On Aedes, Wolbachia and the Control of Urban Arboviruses

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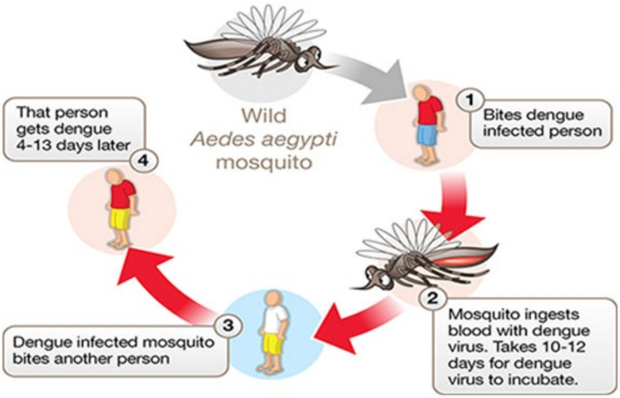
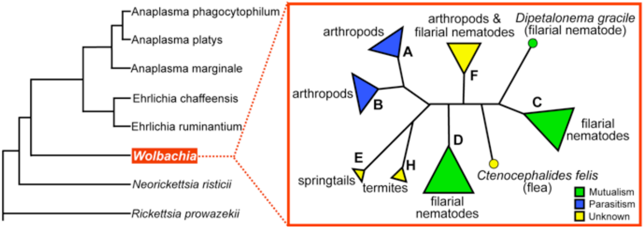
Aedes aegypti



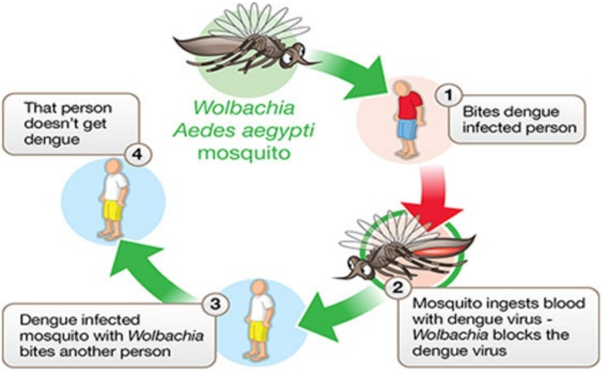
From ELIMINATE DENGUE

Wolbachia



From WERREN LAB

Controlling urban arboviruses



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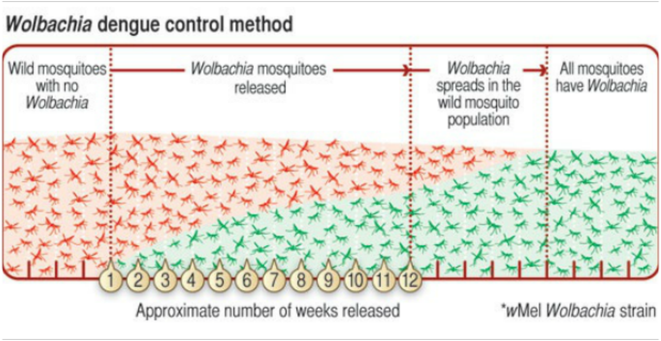
Replacing wild population



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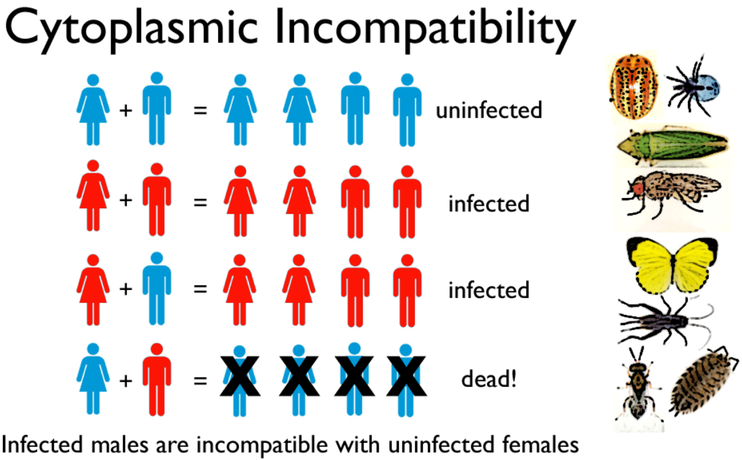

