Reducing mathematical models for *Wolbachia* transmission in mosquitoes to control mosquito-borne diseases

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Outlines

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

– American Mosquito Control Association

- dengue fever: flu-like illness, severe cases: bleeding and shock
- chikungunya: debilitating joint pain, long-term symptoms
- Zika: no or only mild symptoms; microcephaly in the baby

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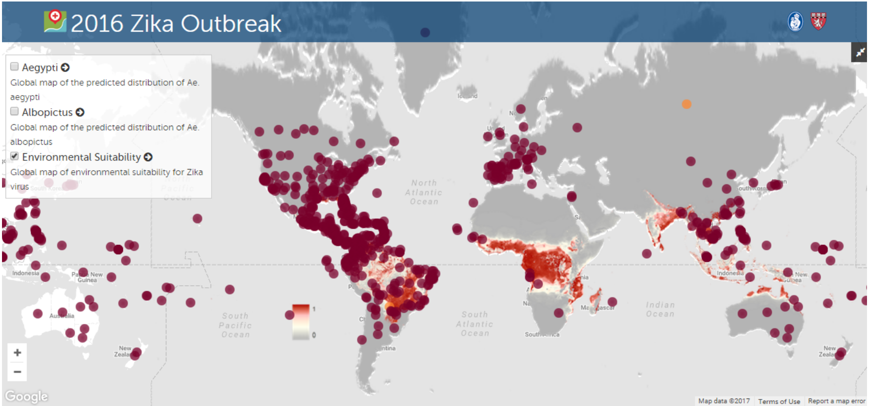
Source: https://www.cdc.gov/ncbddd/birthdefects/microcephaly.html

Areas with Risk of Zika



- Central and South America, sub-Saharan Africa, Southeast Asia, etc...

Source: `http://www.healthmap.org/zika/#timeline`

Aedes aegypti – primary vector for the transmission

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Source: United States Agency for International Development (USAID)

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  - water tank/scrap tires

Source: http://entoplp.okstate.edu/mosquito/control/

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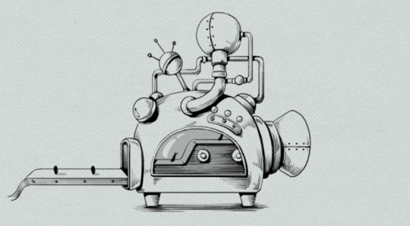

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- sterile insect technique (SIT)
  - release sterilized males
  - not self-replicating

Source: `https://debug.com/how/`

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$\Rightarrow$ reduce the mosquito population size

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Question: More sustainable approach?

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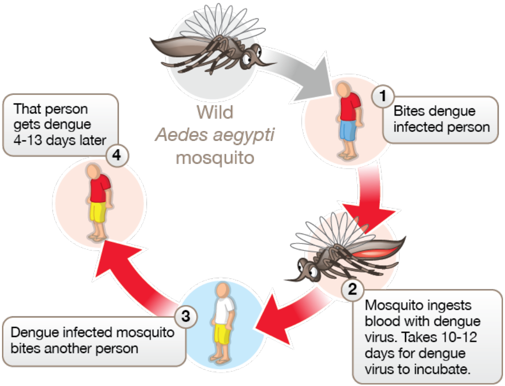

Source: Australias Department of Foreign Affairs and Trade (DFAT) & Eliminate Dengue Program

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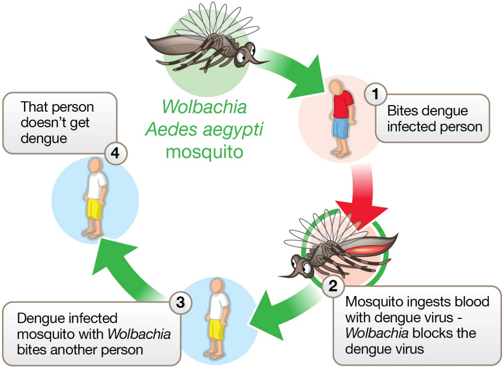

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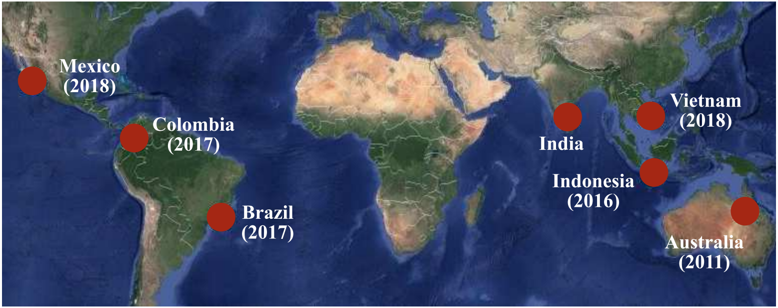
- It is not found in the wild *Aedes aegypti* mosquitoes!
- Create a stable infection in wild mosquitoes — cost-effective control
- Field trials in many countries to suppress dengue/Zika transmission with promising results



Source: http://www.eliminatedengue.com/our-research/wolbachia

Q: How many *Wolbachia*-infected mosquitoes need to be released?

- difficult to sustain such infection in a wild mosquito population

  fitness cost due to *Wolbachia* infection:
  - infected female lifespan $\downarrow$
  - number of eggs produced $\downarrow$
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- [Qu *et al*, '18]: a mathematical model for *Wolbachia* transmission in mosquito population – a critical threshold must be exceeded

$$\frac{\textit{Wolbachia}\text{-infected mosquitoes}}{\text{uninfected mosquitoes}} \begin{cases} < \theta, & \text{infection dies out} \\ > \theta, & \text{stable infection} \end{cases}$$

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Model Reduction

We create an ensemble of reduced models that approximate the solution of a detailed 9-ODE model to ...

- cut analysis burden
- capture the important properties of the original system

Outlines

Wolbachia transmission dynamics in mosquitoes

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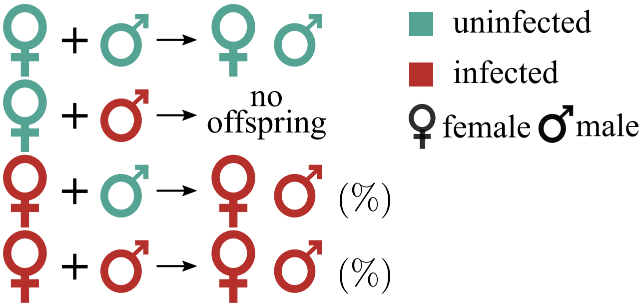
Schematic of the complex maternal transmission mating



