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 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* mosquitos
- 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* can be maternally transmitted from infected mothers to offspring.

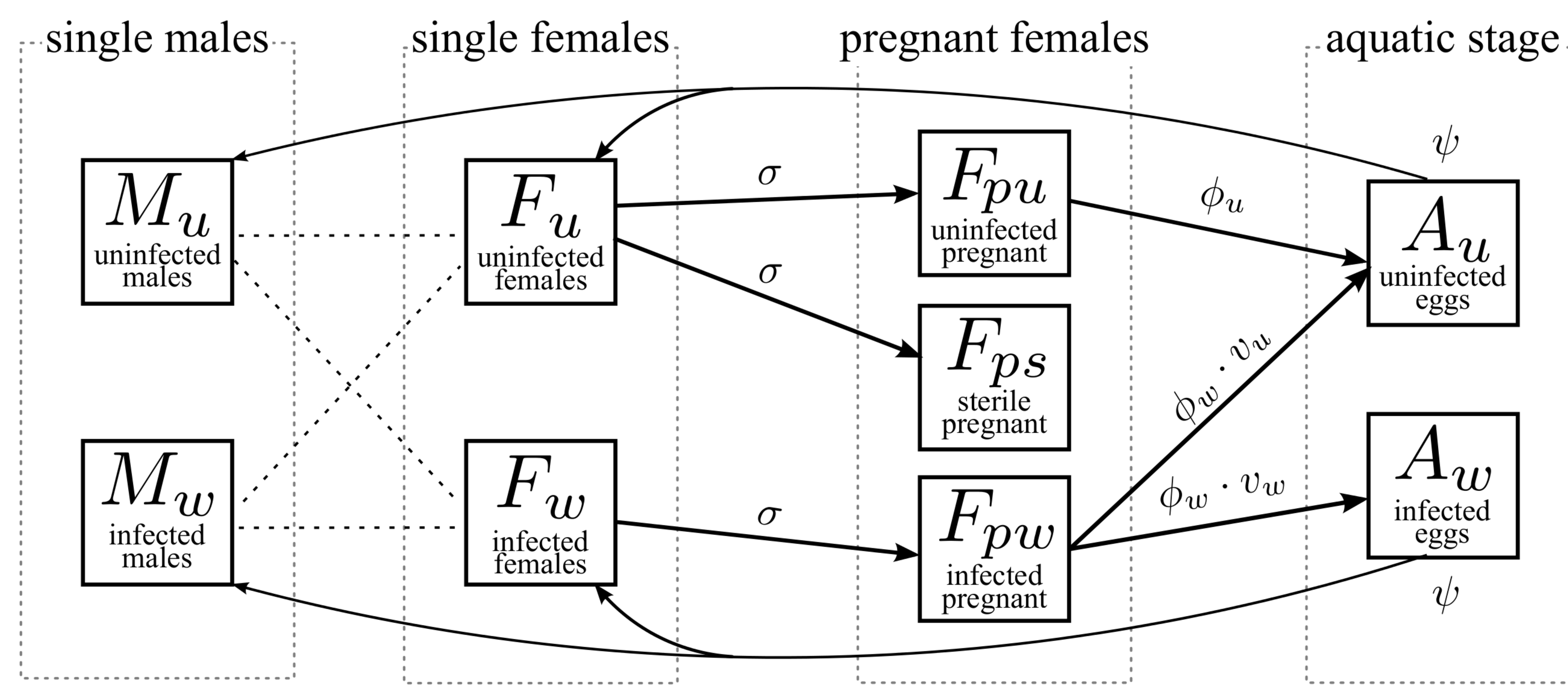
Schematic of the complex vertical transmission mating

♀ + ♂ → ♀ ♂	uninfected F + uninfected M = uninfected offspring
♀ + ♂ → no offspring	uninfected F + infected M = no offspring (CI) cytoplasmic incompatibility
♀ + ♂ → ♀ ♂	infected F + uninfected M = infected offspring (%)
♀ + ♂ → ♀ ♂	infected F + infected M = infected offspring (%)

Vertical Transmission *Wolbachia* Model

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

► heterosexual transmission ► multiple pregnant states for females ► aquatic-life stage



Ordinary differential equation model

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

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

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

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

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

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

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

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

Model parameters

b_f	Fraction of births that are females
b_m	Fraction of births that are males
σ	Mating rate among mosquitoes
ϕ_u	Egg laying rate by F_{pu}
ϕ_w	Egg laying rate by F_{pw}
ν_w	Vertical transmission rate
ν_u	$= 1 - \nu_w$
ψ	Development rate of mosquito eggs
μ_a	Death rate for aquatic stage
μ_{fu}	Death rate for F_u, F_{pu}
μ_{fw}	Death rate for F_w, F_{pw}, F_{ps}
μ_{mu}	Death rate for M_u
μ_{mw}	Death rate for M_w
K_a	Carrying capacity of aquatic stage