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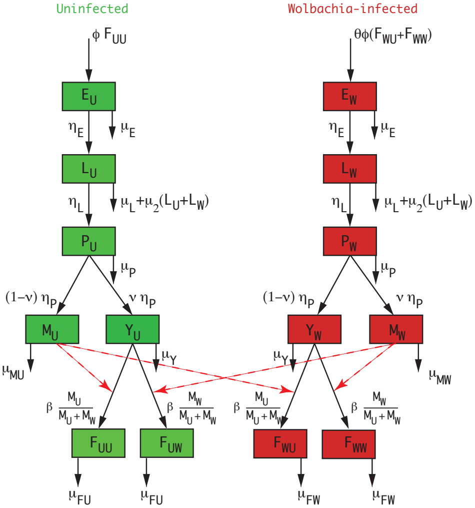
A complete model



Uninfected Equilibrium

$$E_W = L_W = P_W = Y_W = F_{WU} = F_{WW} = F_{UW} = M_W = 0$$

$$\mathcal{R}_{0,\text{offsp},U} = \frac{\phi}{\mu_{FU}} \frac{\eta_E}{\mu_E + \eta_E} \frac{\eta_L}{\mu_L + \eta_L} \frac{\nu\,\eta_P}{\mu_P + \eta_P} \frac{\beta}{\beta + \mu_Y}.$$

$$P_U^* = \frac{\eta_L\,(\mu_L + \eta_L)}{\mu_2\,(\mu_P + \eta_P)} \left(\mathcal{R}_{0,\text{offsp}} - 1\right) > 0$$

$$L_U^* = \frac{\mu_p + \eta_p}{\eta_L} P_U^*, \qquad Y_U^* = \frac{\nu\,\eta_P}{\beta + \mu_Y} P_U^*,$$

$$F_U^* = \frac{\beta}{\beta + \mu_Y} \frac{\nu\,\eta_P}{\mu_F} P_U^*, \qquad M_U^* = \frac{(1-\nu)\,\eta_P}{\mu_M} P^*$$

$$E_U^* = \frac{\phi}{\mu_E + \eta_E} \frac{\beta}{\beta + \mu_Y} \frac{\nu\,\eta_P}{\mu_F} P_U^*.$$

Wolbachia Infected Equilibrium

$$\mathcal{R}_{0,\text{offsp},W} = \frac{\theta\,\phi}{\mu_{FW}}\;\frac{\eta_E}{\mu_E+\eta_E}\;\frac{\eta_L}{\mu_L+\eta_L}\;\frac{\nu\,\eta_P}{\mu_P+\eta_P}\;\frac{\beta}{\beta+\mu_Y}.$$

$$P_W^* = \frac{\eta_L\,(\mu_L+\eta_L)}{\mu_2\,(\mu_P+\eta_P)}\,(\mathcal{R}_{0,\text{offsp},W}-1)$$

$$L_W^* = \frac{\mu_p+\eta_p}{\eta_L}\,P_W^*, \qquad Y_W^* = \frac{\nu\,\eta_P}{\beta+\mu_Y}\,P_W^*,$$

$$F_{WW}^* = \frac{\beta}{\beta+\mu_Y}\,\frac{\nu\,\eta_P}{\mu_{FW}}\,P_W^*, \qquad M_W^* = \frac{(1-\nu)\,\eta_P}{\mu_{MW}}\,P_W^*$$

$$E_W^* = \frac{\theta\,\phi}{\mu_E+\eta_E}\,\frac{\beta}{\beta+\mu_Y}\,\frac{\nu\,\eta_P}{\mu_{FW}}\,P_W^*, \qquad F_{WU}^* = 0 \qquad F_{UW}^* = 0$$