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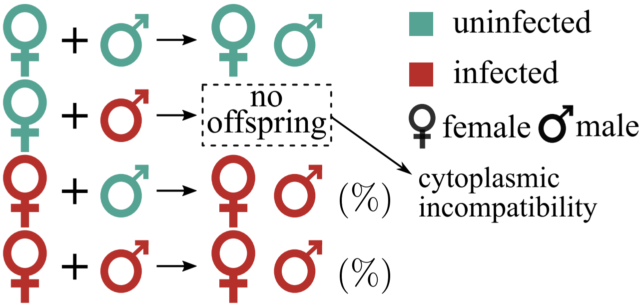

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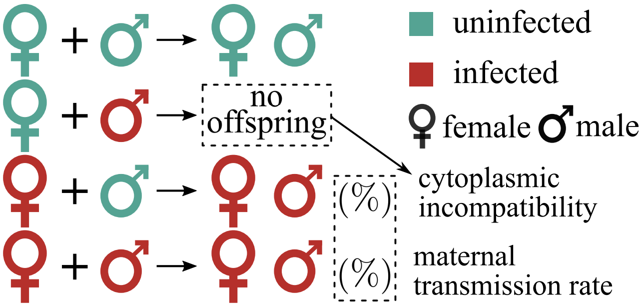
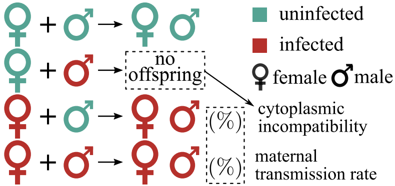
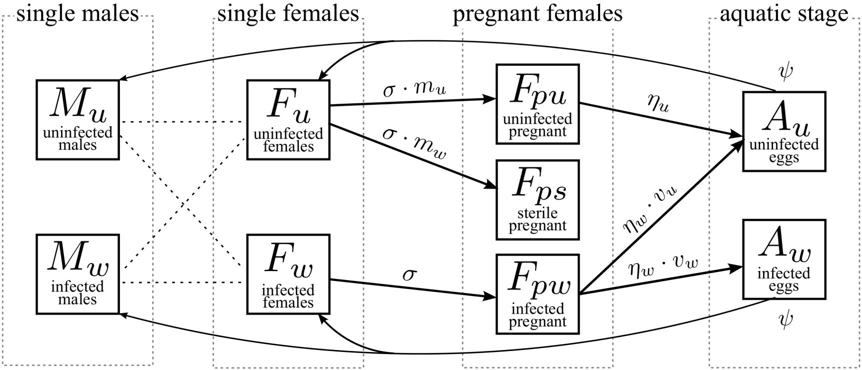


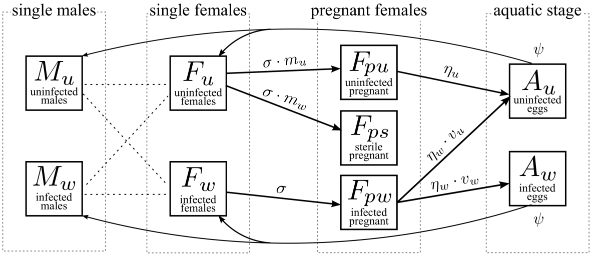
The detailed model captures the complex transmission cycle

by accounting for ...

- heterosexual transmission
- multi-stage female life cycle
- carrying capacity for aquatic stage







$$\left.\begin{aligned} \dot{M}_u &= b_m \psi A_u - \mu_{mu} M_u \\ \dot{M}_w &= b_m \psi A_w - \mu_{mw} M_w \end{aligned}\right\} \text{single males}$$

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$$\left.\begin{aligned} \dot{A}_u &= (\phi_u F_{pu} + v_u \phi_w F_{pw}) \left(1 - \frac{A_u + A_w}{K_a}\right) - (\mu_a + \psi) A_u \\ \dot{A}_w &= v_w \phi_w \left(1 - \frac{A_u + A_w}{K_a}\right) F_{pw} - (\mu_a + \psi) A_w \end{aligned}\right\} \text{aquatic}$$

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}
v_w	Maternal transmission rate
v_u	$= 1 - v_w$
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

Basic reproductive number $\mathbb{R}_0$

In epidemiology, the basic reproductive number $\mathbb{R}_0$

- is the number of new infections that one infectious individual creates in a fully susceptible population
- threshold condition for the disease outbreak
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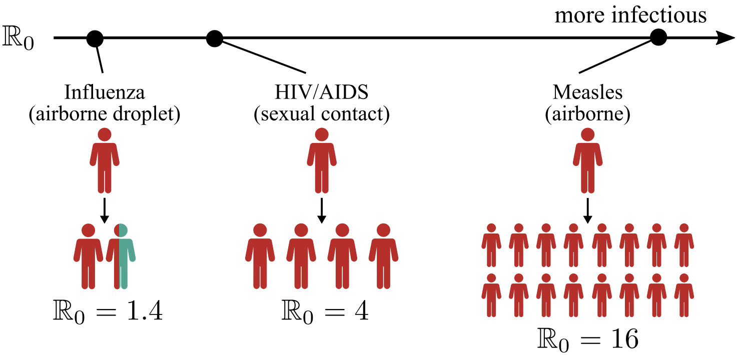

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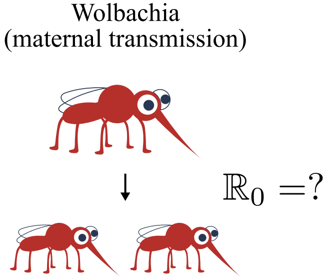
For *Wolbachia* infection in mosquito population,



Basic reproductive number $\mathbb{R}_0$

By *next generation matrix* approach [Diekmann (1990), van den Driessche (2002)] ... (messy calculations) ...

$$\mathbb{R}_0 = v_w \frac{\mu_{fu}\, \phi_w \,(\sigma + \mu_{fu})}{\mu_{fw}\, \phi_u \,(\sigma + \mu_{fw})}$$

v_w	maternal transmission rate
μ_{fu}	death rates for uninfected
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- *Not necessarily!* $\mathbb{R}_0$ is valid for a small perturbation around disease-free state

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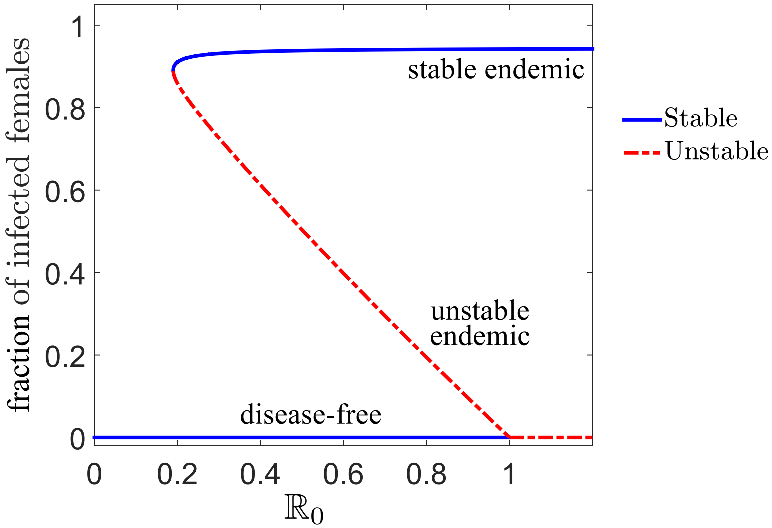
Critical threshold for stable *Wolbachia* infection



