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

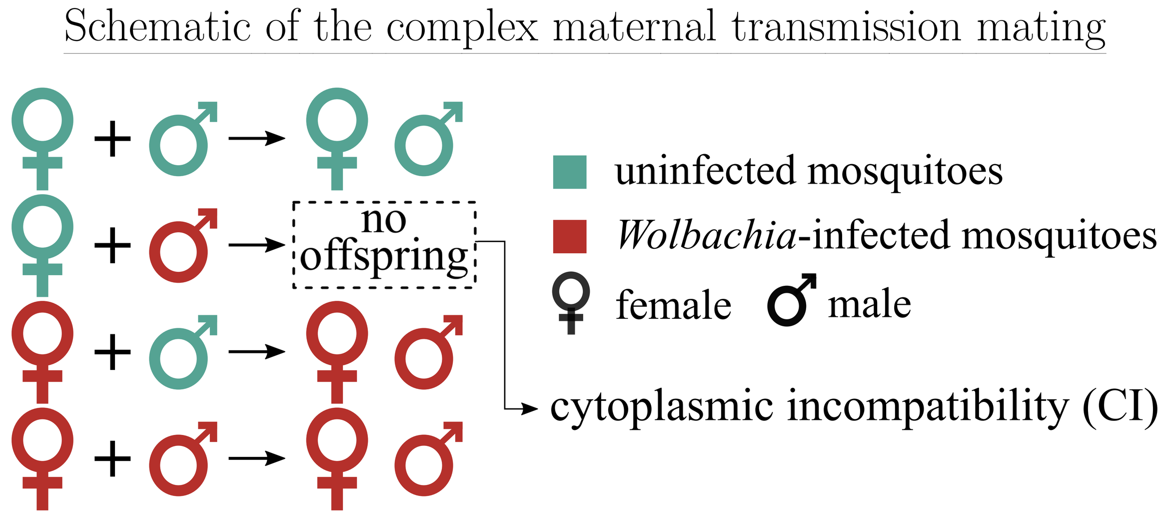
- nearly 700 million people get a mosquito-borne disease each year resulting in greater than one million deaths
- *Aedes aegypti* mosquito: the primary vector for dengue fever, chikungunya and Zika

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.

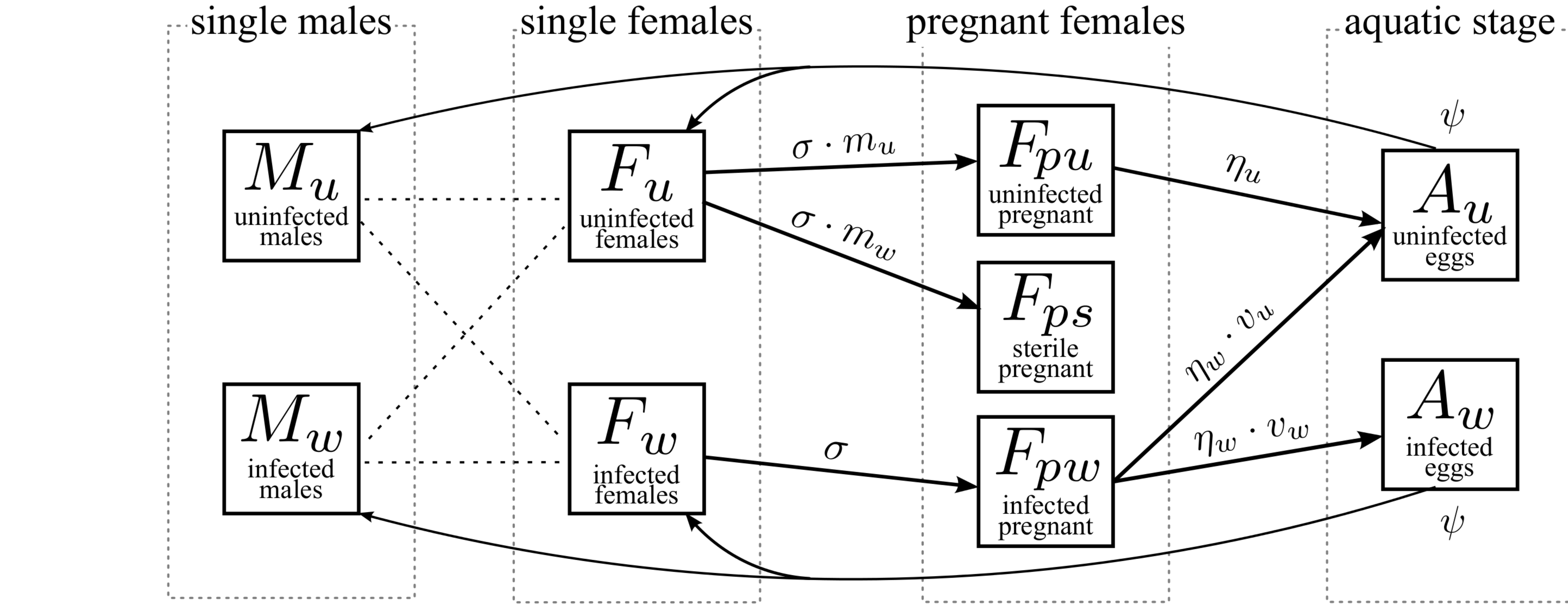
Schematic of the complex maternal transmission mating