The coexistence equilibrium

$$\mathcal{R}_{0,\text{offsp},W} = \frac{\theta\,\mu_{FU}}{\mu_{FW}}\,\mathcal{R}_{0,\text{offsp},U} < \mathcal{R}_{0,\text{offsp},U}.$$

$$P_{U,\text{coex}} = \frac{\eta_L\,\theta\,\mu_{FU}\,\mu_{MU}\,(\mu_L+\eta_L)}{\mu_2\,[\mu_{MW}\,(\mu_{FW}-\theta\,\mu_{FU})+\theta\,\mu_{MU}\,\mu_{FU}]\,(\mu_P+\eta_P)}\,(\mathcal{R}_{0,\text{offsp},W}-1)$$

$$P_{W,\text{coex}} = \frac{\eta_L\,\mu_{MW}\,(\mu_{FW}-\theta\,\mu_{FU})\,(\mu_L+\eta_L)}{\mu_2\,[\mu_{MW}\,(\mu_{FW}-\theta\,\mu_{FU})+\theta\,\mu_{MU}\,\mu_{FU}]\,(\mu_P+\eta_P)}\,(\mathcal{R}_{0,\text{offsp},W}-1)$$

$$M_{U,\text{coex}} = \frac{(1-\nu)\,\eta_P}{\mu_{MU}}\,P_{U,\text{coex}}, \qquad M_{W,\text{coex}} = \frac{(1-\nu)\,\eta_P}{\mu_{MW}}\,P_{W,\text{coex}},$$

$$L_{U,\text{coex}} = \frac{\mu_P+\eta_P}{\eta_L}\,P_{U,\text{coex}}, \qquad L_{W,\text{coex}} = \frac{\mu_P+\eta_P}{\eta_L}\,P_{W,\text{coex}},$$

$$Y_{U,\text{coex}} = \frac{\nu\,\eta_P}{\beta+\mu_Y}\,P_{U,\text{coex}} \qquad Y_{W,\text{coex}} = \frac{\nu\,\eta_P}{\beta+\mu_Y}\,P_{W,\text{coex}}$$

The coexistence equilibrium II

$$F_{UU,\text{coex}} = \frac{\beta\,\nu\,\eta_P\mu_{MW}}{\mu_{FU}\,(\mu_{MU}\,P_{W,\text{coex}} + \mu_{MW}\,P_{U,\text{coex}})\,(\beta + \mu_Y)}\,P^2_{U,\text{coex}},$$

$$F_{WW,\text{coex}} = \frac{\beta\,\nu\,\eta_P\mu_{MU}}{\mu_{FW}\,(\mu_{MU}\,P_{W,\text{coex}} + \mu_{MW}\,P_{U,\text{coex}})\,(\beta + \mu_Y)}\,P^2_{W,\text{coex}},$$

$$F_{WU,\text{coex}} = \frac{\beta\,\nu\,\eta_P\mu_{MW}}{\mu_{FW}\,(\mu_{MU}\,P_{W,\text{coex}} + \mu_{MW}\,P_{U,\text{coex}})\,(\beta + \mu_Y)}\,P_{W,\text{coex}}\,P_{U,\text{coex}},$$

$$F_{UW,\text{coex}} = \frac{\beta\,\nu\,\eta_P\mu_{MU}}{\mu_{FW}\,(\mu_{MU}\,P_{W,\text{coex}} + \mu_{MW}\,P_{U,\text{coex}})\,(\beta + \mu_Y)}\,P_{W,\text{coex}}\,P_{U,\text{coex}},$$

$$E_{U,\text{coex}} = \frac{\beta\,\nu\,\eta_P\mu_{MW}\,\phi}{\mu_{FU}\,(\mu_{MU}\,P_{W,\text{coex}} + \mu_{MW}\,P_{U,\text{coex}})\,(\beta + \mu_Y)\,(\mu_E + \eta_E)}\,P^2_{U,\text{coex}},$$

$$E_{W,\text{coex}} = \frac{\beta\,\nu\,\eta_P\,\theta\,\phi}{\mu_{FW}\,(\beta + \mu_Y)\,(\mu_E + \eta_E)}\,P_{W,\text{coex}}.$$