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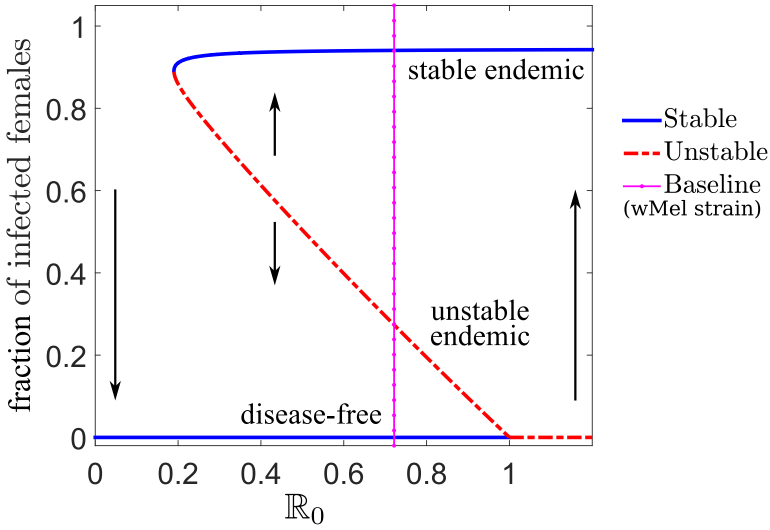

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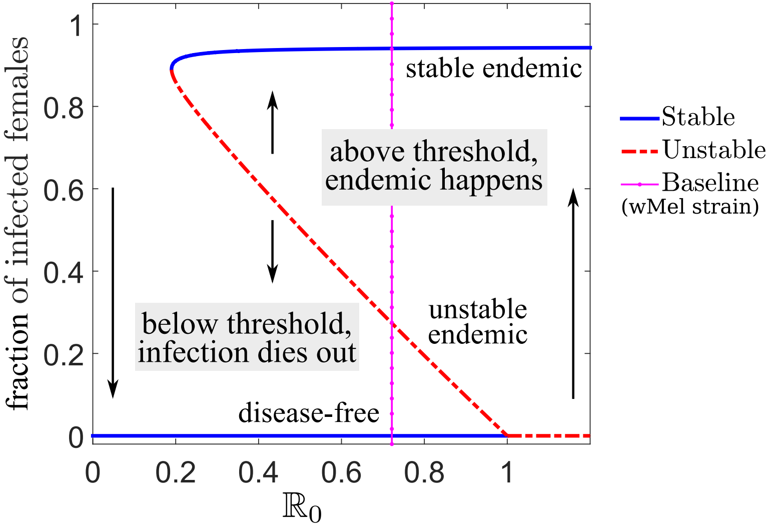
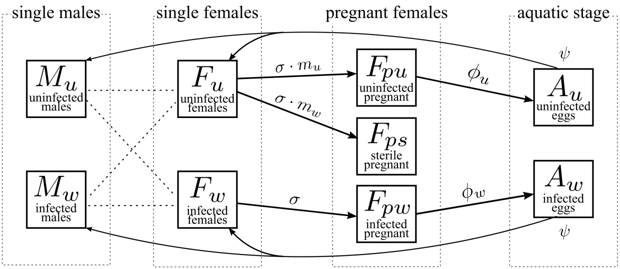
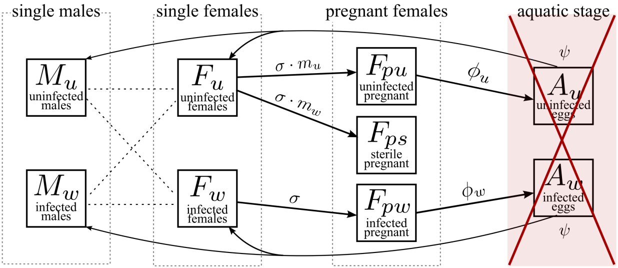


Outlines

For the sake of simplicity, we show the perfect maternal transmission.



Step 1: remove aquatic stage



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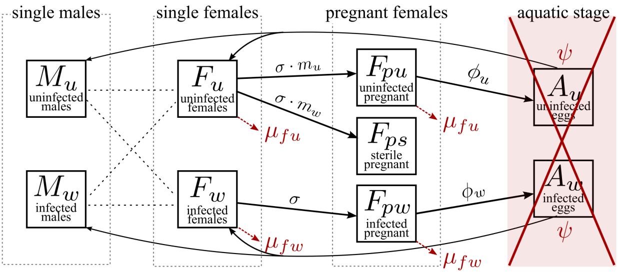

- delay in aquatic stage

$$\underbrace{\frac{1}{\psi}}_{\text{aquatic-stage time}} + \underbrace{\frac{1}{\mu_{fu}}}_{\text{adult-stage time}} = \underbrace{\frac{1}{\mu'_{fu}}}_{\text{entire lifespan}}$$

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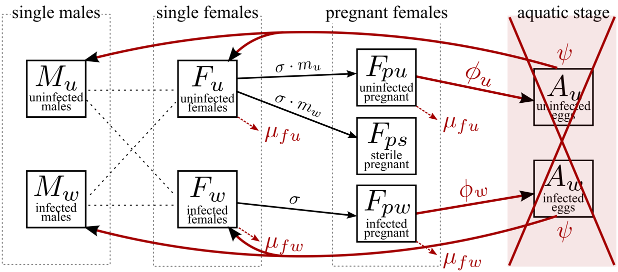

- delay in aquatic stage
- new egg-laying rates

next generation numbers $\mathbb{G}_{0u}$, $\mathbb{G}_{0w}$

$\mathbb{G}_{0u}$ = number of new uninfected eggs reproduced by an uninfected egg

$\mathbb{G}_{0w}$ = number of new infected eggs reproduced by an infected egg

(within one life cycle, around zero-infection state)

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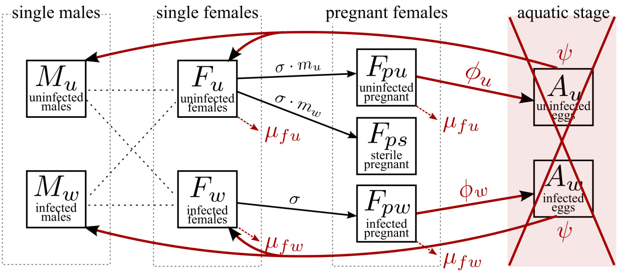