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 $\#F_{pu} \lessgtr A_u$

next generation number for the infected

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

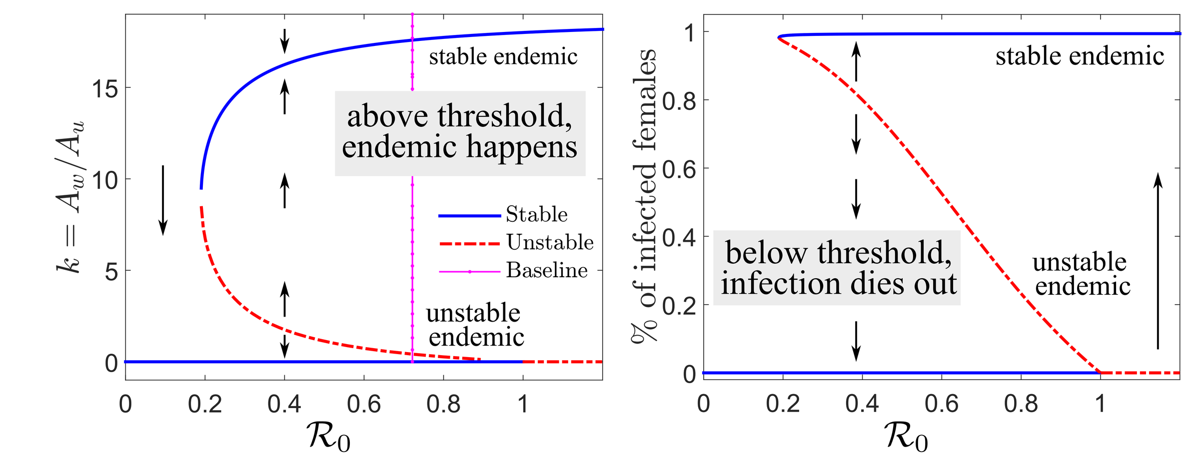
develops $P(A_w \to F_w)$; mates $P(F_w \to F_{pw})$; produces $\#F_{pw} \lessgtr A_w$