Stability

$$\text{Jac}(UE) = \begin{bmatrix} A_{11} & A_{12} \\ 0 & A_{22} \end{bmatrix}.$$

Lemma

Let $\mathbf{M}$ *be a Metzler matrix, which is block decomposed :*

$$\mathbf{M} = \begin{bmatrix} \mathbf{A} & \mathbf{B} \\ \mathbf{C} & \mathbf{D} \end{bmatrix}.$$

Where $\mathbf{A}$ *and* $\mathbf{D}$ *are square matrices.*
Then $\mathbf{M}$ *is Hurwitz if and only if* $\mathbf{A}$ *and* $\mathbf{D} - \mathbf{C}\mathbf{A}^{-1}\mathbf{B}$ *are Metzler stable.*

Stability II

$$\mathcal{R}_{0,W} = \frac{\theta\,\mu_{\mathrm{FU}}}{\mu_{\mathrm{FW}}} < 1.$$

$$1 < \mathcal{R}_{0,\mathrm{offsp},W} = \mathcal{R}_{0,W}\,\mathcal{R}_{0,\mathrm{offsp},U} < \mathcal{R}_{0,\mathrm{offsp},U}.$$

$$\mathrm{Jac}(CWIE) = \begin{bmatrix} A_{11} & A_{12} \\ 0 & A_{22} \end{bmatrix}.$$

$$\det(\mathrm{Jac}(Coex)) = \beta\,\theta\,\phi\,\nu\,\eta_P\,\eta_L\,\eta_E\,\mu_{MU}\,\mu_{MW}\,\mu_{FU}\,(\mu_{FW} - \theta\,\mu_{FU}) \\ \times (\mu_E + \eta_E)\,(\mu_L + \eta_L)\,(\mu_P + \eta_P)\,(\beta + \mu_Y)\,(\mathcal{R}_{0,\mathrm{offsp},W} - 1) > 0$$

Summary

- The trajectories of system are forward bounded.
- When $\mathcal{R}_{0,\text{offsp},U} > 1$ there exists an equilibrium without infection (WFE) which is asymptotically stable.
- When $\mathcal{R}_{0,W} < \dfrac{1}{\mathcal{R}_{0,\text{offsp},U}}$ only the WFE exists and is globally asymptotically stable on the nonnegative orthant minus the manifold $M_W = 0$.
- When $\mathcal{R}_{0,W}\,\mathcal{R}_{0,\text{offsp},U} = \mathcal{R}_{0,\text{offsp},W} > 1$ three equilibria exist. The WFE, an equilibrium with the total population infected (CWIE) and a coexistence equilibrium in the positive orthant. The WFE and CWIE are asymptotically stable, the coexistence equilibrium is unstable.

Asymptotic interlude

Let

$$d_U = \frac{(\bar{\mu}_P + \bar{\eta}_P)\nu\bar{\mu}_{MU}\bar{\mu}_2}{\eta_L(1-\nu)(\bar{\beta}+\bar{\mu}_Y)}, \quad d_W = \frac{(\bar{\mu}_P + \bar{\eta}_P)\nu\bar{\mu}_{MW}\bar{\mu}_2}{\eta_L(1-\nu)(\bar{\beta}+\bar{\mu}_Y)}.$$

$$r_U = \frac{\bar{\beta}\bar{\eta}_E\eta_L}{(\bar{\mu}_P + \bar{\eta}_P)\bar{\mu}_{FU}}, \quad r_W = \frac{\theta\bar{\beta}\bar{\eta}_E\eta_L}{(\bar{\mu}_P + \bar{\eta}_P)\bar{\mu}_{FW}}.$$

$$x = \frac{M_W}{M_U + M_W}$$

Then

$$\dot{x} = \frac{1}{\eta_L + \mu_L + d_U M_U + d_W M_W} x(1-x)(r_W - r_U + r_U x)$$