- delay in aquatic stage
- new egg-laying rates

$$\mathbb{G}_{0u}^{(9)} = b_f \underbrace{\frac{\sigma}{\sigma+\mu_{fu}}}_{\text{successfully mated } F_u} \underbrace{\frac{\phi_u}{\mu_{fu}}}_{\text{number of new offspring per } F_{pu}} \underbrace{\frac{\psi}{\psi+\mu_a}}_{\text{successfully developed } A_u}$$

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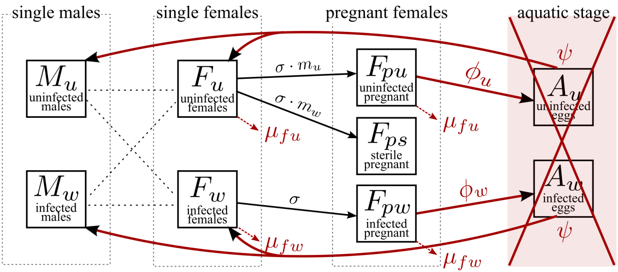

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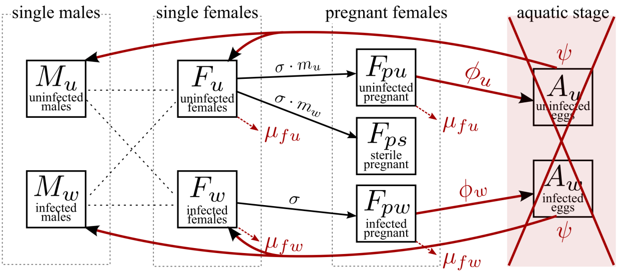

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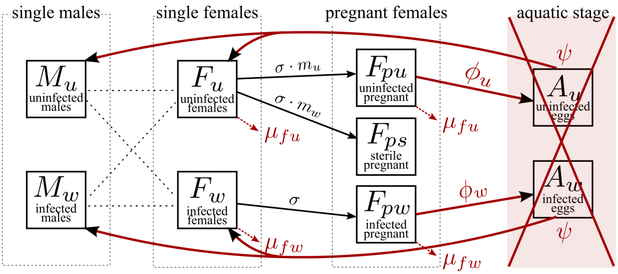

- delay in aquatic stage → timescale of one generation
- new egg-laying rates → change in one generation
- modify carrying capacity

$$K_p = b_f \frac{\sigma}{\sigma+\mu'_{fu}} \frac{\psi}{\mu'_{fu}} K_a$$

egg-laying rate

$$\boxed{\phi_u} \left(1 - \frac{\boxed{A_u + A_w}}{\boxed{K_a}}\right)$$

carrying capacity regularization

$$\downarrow \qquad \qquad \downarrow$$

$$\phi'_u \left(1 - \frac{\boxed{F_{pu} + F_{ps} + F_{pw}}}{\boxed{K_p}}\right)$$

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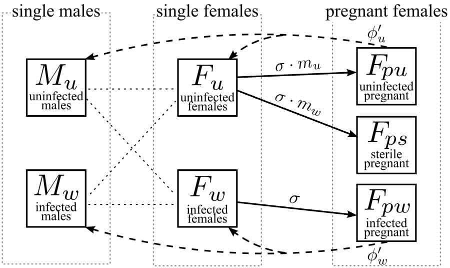

$$\left.\begin{aligned}
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\end{aligned}\right\}\text{single males}$$

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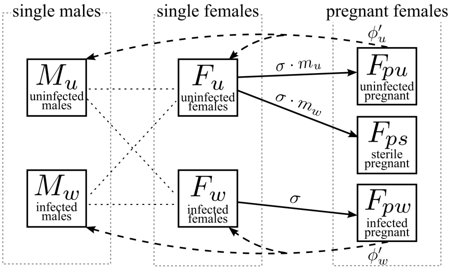
b_m	Male birth probability
σ	Mating rate
$\phi'_u = \frac{\psi}{\psi+\mu_a}\frac{\sigma+\mu'_{fu}}{\sigma+\mu_{fu}}\frac{\mu'_{fu}}{\mu_{fu}}\phi_u$	Natural egg-laying rate for F_{pu}
$\phi'_w = \frac{\psi}{\psi+\mu_a}\frac{\sigma+\mu'_{fw}}{\sigma+\mu_{fw}}\frac{\mu'_{fw}}{\mu_{fw}}\phi_w$	Natural egg-laying rate for F_{pw}
$K_p = b_f \frac{\sigma}{\sigma+\mu'_{fu}}\frac{\psi}{\mu'_{fu}} K_a$	Carrying capacity for pregnant females
$\mu'_{fu} = \frac{\psi}{\psi+\mu_{fu}}\mu_{fu}$	Death rate of uninfected females
$\mu'_{fw} = \frac{\psi}{\psi+\mu_{fw}}\mu_{fw}$	Death rate of infected females
$\mu'_{mu} = \frac{\psi}{\psi+\mu_{mu}}\mu_{mu}$	Death rate of uninfected males
$\mu'_{mw} = \frac{\psi}{\psi+\mu_{mw}}\mu_{mw}$	Death rate of infected males

Step 2: combine infection groups



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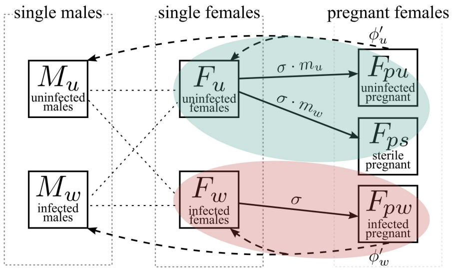

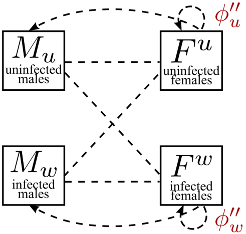

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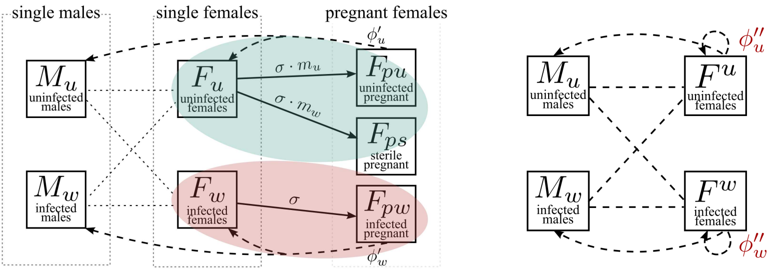
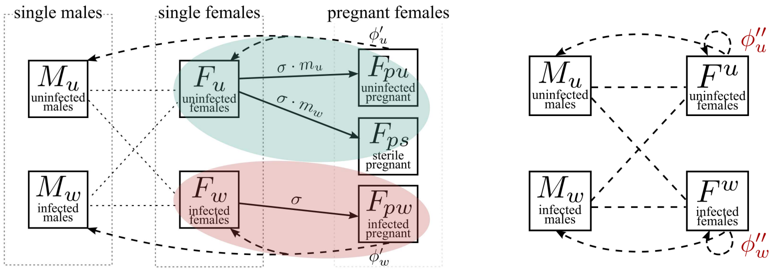


