A hierarchy of reduced mathematical models for *Wolbachia* transmission in mosquitoes to control mosquito-borne diseases

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Abstract

- We create and analyze reduced models for the spread of a *Wolbachia* bacteria infection in mosquitoes.
- Mosquitoes that are infected with *Wolbachia* are much less effective at transmitting zoonotic diseases. The infection persists in wild mosquitoes only if the fraction of infection exceeds a minimum threshold.
- Although the large system of differential equations capture the detailed transmission dynamics, they are difficult to analyze, which prevents practical extensions.
- The reduced models cut the analysis burden, yet capture the important properties of the original system.
- **The parameters for the reduced models are defined in terms of the ones in full model.**

Mosquito-born Diseases v.s. *Wolbachia*

- 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

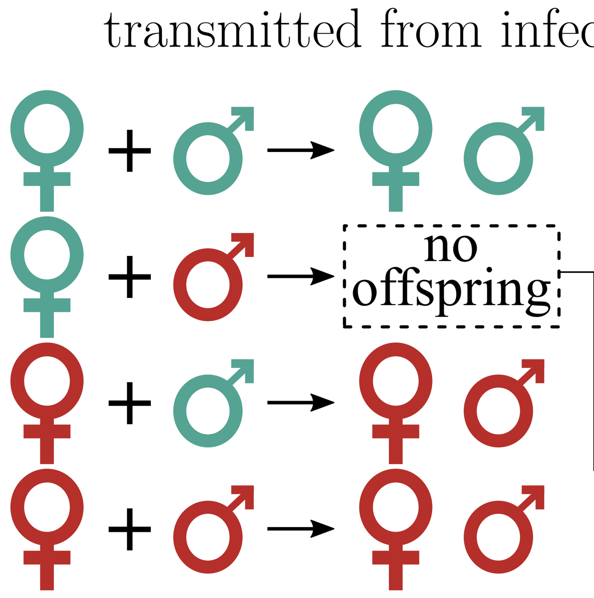
Wolbachia A promising strategy to stop diseases at source.

- a natural parasitic microbe, found in 60% insects species
- inhibits the proliferation of viruses inside the mosquito $\Rightarrow$ blocks the disease transmission
- is not found in the wild *Aedes aegypti* mosquitoes

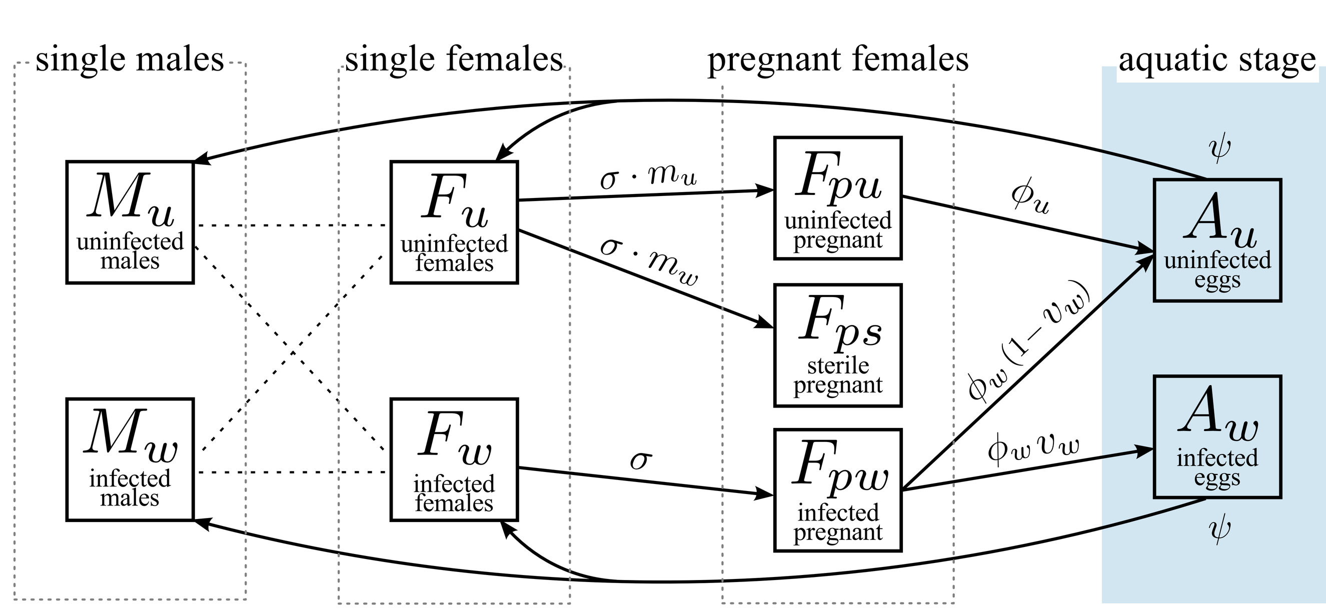
We need to create a *stable* infection in wild mosquitoes.