The last system is conjugated to

$$\dot{x} = x(1-x)\left(x - \frac{r_U - r_W}{r_U}\right).$$

which is bistable as expected, with the critical frequency given by the equilibrium point:

$$x^* = 1 - \frac{r_W}{r_U} = 1 - \theta\frac{\bar{\mu}_{FU}}{\bar{\mu}_{FW}} = 1 - \mathcal{R}_{0,W}$$

Wolbachia and dengue

$$
\begin{cases}
\dot{S}_h &= \Lambda - \left[\beta_{Wvh}\left(F_{WUI} + F_{WWI}\right) + \beta_{Uvh}\left(F_{UUI} + F_{UWI}\right)\right] \dfrac{S_h}{N_h} - \mu_h S_h \\
\dot{E}_h &= \left[\beta_{Wvh}\left(F_{WUI} + F_{WWI}\right) + \beta_{Uvh}\left(F_{UUI} + F_{UWI}\right)\right] \dfrac{S_h}{N_h} - \left(\gamma_h + \mu_h\right) E_h \\
\dot{I}_h &= \gamma_h E_h - \left(\delta_h + \mu_h\right) I_h \\
\dot{R}_h &= \delta_h I_h - \mu_h R_h \\
\dot{F}_{WUI} &= \beta_{Whv}\left(F_{WU} - F_{WUI}\right) \dfrac{I_h}{N_h} - \mu_{FW} F_{WUI} \\
\dot{F}_{WWI} &= \beta_{Whv}\left(F_{WW} - F_{WWI}\right) \dfrac{I_h}{N_h} - \mu_{FW} F_{WWI} \\
\dot{F}_{UUI} &= \beta_{Uhv}\left(F_{UU} - F_{UUI}\right) \dfrac{I_h}{N_h} - \mu_{FU} F_{UUI} \\
\dot{F}_{UWI} &= \beta_{Uhv}\left(F_{UW} - F_{UWI}\right) \dfrac{I_h}{N_h} - \mu_{FU} F_{UUI}
\end{cases}
$$

Theorem (Vidyasagar)

Consider the following triangular system, $\mathcal{C}^1$ on a neighborhood of (x^*, y^*) :

$$\begin{cases} \dot{x} = f(x) & x \in \mathbb{R}^n\,, y \in \mathbb{R}^m \\ \dot{y} = g(x, y) \\ \text{ with an equilibrium point, } (x^*, y^*),\ \text{ i.e.,} \\ f(x^*) = 0 \text{ and } g(x^*, y^*) = 0. \end{cases}$$

If x^* is LAS, if y^* is asymptotically stable for $\dot{y} = g(x^*, y)$ then (x^*, y^*) is asymptotically stable for the complete system.
If x^* is unstable then (x^*, y^*) is unstable for the complete system.

$$N_h^* = \frac{\Lambda}{\mu_h}$$

$$\begin{cases} \dot{S}_h & = \Lambda - \beta_{Wvh} \, F_{WWI} \, \dfrac{S_h}{N_h^*} - \mu_h \, S_h \\ \\ \dot{E}_h & = \beta_{Wvh} \, F_{WWI} \, \dfrac{S_h}{N_h^*} - (\gamma_h + \mu_h) \, E_h \\ \\ \dot{I}_h & = \gamma_h \, E_h - (\delta_h + \mu_h) \, I_h \\ \\ \dot{F}_{WWI} & = \beta_{Whv} \, (F_{WW}^* - F_{WWI}) \, \dfrac{I_h}{N_h^*} - \mu_{FW} \, F_{WWI} \end{cases}$$

$$\mathcal{R}_{0,\text{dengue},W} = \frac{\beta_{Wvh}\,\beta_{Whv}\,F^*_{WW}}{\mu_{FW}}\,\frac{\gamma_h}{(\gamma_h+\mu_h)\,(\delta_h+\mu_h)\,N^*_h}$$