- $F^u := F_u + F_{pu} + F_{ps}, \quad F^w := F_w + F_{pw}$
- define new reproduction rate

$$\mathbb{G}_u^{(7)} = b_f \underset{\text{successfully mated } F_{pu}}{\frac{\sigma\, m_u}{\sigma+\mu'_{fu}}} \; \underset{\text{number of new offspring per } F_{pu}}{\frac{\phi'_u}{\mu'_{fu}}} = b_f \frac{\phi''_u}{\mu'_{fu}} = \mathbb{G}_u^{(4)}$$

$$\left(m_u = \frac{M_u}{M_u + M_w} \right)$$

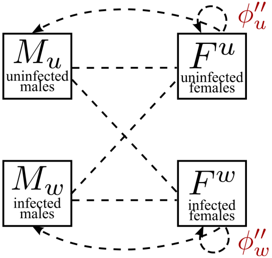
Step 2: combine infection groups



- $F^u := F_u + F_{pu} + F_{ps}, \quad F^w := F_w + F_{pw}$
- define new reproduction rate
- modify carrying capacity

put on all females $\Rightarrow \left(1 - \dfrac{F^u + F^w}{K_f}\right), \quad K_f = b_f \dfrac{\psi}{\mu'_{fu}} K_a$

Step 2: combine infection groups



$$\dot{F^u} = b_f \phi''_u \frac{M_u}{M_u + M_w}\left(1 - \frac{F^u + F^w}{K_f}\right) F^u - \mu'_{fu} F^u$$

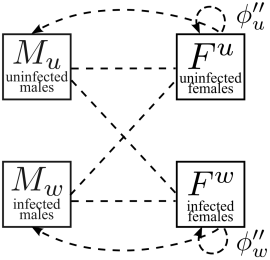
$$\dot{F^w} = b_f \phi''_w \left(1 - \frac{F^u + F^w}{K_f}\right) F^w - \mu'_{fw} F^w$$

$$\dot{M}_u = b_m \phi''_u \frac{M_u}{M_u + M_w}\left(1 - \frac{F^u + F^w}{K_f}\right) F^u - \mu'_{mu} M_u$$

$$\dot{M}_w = b_m \phi''_w \left(1 - \frac{F^u + F^w}{K_f}\right) F^w - \mu'_{mw} M_w$$

b_f	Female birth probability
b_m	Male birth probability
$\phi''_u = \frac{\sigma}{\sigma+\mu'_{fu}}\phi'_u$	reproduction rate for F^u
$\phi''_w = \frac{\sigma}{\sigma+\mu'_{fw}}\phi'_w$	reproduction rate for F^w
K_f	Carrying capacity for females
μ'_{fu}	Death rate for F^u
μ'_{fw}	Death rate for F^w
μ'_{mu}	Death rate for M_u
μ'_{mw}	Death rate for M_w

Step 3: remove males?



$$\dot{F^u} = b_f \phi''_u \frac{M_u}{M_u + M_w}\left(1 - \frac{F^u + F^w}{K_f}\right) F^u - \mu'_{fu} F^u$$

$$\dot{F^w} = b_f \phi''_w \left(1 - \frac{F^u + F^w}{K_f}\right) F^w - \mu'_{fw} F^w$$

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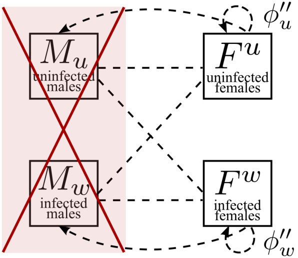

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$$\dot{F^w} = b_f \phi''_w \left(1 - \frac{F^u + F^w}{K_f}\right) F^w - \mu'_{fw} F^w$$

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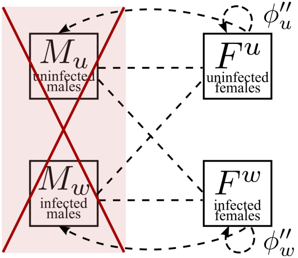
Step 3: remove males?



$$\dot{F^u} = b_f \phi_u'' \frac{M_u}{M_u + M_w} \left(1 - \frac{F^u + F^w}{K_f}\right) F^u - \mu_{fu}' F^u$$

$$\dot{F^w} = b_f \phi_w'' \left(1 - \frac{F^u + F^w}{K_f}\right) F^w - \mu_{fw}' F^w$$

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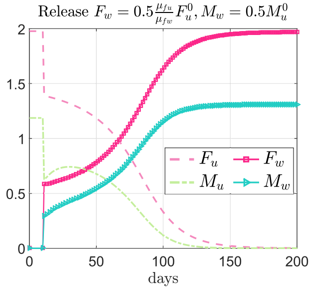

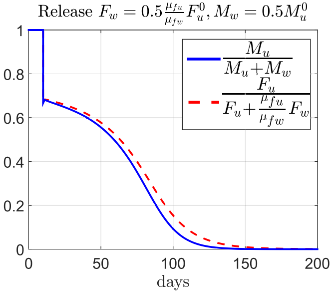

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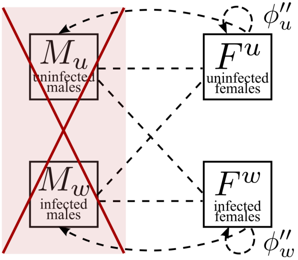

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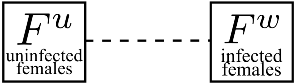
$$\dot{M_w} = b_m \phi''_w \left(1 - \frac{F^u + F^w}{K_f}\right) F^w - \mu'_{mw} M_w$$

- We observe that...

$$\frac{M_u}{M_u + M_w} \approx \frac{F^u}{F^u + \frac{\mu'_{fw}}{\mu'_{fu}} F^w},$$

given a proportional initial condition

Reduced 2-ODE model



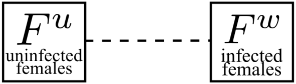
$$\dot{F^u} = b_f \phi''_u \frac{F^u}{F^u + \frac{\mu'_{fw}}{\mu'_{fu}} F^w} \left(1 - \frac{F^u + F^w}{K_f}\right) F^u - \mu'_{fu} F^u$$

$$\dot{F^w} = b_f \phi''_w \left(1 - \frac{F^u + F^w}{K_f}\right) F^w - \mu'_{fw} F^w$$

- complex nonlinearity in the equation
- parameters are defined in terms of the original ones

$$\phi''_u = \frac{\psi}{\psi + \mu_a} \frac{\psi}{\psi + \mu_{fu}} \frac{\sigma}{\sigma + \mu_{fu}} \phi_u, \quad \mu'_{fu} = \frac{\psi}{\psi + \mu_{fu}} \mu_{fu}$$

Reduced 2-ODE model



$$\dot{F^u} = b_f \phi''_u \frac{F^u}{F^u + \frac{\mu'_{fw}}{\mu'_{fu}} F^w} \left(1 - \frac{F^u + F^w}{K_f}\right) F^u - \mu'_{fu} F^u$$

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- Does it preserve the key properties?

