Modeling the mitigation of dengue fever, chikungunya and Zika by infecting mosquitoes with *Wolbachia* bacteria

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Abstract

▶ The ongoing mosquito-borne epidemics are of increasing concern worldwide. *Wolbachia* bacteria is a natural parasitic microbe that reduces the disease transmission.

▶ It is difficult to sustain an infection of the maternally transmitted *Wolbachia* bacteria in a wild mosquito population due to the reduced fitness of the infected mosquitoes and incompatibility in the maternal transmission.

▶ We identify important dimensionless numbers and analyze the critical threshold condition for achieving a sustained *Wolbachia* infection.

Mosquito-born Diseases v.s. *Wolbachia*

"Mosquitoes cause more human suffering than any other organism."

– American Mosquito Control Association

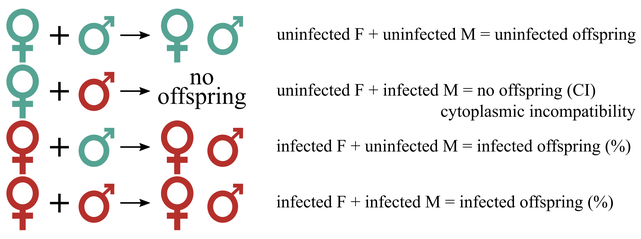
- nearly 700 million people get a mosquito-borne disease each year resulting in greater than one million deaths
- *Aedes aegypti* mosquito: the primary vector for dengue fever, chikungunya and Zika

Wolbachia bacteria A promising strategy to stop diseases at source.

- a natural parasitic microbe, found in 60% insects, but not in the wild *Aedes aegypti* mosquitoes
- stops the proliferation of harmful viruses inside the mosquito ⇒ reduces the disease transmission in dengue fever, chikungunya and Zika
- fitness-cost in the infected female mosquitoes

Maternal transmission *Wolbachia* is maternally transmitted from infected mothers to offspring.

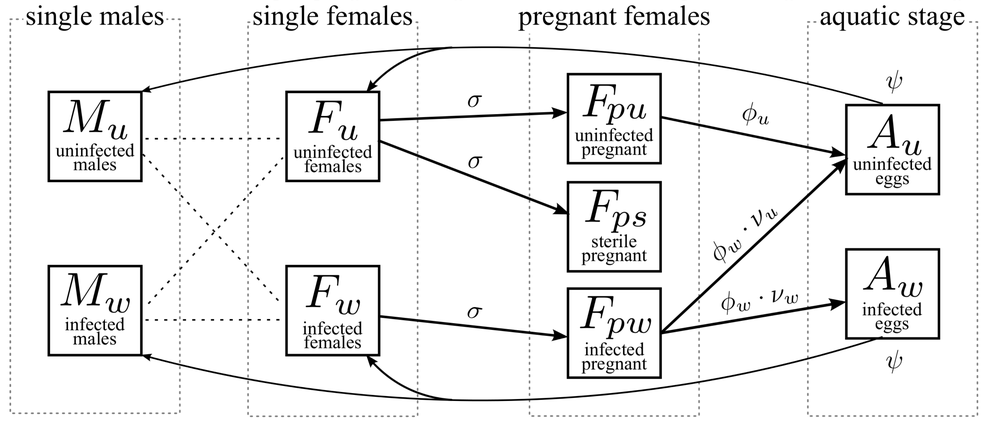
Schematic of the complex maternal transmission mating



Maternal Transmission *Wolbachia* Model

Our new model captures the complex transmission cycle by accounting for:

▶ heterosexual contact ▶ multiple pregnant stages for females ▶ aquatic-stage with carrying capacity



Ordinary differential equation model

$$\frac{dA_u}{dt} = (\phi_u F_{pu} + \nu_u \phi_w F_{pw})\left(1 - \frac{A_u + A_w}{K_a}\right) - (\mu_a + \psi)A_u$$

$$\frac{dA_w}{dt} = \nu_w \phi_w \left(1 - \frac{A_u + A_w}{K_a}\right) F_{pw} - (\mu_a + \psi)A_w$$

$$\frac{dF_u}{dt} = b_f \psi A_u - (\sigma + \mu_{fu})F_u$$

$$\frac{dF_w}{dt} = b_f \psi A_w - (\sigma + \mu_{fw})F_w$$

$$\frac{dF_{pu}}{dt} = \sigma F_u \frac{M_u}{M_u + M_w} - \mu_{fu} F_{pu}$$

$$\frac{dF_{pw}}{dt} = \sigma F_w - \mu_{fw} F_{pw}$$

$$\frac{dM_u}{dt} = b_m \psi A_u - \mu_{mu} M_u$$

$$\frac{dM_w}{dt} = b_m \psi A_w - \mu_{mw} M_w$$

Model parameters

b_f	Female birth probability
b_m	Male birth probability
σ	Mating rate
ϕ_u	Egg-laying rate of F_{pu}
ϕ_w	Egg-laying rate of F_{pw}
ν_w	Maternal transmission rate
ν_u	$= 1 - \nu_w$
ψ	Development rate
μ_a	Death rate of aquatic-stage
μ_{fu}	Death rate of uninfected females
μ_{fw}	Death rate of infected females
μ_{mu}	Death rate of uninfected males
μ_{mw}	Death rate of infected males
K_a	Carrying capacity of aquatic-stage