- field trials in Australia, Brazil, Colombia, Indonesia, Vietnam to control dengue/Zika epidemics
- Fraction of infection has to exceed a critical threshold.

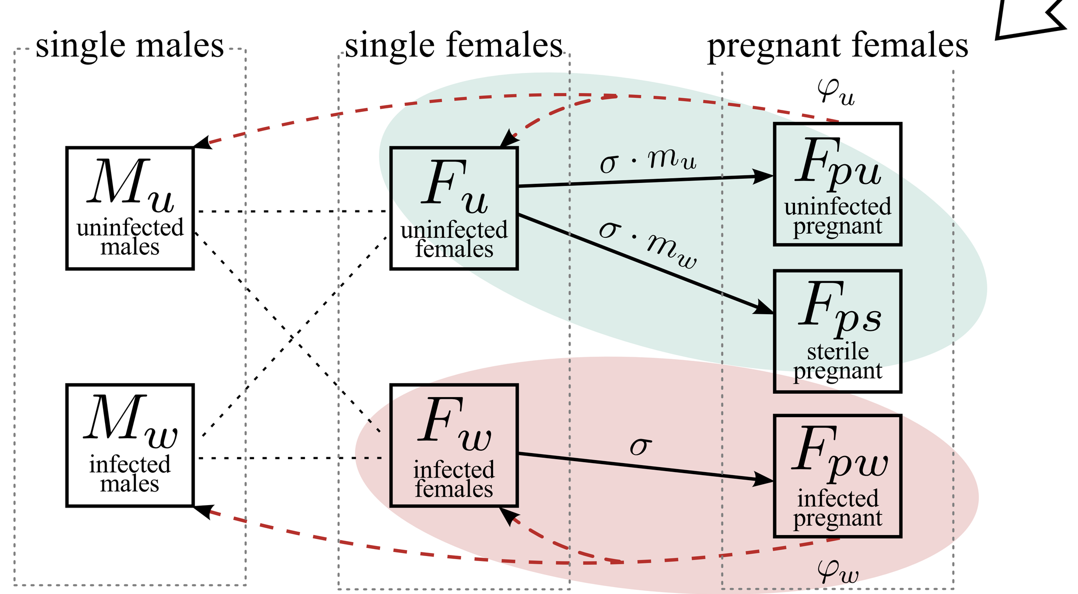
Maternal transmission *Wolbachia* is maternally transmitted from infected mothers to offspring.



Model Reductions 9-ODEs $\rightarrow$ 2-ODEs



σ	Mating rate
ϕ_u	Egg-laying rate for F_{pu}
ϕ_w	Egg-laying rate for F_{pw}
v_w	Maternal transmission rate
ψ	Development rate
μ_a	Death rate for aquatic
μ_{fu}	Death rate for uninf. females
μ_{fw}	Death rate for inf. females
μ_{mu}	Death rate for uninf. males
μ_{mw}	Death rate for inf. males
K_a	Carrying capacity of aquatic

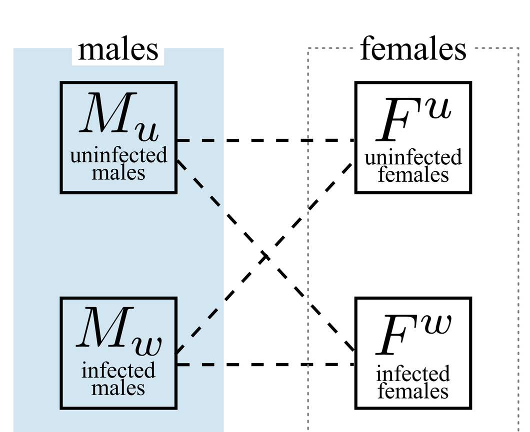


- remove aquatic (pregnant $\rightarrow$ adult)

$$\left.\begin{aligned}\varphi_u &= \frac{\psi}{\psi+\mu_a}\phi_u\\ \varphi_w &= \frac{\psi}{\psi+\mu_a}\phi_w\end{aligned}\right\} \textit{Natural}\text{ reproduction rate}$$