Bifurcation Analysis

Important dimensionless numbers

of uninfected eggs generated by an uninfected egg

$$R_{0u} = b_f \underbrace{\frac{\psi}{\mu_a + \psi}}_{\text{develops } P(A_u \to F_u)} \underbrace{\frac{\sigma}{\sigma + \mu_{fu}}}_{\text{mates } P(F_u \to F_{pu})} \underbrace{\frac{\phi_u}{\mu_{fu}}}_{\text{produces } \#F_{pu} \to A_u}$$

# of infected eggs generated by an infected egg

$$R_{0w} = v_w b_f \underbrace{\frac{\psi}{\mu_a + \psi}}_{\text{develops } P(A_w \to F_w)} \underbrace{\frac{\sigma}{\sigma + \mu_{fw}}}_{\text{mates } P(F_w \to F_{pw})} \underbrace{\frac{\phi_w}{\mu_{fw}}}_{\text{produces } \#F_{pw} \to A_w}$$

basic reproduction number

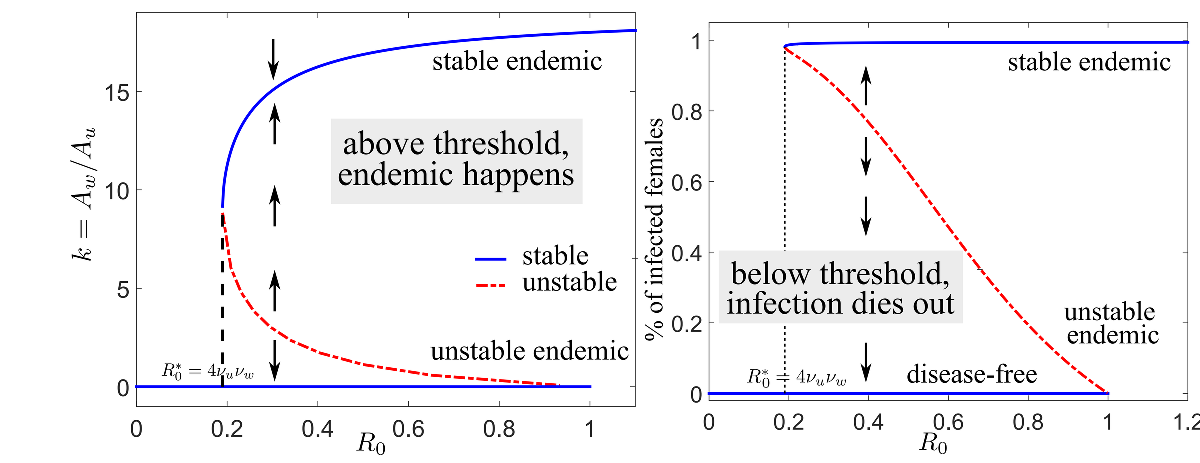
$$R_0 = \nu_w \frac{\mu_{fu}\phi_w(\sigma + \mu_{fu})}{\mu_{fw}\phi_u(\sigma + \mu_{fw})} = \frac{R_{0w}}{R_{0u}}$$

○ $R_{0u} < 1$ ⇒ wild population dies out

○ $R_{0w} > R_{0u}$ ⇒ infected population dominates

○ $R_{0w} < R_{0u}$ ⇒ there is a critical threshold to maintain *Wolbachia* infection