- $\mathbb{R}_0$ & threshold condition

Outlines

$\mathbb{R}_0$'s for the reduced models

- Full 9-ODE model

$$\mathbb{R}_0^{(9)} = \frac{\mu_{fu}\,\phi_w\,(\sigma + \mu_{fu})}{\mu_{fw}\,\phi_u\,(\sigma + \mu_{fw})}$$

$\mathbb{R}_0$'s are the same for all the reduced models

- Full 9-ODE model

$$\mathbb{R}_0^{(9)} = \frac{\mu_{fu}\,\phi_w\,(\sigma+\mu_{fu})}{\mu_{fw}\,\phi_u\,(\sigma+\mu_{fw})} = \mathbb{R}_0^{(7)} = \mathbb{R}_0^{(4)} = \mathbb{R}_0^{(2)}$$

- 7-ODE model

$$\mathbb{R}_0^{(7)} = \frac{\mu'_{fu}\,\phi'_w\,(\sigma+\mu'_{fu})}{\mu'_{fw}\,\phi'_u\,(\sigma+\mu'_{fw})}$$

$$\phi'_u = \frac{\psi}{\psi+\mu_a}\frac{\sigma+\mu'_{fu}}{\sigma+\mu_{fu}}\frac{\mu'_{fu}}{\mu_{fu}}\phi_u,\ \ \phi'_w = \frac{\psi}{\psi+\mu_a}\frac{\sigma+\mu'_{fw}}{\sigma+\mu_{fw}}\frac{\mu'_{fw}}{\mu_{fw}}\phi_w,$$

$$\mu'_{fu} = \frac{\psi}{\psi+\mu_{fu}}\mu_{fu},\ \ \mu'_{fw} = \frac{\psi}{\psi+\mu_{fw}}\mu_{fw}$$

- 4-ODE model

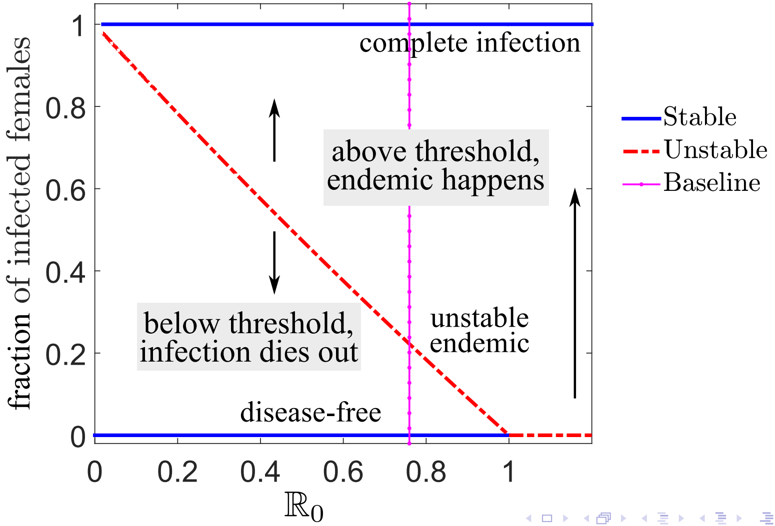
$$\mathbb{R}_0^{(4)} = \frac{\mu'_{fu}\,\phi''_w}{\mu'_{fw}\,\phi''_u} \quad \left(\phi''_u = \tfrac{\sigma}{\sigma+\mu'_{fu}}\phi'_u,\ \ \phi''_w = \tfrac{\sigma}{\sigma+\mu'_{fw}}\phi'_w\right)$$

- 2-ODE model

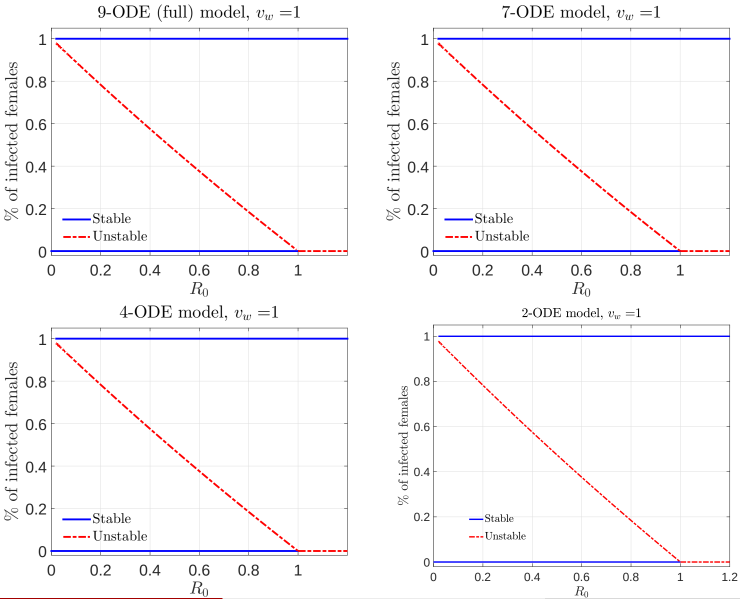
$$\mathbb{R}_0^{(2)} = \frac{\mu'_{fu}\,\phi''_w}{\mu'_{fw}\,\phi''_u}$$

Critical threshold for stable *Wolbachia* infection

For the full model, assuming $v_w = 1$, perfect maternal transmission...