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

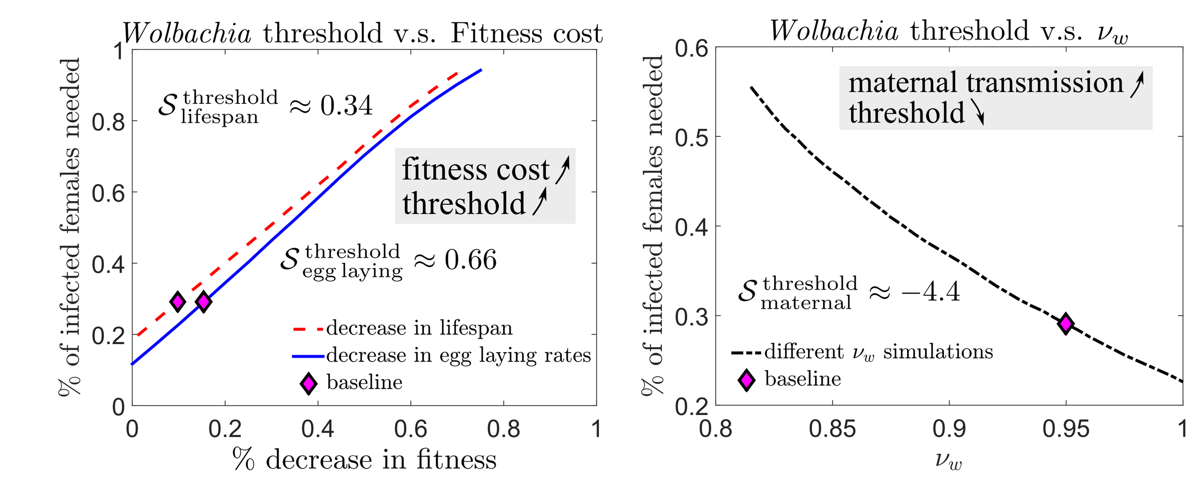


Numerical Results

Sensitivity analysis

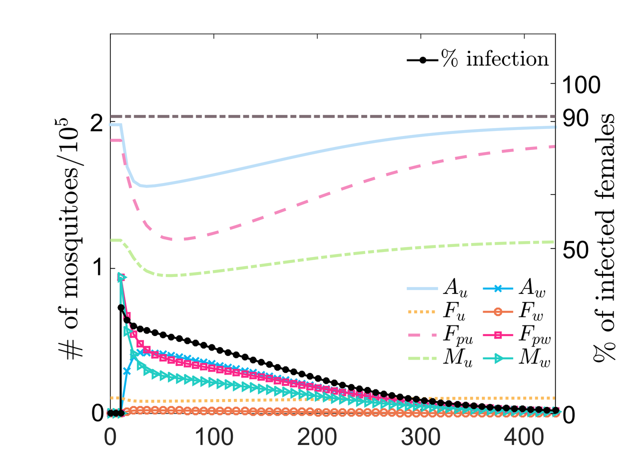
sensitivity index: $\mathcal{S}_p^q := \frac{p}{q} \times \frac{\partial q}{\partial p}$

p = parameters of interest; q = quantities of interest

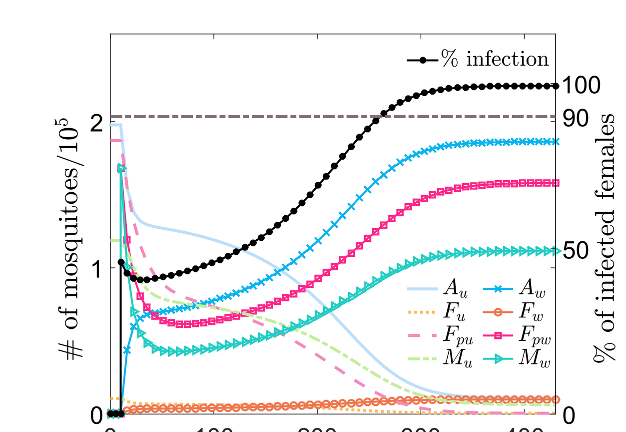


Integrated mosquito management

1. pre-release mitigations
   - kill aquatic-stage mosquitoes: larval control
   - kill adult mosquitoes: residual spraying, sticky ovitraps
2. release *Wolbachia*-infected mosquitoes



At day 10, we release $0.5X$ infected adult mosquitoes to the field. However, it's not sufficient to surpass the threshold condition. The initial infection is eventually wiped out by natural population. (X= size of natural pregnant females population)



We then release more infected population ($0.9X$). The system is able to surpass the threshold condition. 90% of female population is infected at day 261, and a stable *Wolbachia*-endemic state is achieved.

Comparison using different pre-release mitigations

Approach	Target	$T_{90\%\ in\ F}$
None	N/A	261
Residual spraying	Adults	**52**
Larval control	Aquatic-stage	203
Sticky ovitrap	Pregnant females	105
Acoustic attraction	Males	215

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