- carrying capacity on pregnant females

$$K_p = \frac{\sigma}{\sigma+\mu_{fu}}\frac{b_f\psi}{\mu_{fu}}K_a$$



- combine infection groups

$$F^u = F_u + F_{pu} + F_{ps}$$
$$F^w = F_w + F_{pw}$$

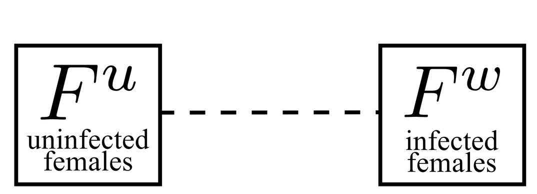
- single females ≈ 0

$$F_{pu} \rightarrow F^u\frac{M_u}{M_u+M_w}$$
$$F_{ps} \rightarrow F^u\frac{M_w}{M_u+M_w} \qquad F_{pw} \rightarrow F^w$$

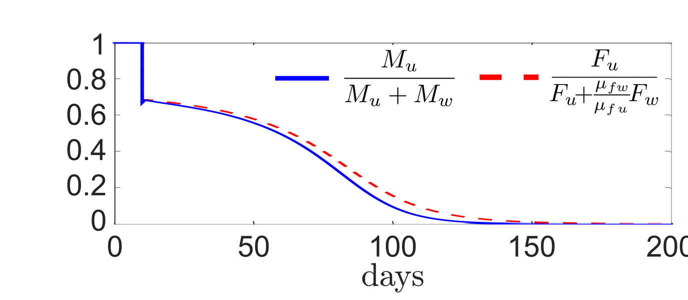
$$\left.\begin{aligned}\varphi_u' &= \frac{\psi}{\psi+\mu_a}\frac{\sigma}{\sigma+\mu_{fu}}\phi_u\\ \varphi_w' &= \frac{\psi}{\psi+\mu_a}\frac{\sigma}{\sigma+\mu_{fw}}\phi_w\end{aligned}\right\} \textit{Mixing}\text{ reproduction rate}$$

- carrying capacity on all the females

$$K_f = \frac{b_f\psi}{\mu_{fu}}K_a$$



- remove males
- proportional infection fraction in males and females



Reduced model

$$(F^u)_t = b_f\varphi_u'\frac{F^u}{F^u+\frac{\mu_{fw}}{\mu_{fu}}F^w}\left(1-\frac{F^u+F^w}{K_f}\right)F^u + b_f(1-v_w)\varphi_w'\left(1-\frac{F^u+F^w}{K_f}\right)F^w - \mu_{fu}F^u + d(F^u_{xx}+F^u_{yy})$$

$$(F^w)_t = b_f v_w\varphi_w'\left(1-\frac{F^u+F^w}{K_f}\right)F^w - \mu_{fw}F^w + d(F^w_{xx}+F^w_{yy})$$

Future work

Include practical extensions

- spatial heterogeneity
- temporal variation

Full model

$$\dot{A}_u = (\phi_u F_{pu} + (1-v_w)\phi_w F_{pw})\left(1-\frac{A_u+A_w}{K_a}\right) - (\mu_a+\psi)A_u$$
$$\dot{A}_w = v_w\phi_w F_{pw}\left(1-\frac{A_u+A_w}{K_a}\right) - (\mu_a+\psi)A_w$$
$$\dot{F}_u = b_f\psi A_u - (\sigma+\mu_{fu})F_u$$
$$\dot{F}_w = b_f\psi A_w - (\sigma+\mu_{fw})F_w$$
$$\dot{F}_{pu} = \sigma m_u F_u - \mu_{fu}F_{pu}, \quad m_u = M_u/(M_u+M_w)$$
$$\dot{F}_{ps} = \sigma m_w F_u - \mu_{fu}F_{ps}, \quad m_w = M_w/(M_u+M_w)$$
$$\dot{F}_{pw} = \sigma F_w - \mu_{fw}F_{pw}$$
$$\dot{M}_u = b_m\psi A_u - \mu_{mu}M_u$$
$$\dot{M}_w = b_m\psi A_w - \mu_{mw}M_w$$

Model Comparisons

Reduced models preserve two important properties of the detailed 9-ODE model.