Thresholds for reduced models (perfect maternal transmission)



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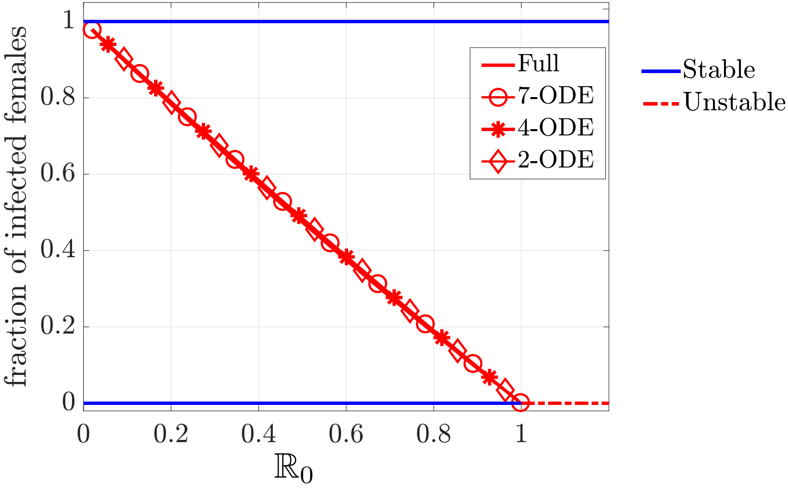
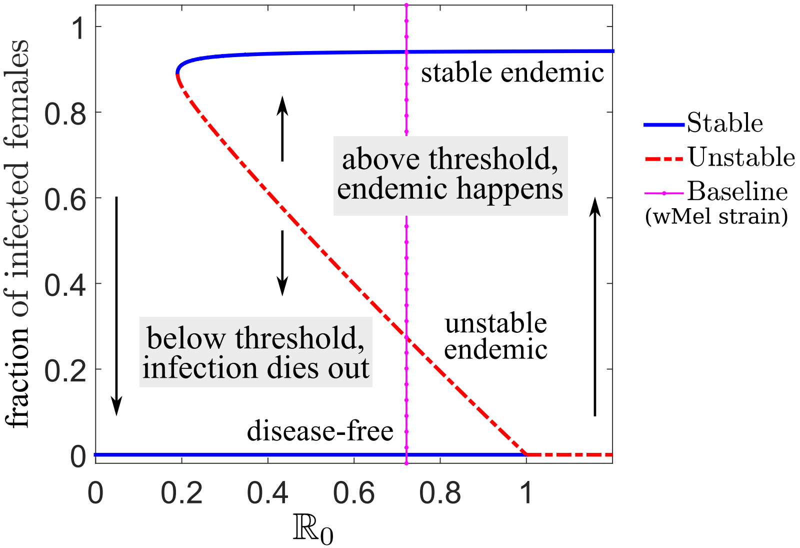


Thresholds comparisons (baseline case $v_w = 0.95$)



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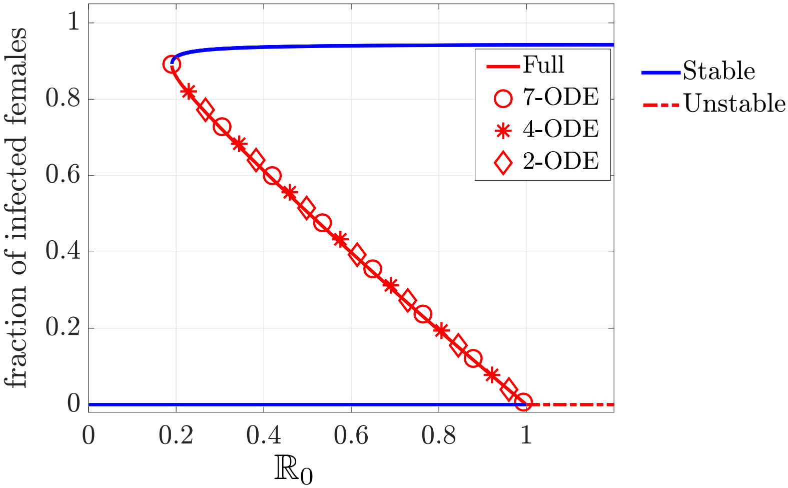

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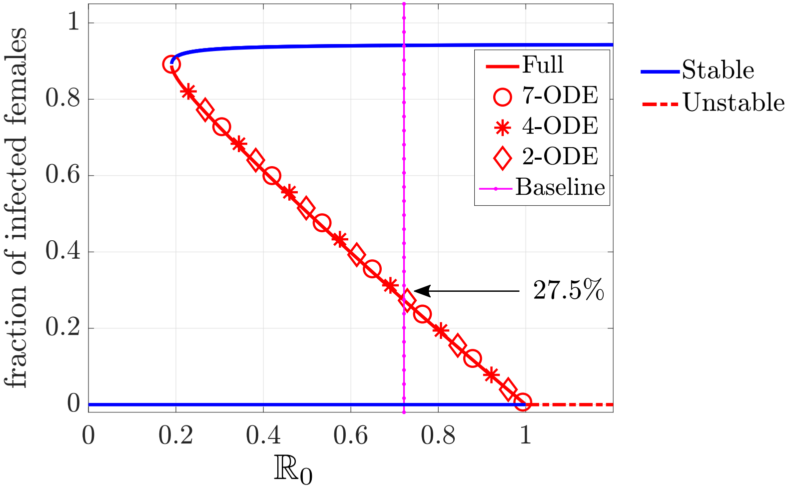

Reducing mathematical models (perfect transmission rate)

Full 9-ODE model

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

$\longrightarrow$

Reduced 2-ODE model

$$
\begin{aligned}
\dot{F^u} &= b_f \varphi'_u \frac{F^u}{F^u + \frac{\mu_{fw}}{\mu_{fu}} F^w} \left(1 - \frac{F^u + F^w}{K_f}\right) F^u - \mu_{fu} F^u \\
\dot{F^w} &= b_f \varphi'_w \left(1 - \frac{F^u + F^w}{K_f}\right) F^w - \mu_{fw} F^w
\end{aligned}
$$

- preserves the basic reproductive number $\mathbb{R}_0$
- preserves the threshold condition for a stable *Wobachia* infection

Future work

- Add spatial heterogeneity

- for real field releases, variation in environment, population, several distant releasing locations

$$\dot{F^u} = b_f \phi''_u \frac{F^u}{F^u + \frac{\mu'_{fw}}{\mu'_{fu}} F^w} \left(1 - \frac{F^u + F^w}{K_f}\right) F^u - \mu'_{fu} F^u \ + \delta F^u_{xx}$$

$$\dot{F^w} = b_f \phi''_w \left(1 - \frac{F^u + F^w}{K_f}\right) F^w - \mu'_{fw} F^w \ + \delta F^w_{xx}$$

Future work: Add spatial heterogeneity

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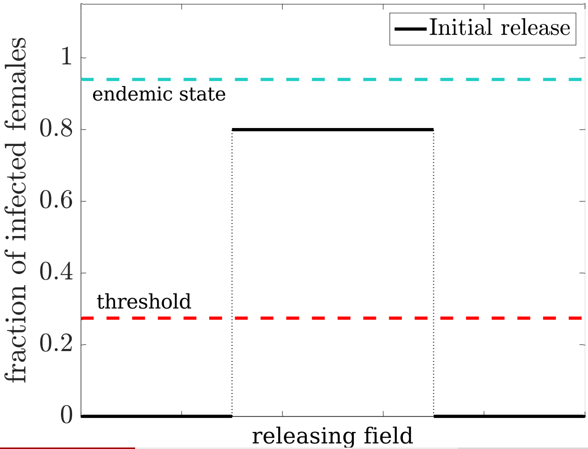