Threshold condition: backward bifurcation

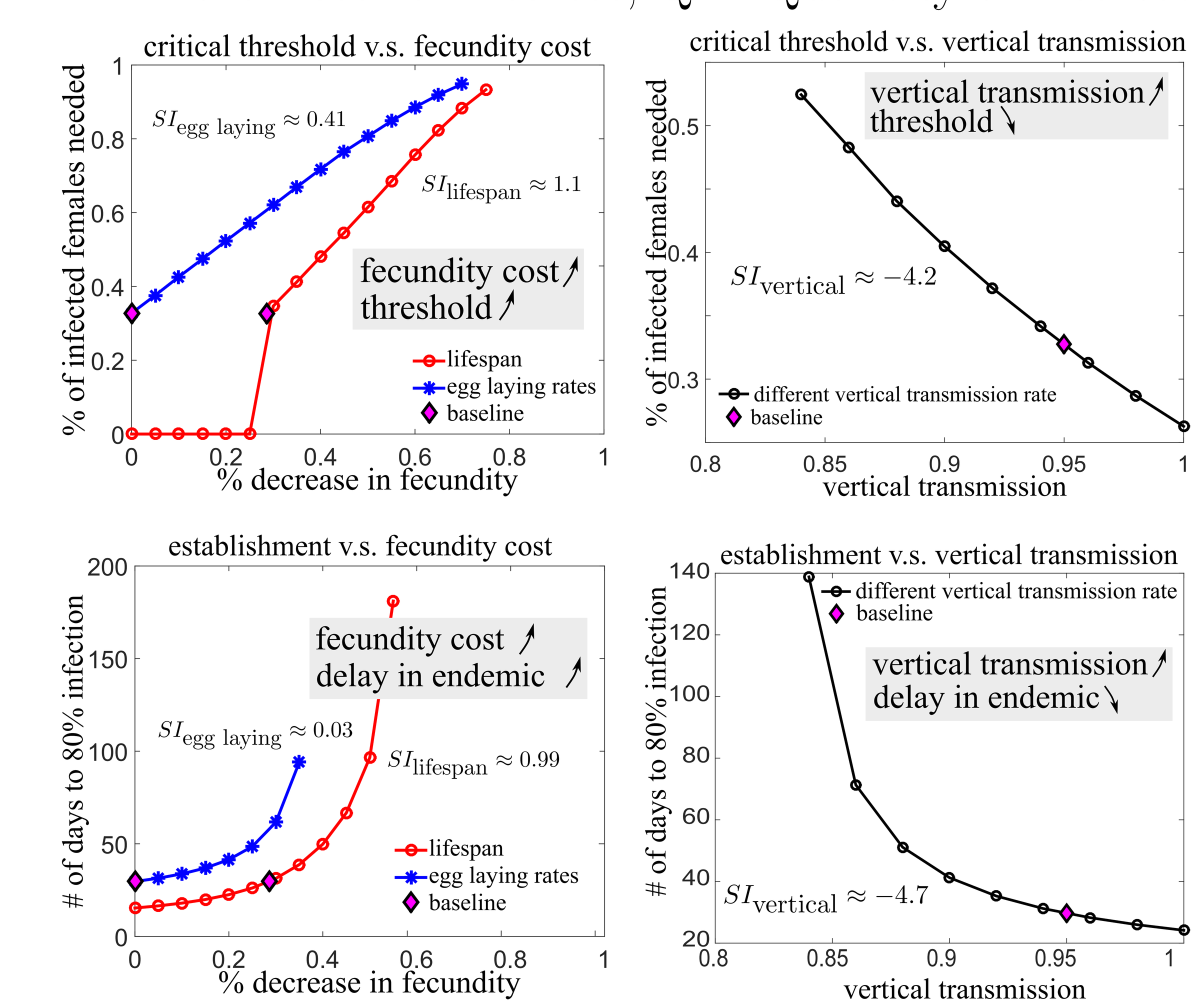


Numerical Results

Sensitivity Analysis

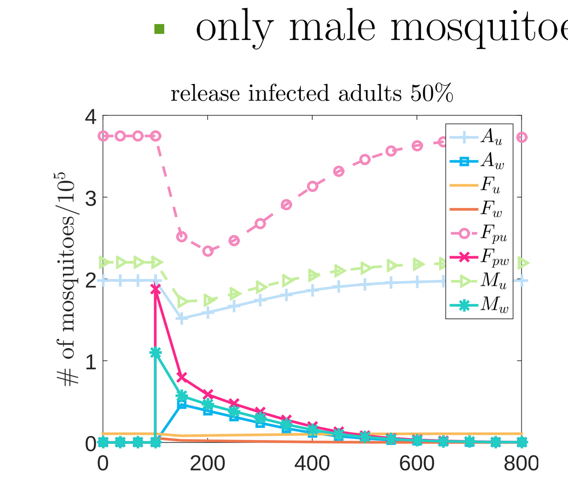
sensitivity index: $SI = \frac{\partial Q}{\partial P} \times \frac{P}{Q}$

P = Parameter of interest; Q = Quantity of interest

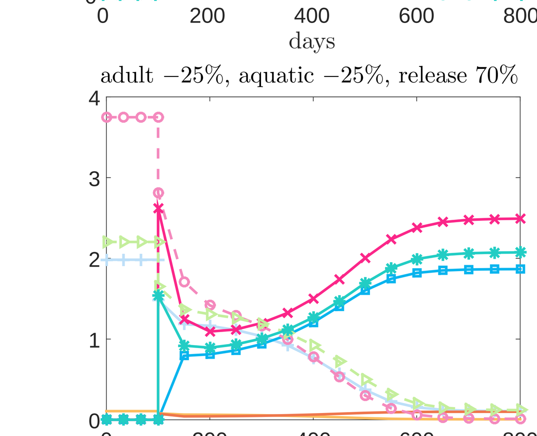


Mitigation Strategies

1. before releasing infected population:
   - kill aquatic-stage mosquitoes: larval control
   - kill adult mosquitoes: spraying
2. release *Wolbachia*-infected mosquitoes
   - both male and female mosquitoes → endemic
   - only male mosquitoes repetitively → population ↓



At day 100, 50% (compared to the size of the wild population) infected adults are released to the field. But, it's not sufficient to pass the threshold condition. Infection is eventually wiped out by the natural population around day 600.



First kill 25% of the adults and 25% of the aquatic stage mosquitoes before releasing. Then release 70% mosquitoes. Such pretreatment and larger release number help to surpass the threshold condition. Stable endemic occurs around day 600.

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