$$\mathcal{R}_{0,\text{dengue},U} = \frac{\beta_{Uvh}\,\beta_{Uhv}\,F^*_{UU}}{\mu_{FU}}\,\frac{\gamma_h}{(\gamma_h+\mu_h)\,(\delta_h+\mu_h)\,N^*_h}.$$

$$\mathcal{R}_{0,\text{dengue},W} = \frac{\beta_{Wvh}\,\beta_{Whv}}{\beta_{Uvh}\,\beta_{Uhv}}\,\frac{\mu_{FU}}{\mu_{FW}}\,\frac{\mathcal{R}_{0,\text{offsp},W}-1}{\mathcal{R}_{0,\text{offsp},U}-1}\mathcal{R}_{0,\text{dengue},U}.$$

Proposition

If $\mathcal{R}_{0,dengue,W} \leq 1$ *then* $(N_h^*, 0, 0, 0)$ *the DFE is globally asymptotically stable.*

Proof

The set
$K = \{(S_h, E_h, I_h, F_{WWI}) \in \mathbb{R}^3_+ \times [0, F_{W^*}] \mid N_h \leq N\,;\; F_{WWI} \leq F_W^*\}$
is a positively invariant absorbing compact set for the system considered. We consider the following function

$$V((E_h, I_h, F_{WWI}) = \gamma_h\, E_h + (\gamma_h + \mu_h)\, I_h + \beta_{Wvh}\, \frac{\gamma_h}{\mu_{FW}}\, F_{WWI}.$$

We have

$$\dot{V} = \left[-(\gamma_h + \mu_h)\,(\delta_h + \mu_h) + \frac{\beta_{Wvh}\, \beta_{Whv}\, (F^*_{WW} - F_{WWI})\, \gamma_h}{\mu_{FW}\, N_h^*}\, I_h + \beta_{Wvh}\, \gamma_h \left[-1 + \frac{S_h}{N_h^*} \right] \right]$$
$$= -(\gamma_h + \mu_h)\,(\delta_h + \mu_h)\, \left(1 - \mathcal{R}_{0,\text{dengue},W}\, (1 - \frac{F_{WWI}}{F^*_{WW}} \right) + \beta_{Wvh}\, \gamma_h \left[-1 + \frac{S_h}{N_h^*} \right] \leq 0$$

Checking

Newton and Reiter [NR92] 1.9

Koopman et al. [KPVM+91] 1.3

Marques et al. [MFM94] $1.6 - -2.5$

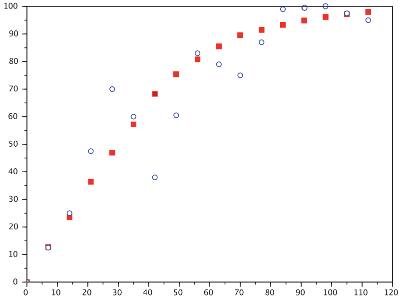
Favier et al.[DFB+05] $8 - -22.8$

Ferguson [FDA99] $1.38 - -8.47$

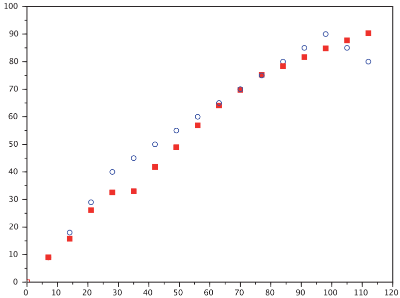
Chowell [CDDM+07] $2.0 - -2.4$

Massad et al. [MCBL01] $3.6 - -12.9$

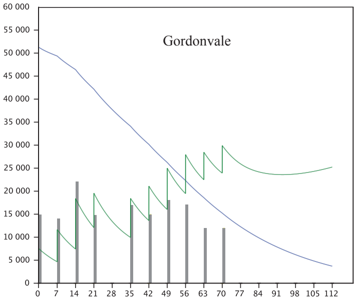
In the worst case, we have $\mathcal{R}_{0,\text{dengue},U} = 22.8$, and hence we obtain $\mathcal{R}_{0,\text{dengue},W} \leq 0.95$ after the introduction of *w*Mel.

