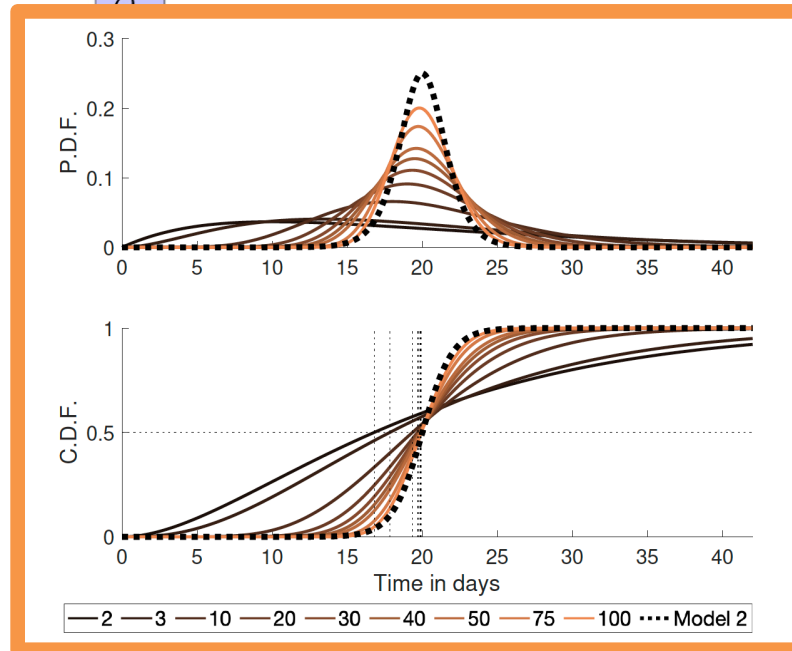
# Our models

Models differ by how we incorporate bursting



(b) Model 2

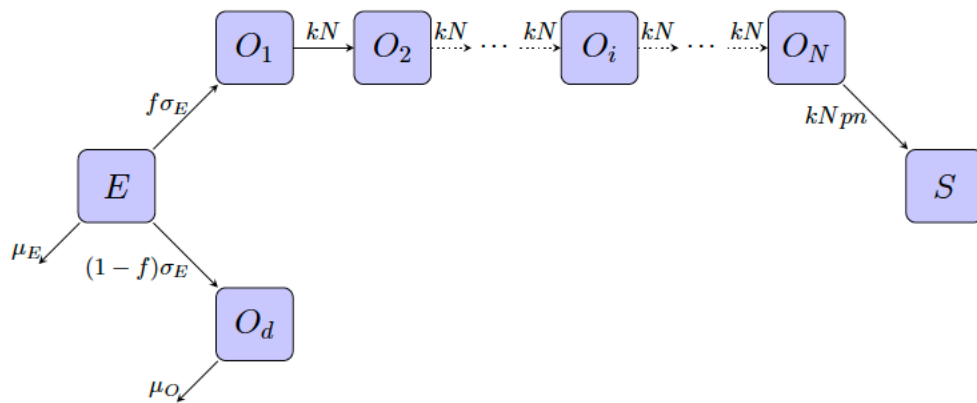
$$f(x) = \frac{1}{\Gamma(k)\theta^k} x^{k-1} e^{-\frac{x}{\theta}}$$



