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From Discovery to Innovation...

Transmission Dynamics of Drug-resistant Strains Driven by Treatment

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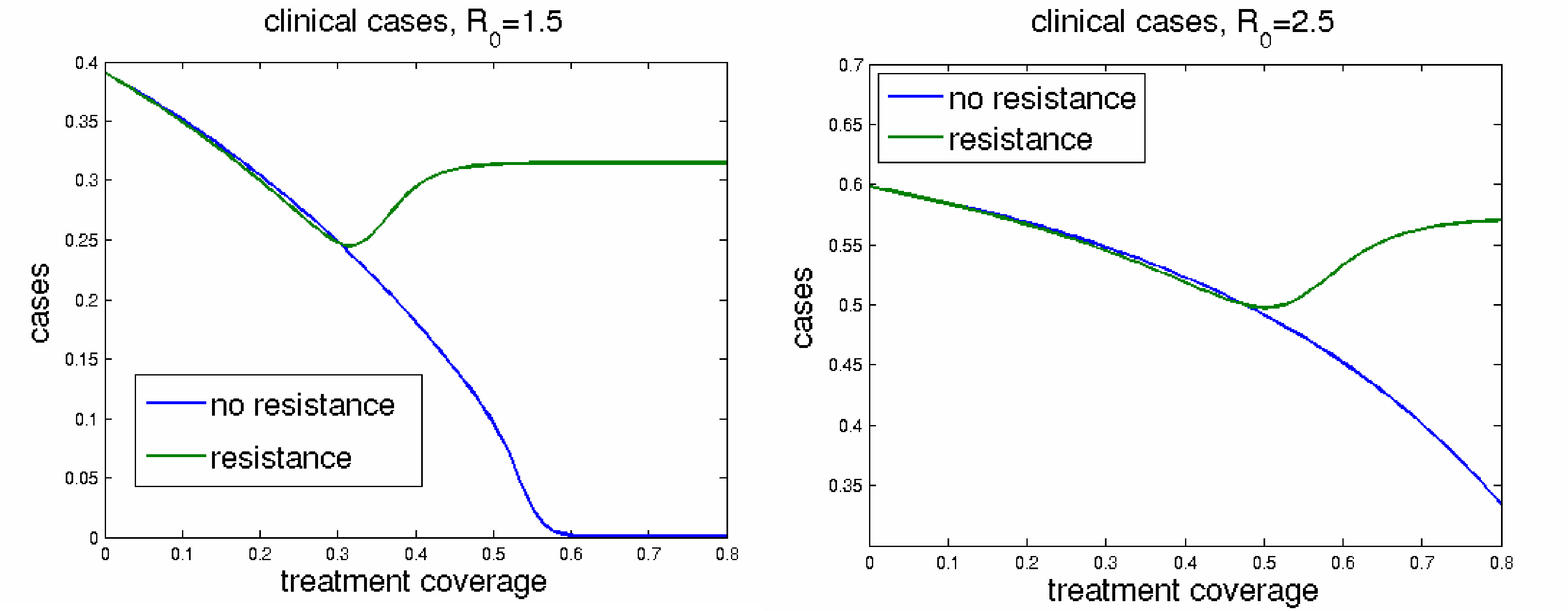
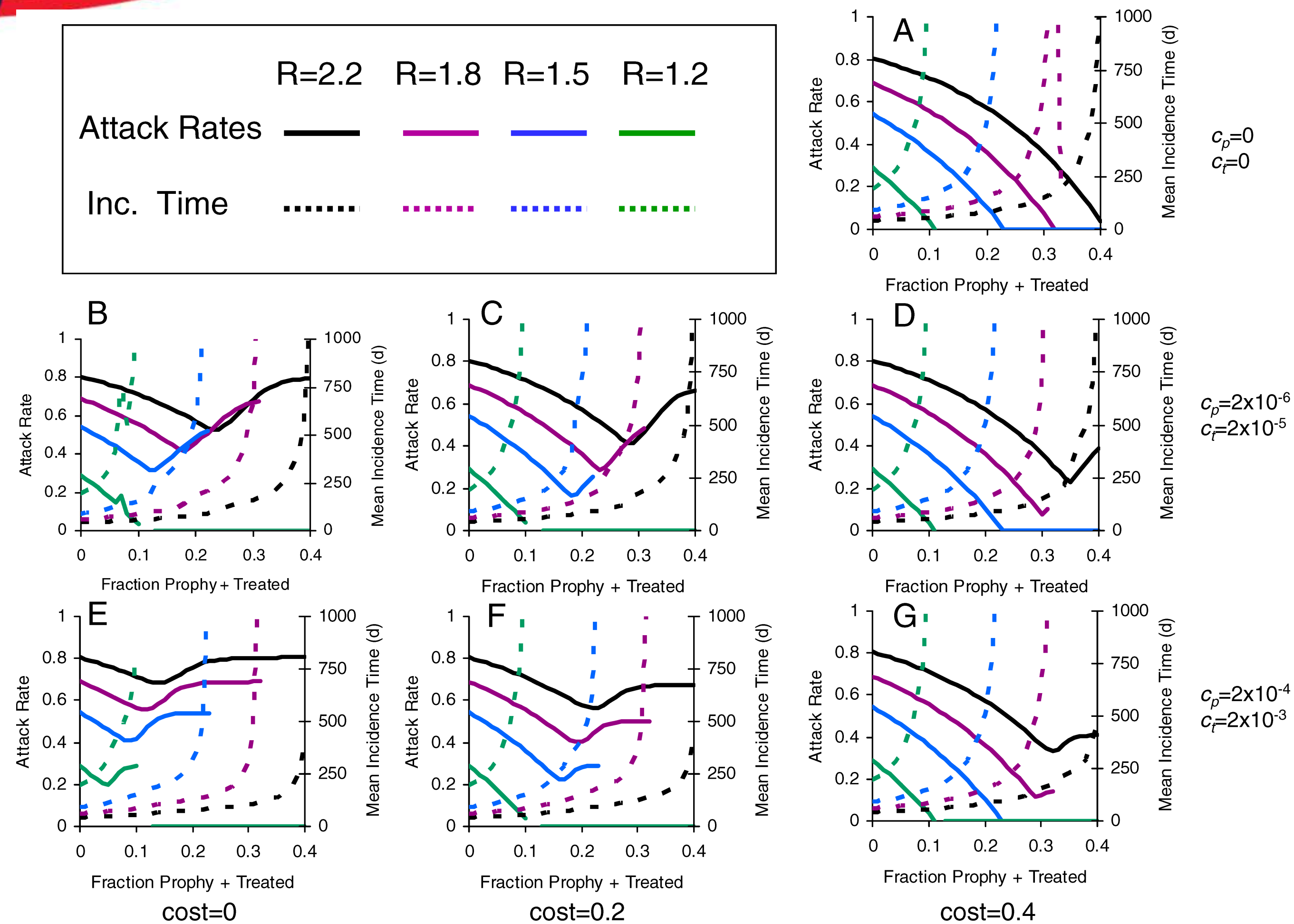
Constant treatment, Transmissible resistance