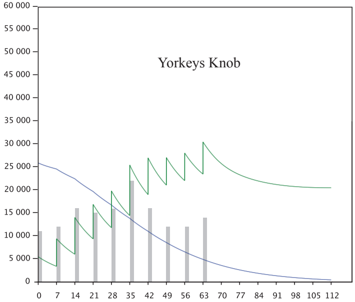


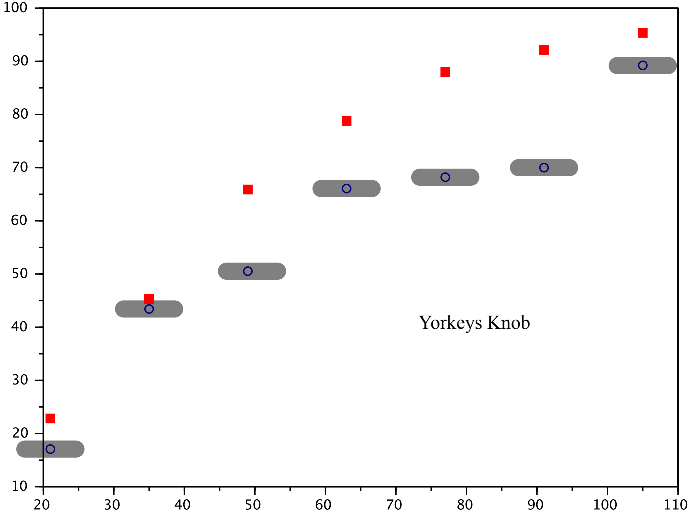
Infection frequencies at Yorleys Knob



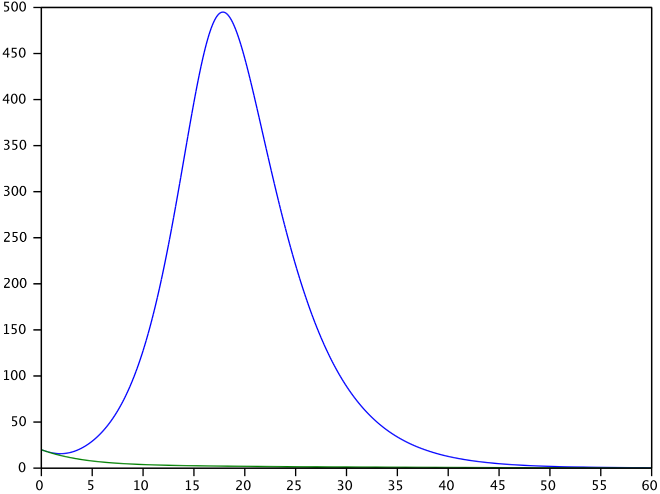
Infection frequencies at Gordonval


Gordonvale
60 000
55 000
50 000
45 000
40 000
35 000
30 000
25 000
20 000
15 000
10 000
5 000
0
0 7 14 21 28 35 42 49 56 63 70 77 84 91 98 105 112


Yorkeys Knob
60 000
55 000
50 000
45 000
40 000
35 000
30 000
25 000
20 000
15 000
10 000
5 000
0
0 7 14 21 28 35 42 49 56 63 70 77 84 91 98 105 112


Yorkeys Knob
100
90
80
70
60
50
40
30
20
10
20
30
40
50
60
70
80
90
100
110

Simulating dengue with Wolbachia



Epilogo

- Jair Koiller (INMETRO)
- Moacyr Silva (FGV)
- Claudia Codeço (FIOCRUZ)
- Abderrahman Iggidr (INRIA Nancy - Grand est)
- Abderrahman Iggidr (INRIA Nancy - Grand est)
- Gauthier Sallet (INRIA Nancy - Grand est)

Obrigado!

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