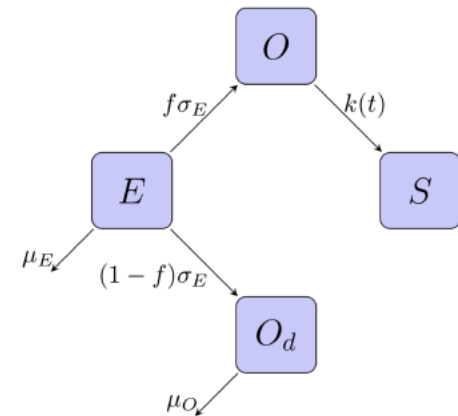
$$k(t) = \frac{k}{1 + \exp(t_b - t)}$$

# Choosing between models

- Number of oocyst compartments in Model 1
- Model 1 vs Model 2

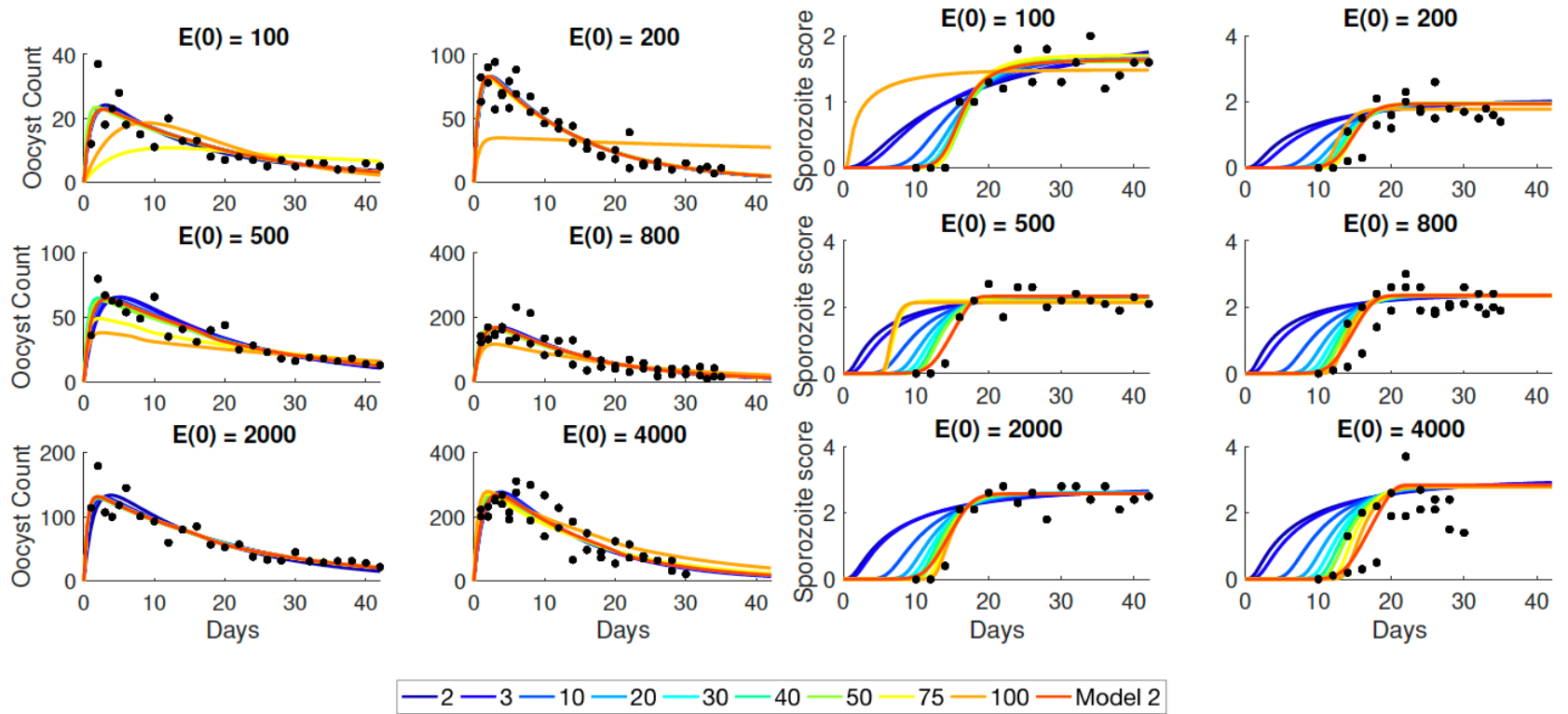


(a) Model 1



(b) Model 2