Lipsitch paper



From Lipsitch et. al., PLoS Med 4(1): e15.

Robust Behaviour

- The dip/overshoot has been demonstrated in:
  - (several) ODE models
  - Delay DE models
  - Stochastic
  - Network
  - Exists over large parameter ranges (but not universal)

Simple Model

$$
\begin{aligned}
S' &= -S[\beta_1 Q_1 + \beta_2 Q_2], \quad S(0) = S_0 \\
I_1' &= S\beta_1 Q_1 - (\alpha_1 + \gamma) I_1, \quad I_1(0) = I_0 \\
T_1' &= \gamma I_1 - (\eta + \varphi) T_1, \quad T_1(0) = 0 \\
I_2' &= S\beta_2 Q_2 - (\alpha_2 + \gamma) I_2, \quad I_2(0) = 0 \\
T_2' &= \gamma I_2 - \alpha_2 T_2 + \varphi T_1, \quad T_2(0) = 0,
\end{aligned}
$$

$$
Q_1 = I_1 + \delta T_1, \quad Q_2 = I_2 + T_2.
$$

Important numbers

$$\mathcal{R}_1(\gamma) = \beta_1 N \left[\frac{1}{\alpha_1 + \gamma} + \delta \frac{\gamma}{\alpha_1 + \gamma} \frac{1}{\eta + \varphi}\right]$$

$$\mathcal{R}_2 = \frac{\beta_2 N}{\alpha_2}$$

$$\hat{\mathcal{R}}(\gamma) = \beta_1 N \left[\frac{1}{\alpha_1 + \gamma} + \delta \frac{\gamma}{\alpha_1 + \gamma} \frac{1}{\eta + \varphi}\right] + \frac{\beta_2 N}{\alpha_2} \frac{\gamma}{\alpha_1 + \gamma} \frac{\varphi}{\eta + \varphi},$$