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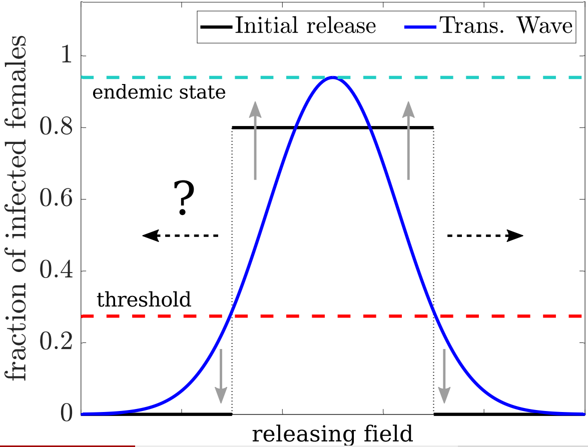

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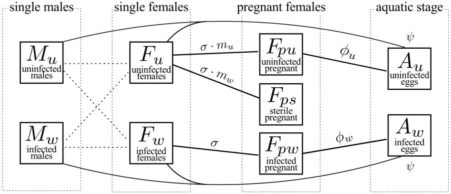
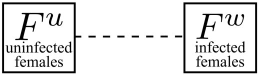
- Panpim Thongsripong, California Academy of Sciences

This research was partially supported by

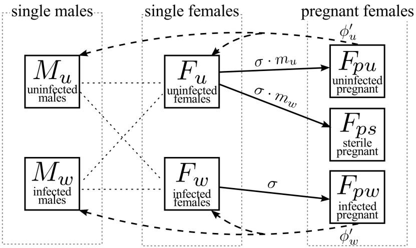
- NSF/MPS/DMS - NIH/NIGMS award
- NIH-NIGMS Models of Infectious Disease Agent Study (MIDAS) award

Thank you!

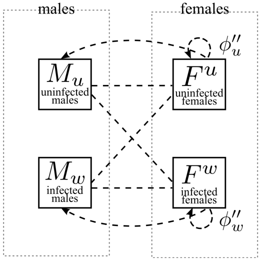




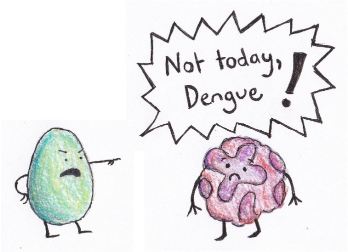
$\Downarrow$ **model reduction** $\Uparrow$



$\Rightarrow$



How does *Wolbachia* block the pathogens?



To date, the mechanism that underpins *Wolbachia*-mediated pathogen blocking is unknown.

There are two main hypotheses:

- immune priming
  - pre-activation of the immune response could then theoretically protect the insect from a range of pathogens

- resource competition
  - *Wolbachia* and pathogens would compete for limited host resources, including physical space (tissue or cellular location), macronutrients (carbohydrates and nitrogen), and lipids (cholesterol)

Terradas, Gerard, and Elizabeth A. McGraw. "Wolbachia-mediated virus blocking in the mosquito vector Aedes aegypti." *Current opinion in insect science* 22 (2017): 37-44; Images: Perran Ross

Impact of a *Wolbachia*-based strategy...

- transferred to humans?
  - *Wolbachia* are naturally found in 60% of insect species, including mosquito species (e.g. Aedes albopictus)
  - humans have been in contact with generations of *Wolbachia*-infected mosquitoes, but no report on negative effects
- transferred to other organisms?
  - *Wolbachia* is not infectious, only maternally transmitted
  - intracellular bacterium, only live inside the hosts cells, can't survive outside the host
  - degrade together when mosquitoes die, no toxicological significance

Popovici, Jean, et al. "Assessing key safety concerns of a *Wolbachia*-based strategy to control dengue transmission by Aedes mosquitoes." *Memorias do Instituto Oswaldo Cruz* 105.8 (2010): 957-964.

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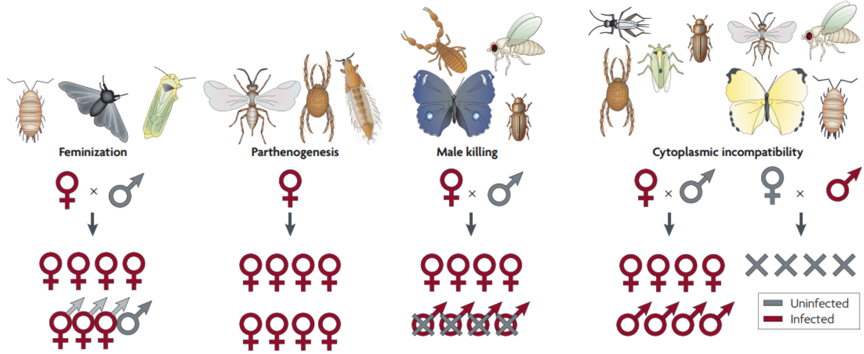
- potential consequences over a long-term period and large geographic scale?
- evolution of the virus in response to the presence of *Wolbachia*?

Popovici, Jean, et al. "Assessing key safety concerns of a *Wolbachia*-based strategy to control dengue transmission by Aedes mosquitoes." *Memorias do Instituto Oswaldo Cruz* 105.8 (2010): 957-964.

Cytoplasmic incompatibility in mosquitoes



There are two events during the *Wolbachia* manipulation:

1. modification of sperm during spermatogenesis
2. rescue of the modification in embryos infected with same strain

If the sperm is modified, but no appropriate *Wolbachia* present, development is disrupted

Werren, John H., Laura Baldo, and Michael E. Clark. "Wolbachia: master manipulators of invertebrate biology." *Nature Reviews Microbiology* 6, no. 10 (2008): 741.

Baseline parameter values and ranges

	Description	Baseline	Range
b_f	Female birth probability	0.5	0.50 – 0.57
b_m	Male birth probability $= 1 - b_f$	0.5	0.43 – 0.50
σ	Per capita mating rate	1	-
ϕ_u	Per capita egg F_{pu} laying rate	13	12 – 18
ϕ_w	Per capita egg F_{pw} laying rate	11	8 – 12
v_w	Maternal transmission efficiency	0.95	0.89 – 1
ψ	Per capita development rate	1/8.75	1/9.2 – 1/8.1
μ_a	Death rate for A_u or A_w	0.02	0.01 – 0.04
μ_{fu}	Death rate for F_u	1/17.5	1/21 – 1/14
μ_{fw}	Death rate for F_w	1/15.8	1/19 – 1/12.6
μ_{mu}	Death rate for M_u	1/10.5	1/14 – 1/7
μ_{mw}	Death rate for M_w	1/10.5	1/14 – 1/7
K_a	Carrying capacity of A_u or A_w	2×10^5	-