# Comparing Models



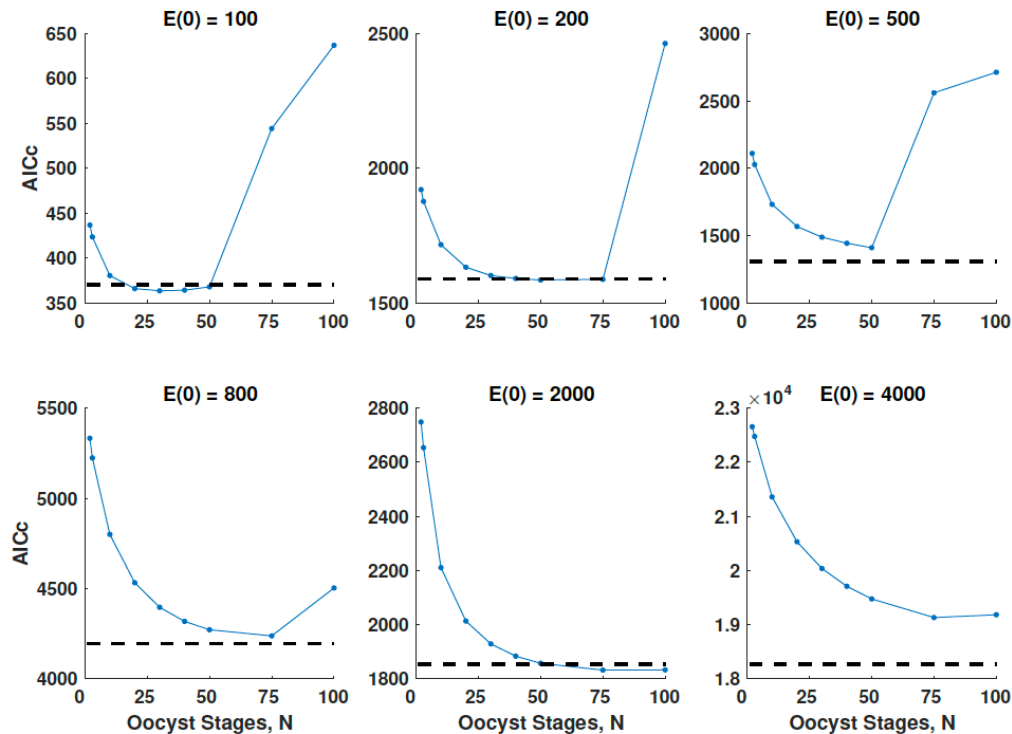


# Comparing models

Akaike information criteria with correction (AICc)

$$\text{AICc} = 2D - 2 \ln(\mathcal{L}) + \frac{2D^2 + 2D}{M - D - 1}$$

$D$  is number of parameters,  $\mathcal{L}$  is likelihood,  $M$  is sample size