Bifurcation Analysis

Important dimensionless numbers

next generation number for the uninfected

$$\mathcal{G}_{0u} = b_f \frac{\psi}{\mu_a + \psi} \frac{\sigma}{\sigma + \mu_{fu}} \frac{\phi_u}{\mu_{fu}}$$

develops $P(A_u \to F_u)$ mates $P(F_u \to F_{pu})$ produces $\#F_{pu} \rightleftarrows A_u$

next generation number for the infected

$$\mathcal{G}_{0w} = \nu_w b_f \frac{\psi}{\mu_a + \psi} \frac{\sigma}{\sigma + \mu_{fw}} \frac{\phi_w}{\mu_{fw}}$$

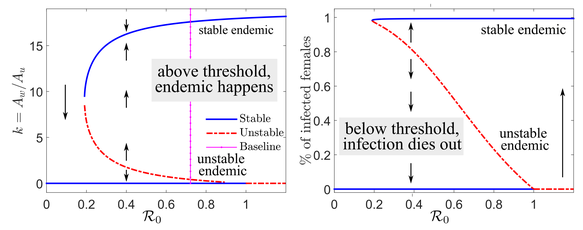
develops $P(A_w \to F_w)$ mates $P(F_w \to F_{pw})$ produces $\#F_{pw} \rightleftarrows A_w$

basic reproduction number

$$\mathcal{R}_0 = \nu_w \frac{\mu_{fu}\phi_w(\sigma + \mu_{fu})}{\mu_{fw}\phi_u(\sigma + \mu_{fw})} = \frac{\mathcal{G}_{0w}}{\mathcal{G}_{0u}}$$

- $\mathcal{G}_{0u} < 1 \Rightarrow$ wild population dies out
- $\mathcal{G}_{0w} > \mathcal{G}_{0u} \Rightarrow$ infected population dominates
- $\mathcal{G}_{0w} < \mathcal{G}_{0u} \Rightarrow$ there is a critical threshold to maintain *Wolbachia* infection

Threshold condition: backward bifurcation

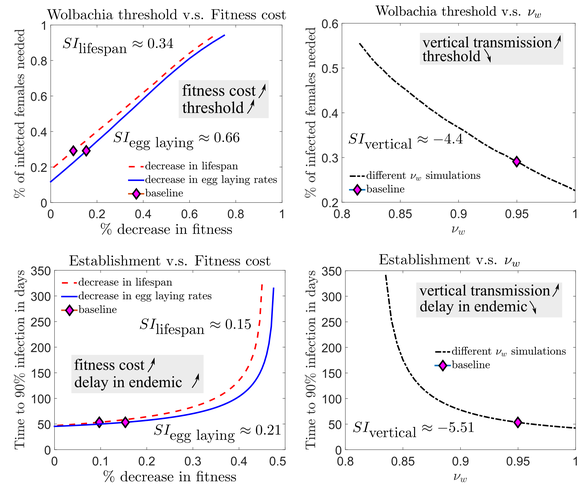


Numerical Results

Sensitivity analysis

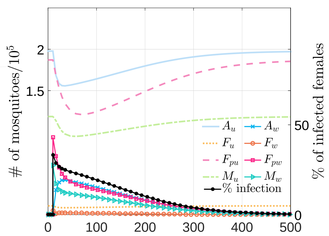
sensitivity index: $SI = \frac{\partial Q}{\partial P} \times \frac{P}{Q}$

P = Parameter of interest; Q = Quantity of interest

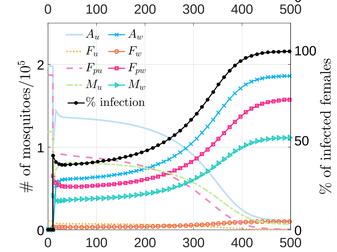


Integrated mitigation strategy

1. pre-release mitigations:
   - kill aquatic-stage mosquitoes: larval control
   - kill adult mosquitoes: residual spraying
2. release *Wolbachia*-infected mosquitoes
   - both males and pregnant females → endemic infection



At day 10, we release $0.5X$ infected adult mosquitoes to the field. However, it's not sufficient to surpass the threshold condition. The infection is wiped out by the natural population around day 500, and the mitigation fails. (X=natural population size)



We first kill $0.5X$ mosquitoes and then release $0.35X$ infected adult mosquitoes. This pre-release mitigation has lowered the releasing number needed to surpass the threshold condition. A stable *Wolbachia*-endemic state is achieved around day 500.

Acknowledgment: This research was partially supported by the NSF-MPS/NIH-NIGMS award NSF-1563531 and the NIH-NIGMS MIDAS award U01GM097661. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NSF or the NIH.

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