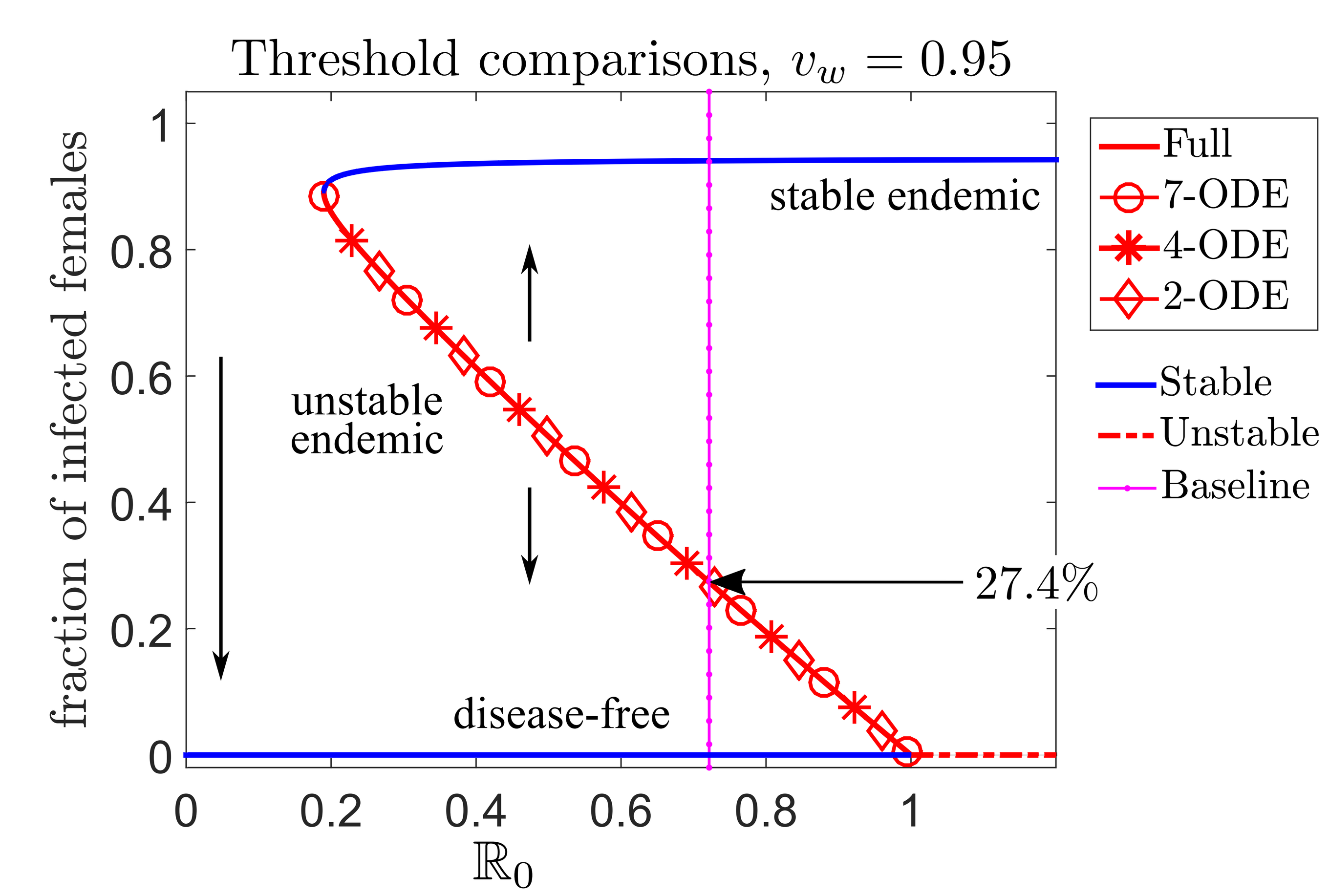
Basic reproductive number $\mathbb{R}_0$

- number of new infections created by a single *Wolbachia*-infected mosquito, given all the rest mosquitoes are fully susceptible
- often used as a threshold condition for disease outbreak (predict early epidemic)
- Full model: $\mathbb{R}_0^{(9)} = v_w\frac{\mu_{fu}\,\phi_w\,(\sigma+\mu_{fu})}{\mu_{fw}\,\phi_u\,(\sigma+\mu_{fw})} \approx 0.722$

$$\mathbb{R}_0^{(9)} = \mathbb{R}_0^{(7)} = \mathbb{R}_0^{(4)} = \mathbb{R}_0^{(2)}$$

Critical threshold for a stable *Wolbachia* infection

- a minimum threshold must be exceeded to establish a stable infection in wild mosquitoes
- backward bifurcation with an unstable steady-state



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