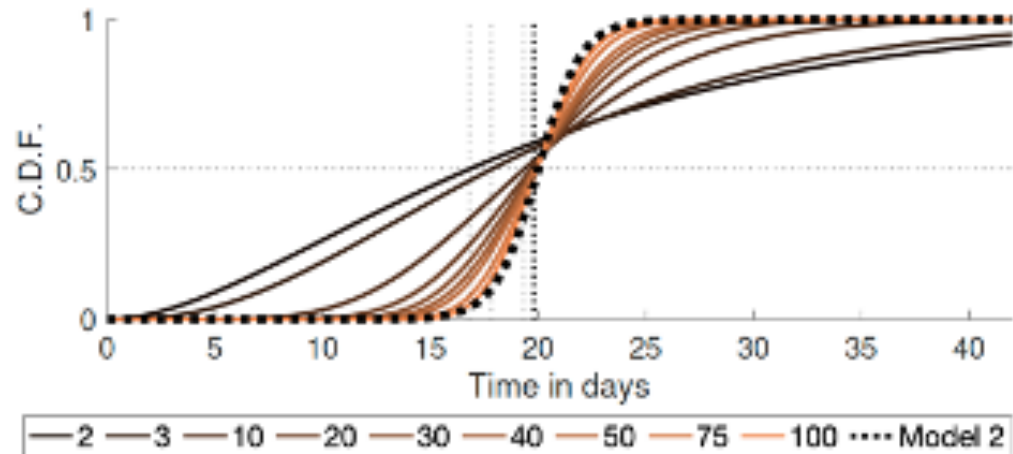


# Calculating time to infectiousness (EIP)

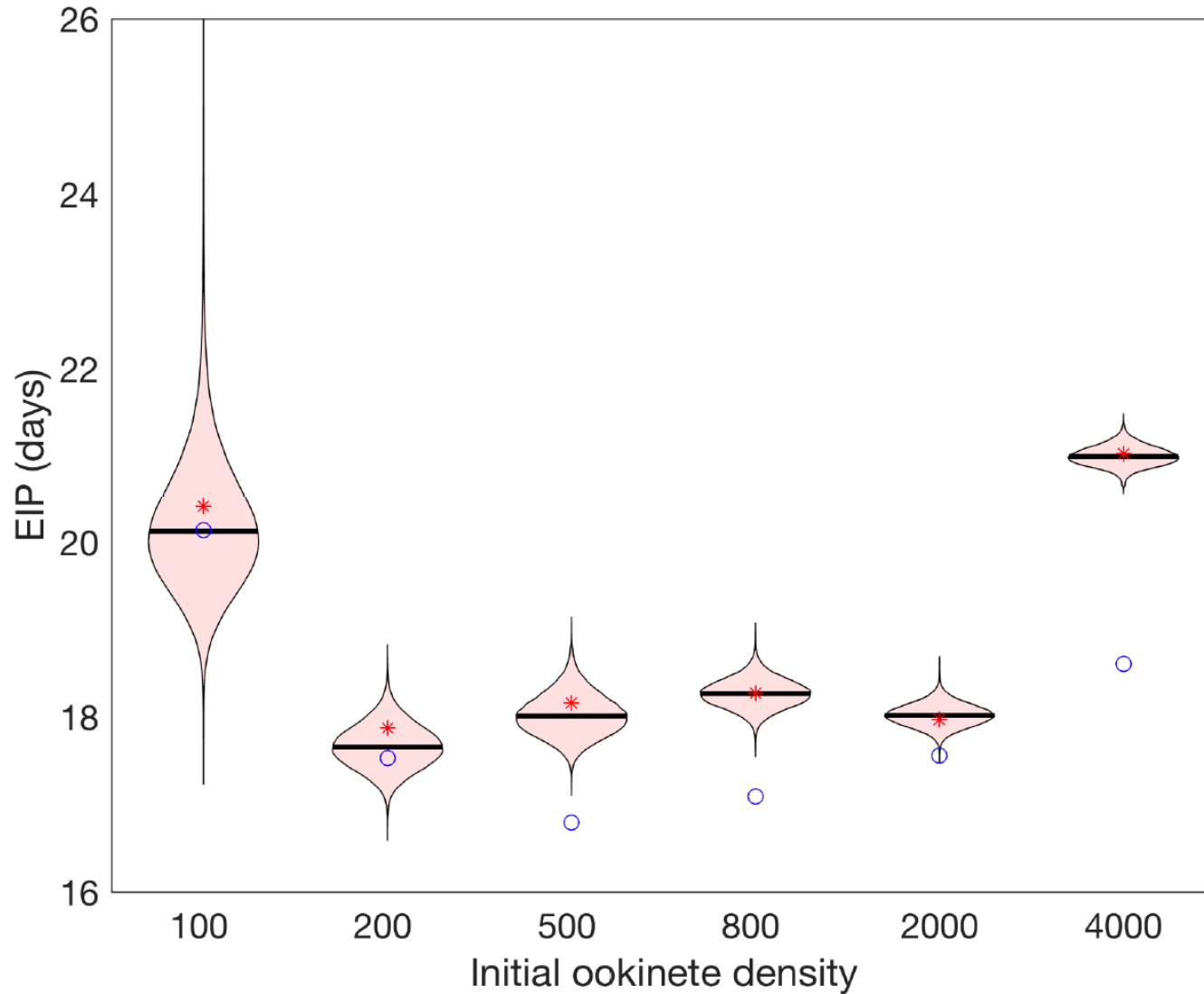
Time when half of  
bursting oocysts  
have burst

$$\frac{1}{\mu_E + \sigma_E} + t^*$$

Average length of  
ookinete stage

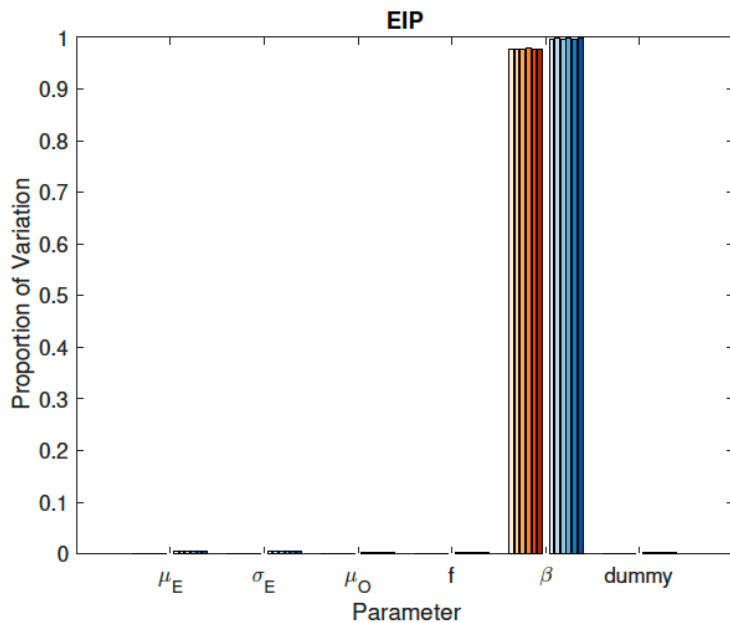


# Time to infectiousness

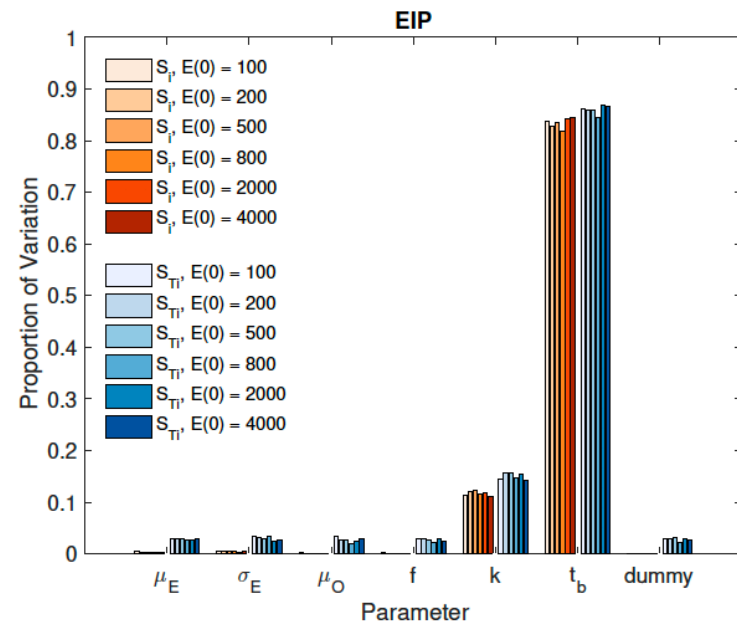


# Sensitivity of EIP to parameters

## Model 1



## Model 2



# Summary

- Parasite diversity
  - Stochasticity in parasite dynamics is important
  - New parasite sequences are frequently passed on
- Estimating time to infectiousness
  - Identified parameters of interest
  - Fraction of bursting oocysts is important
  - Intermediate initial ookinete densities promote transmission
  - Caveats:
    - Ignores variation early in mosquito
    - Particular parasite species and mosquito combination
    - Disagreement in model of choice

# Thank you!

- Questions?

oprosp@utk.edu

Childs and Prosper. "Simulating within-vector generation of the malaria parasite diversity." *PloS One* 12.5 (2017): e0177941.

Childs and Prosper. "The impact of within-vector parasite development on the extrinsic incubation period." *R. Soc. Open. Sci.* (2020): **7** 192173.