Four cases

$$R_2 > \hat{R}_1(0); \varphi > \frac{\eta - \delta\alpha_1}{R_2 - \hat{R}_1(0)}$$

$$R_2 > \hat{R}_1(0); \varphi < \frac{\eta - \delta\alpha_1}{R_2 - \hat{R}_1(0)}$$

$$\hat{R}_1(\infty) < R_2 < \hat{R}_1(0)$$

$$\hat{R}_1(\infty) > R_2; R_2 < \hat{R}_1(0)$$

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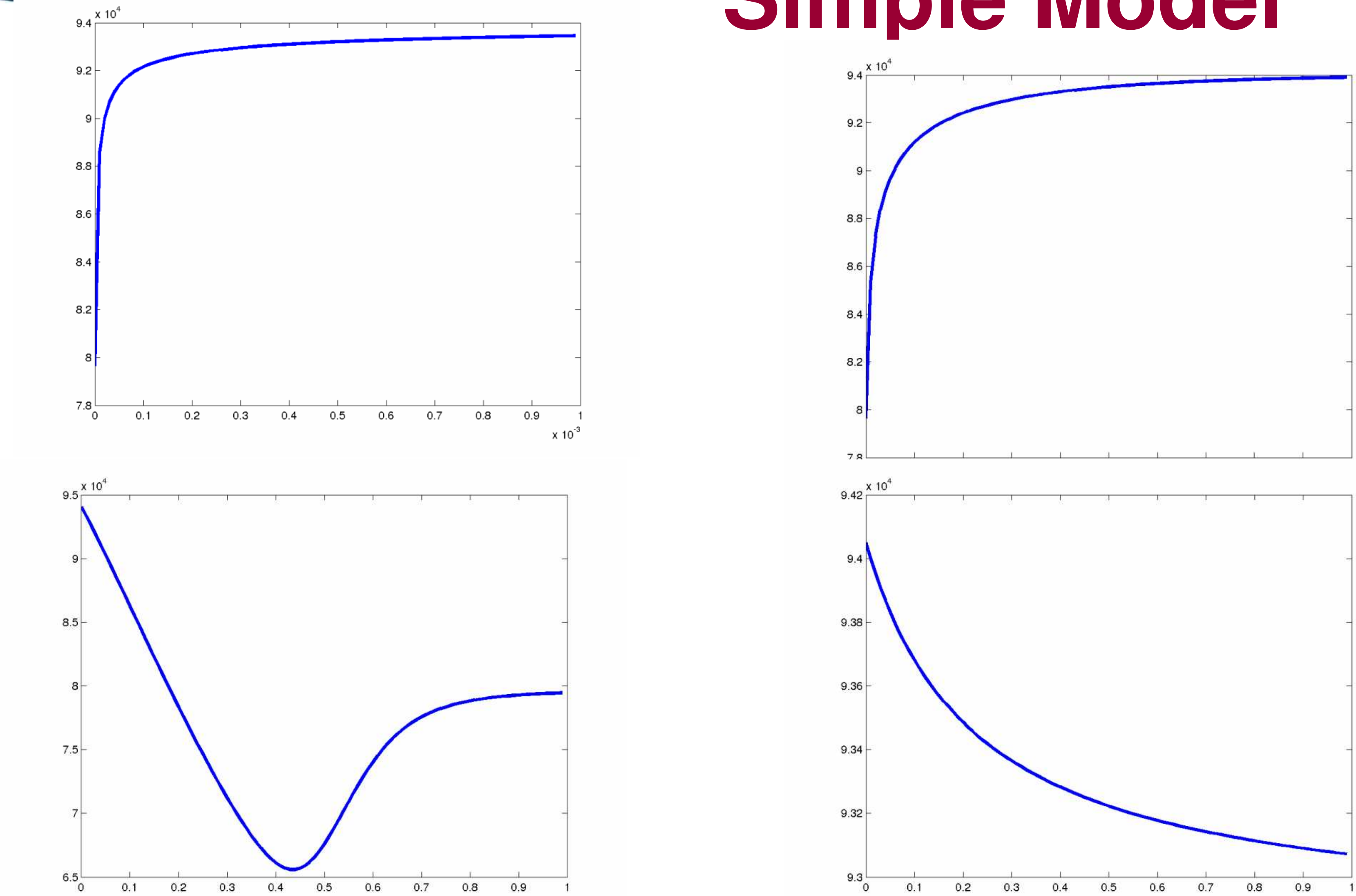
Case 3

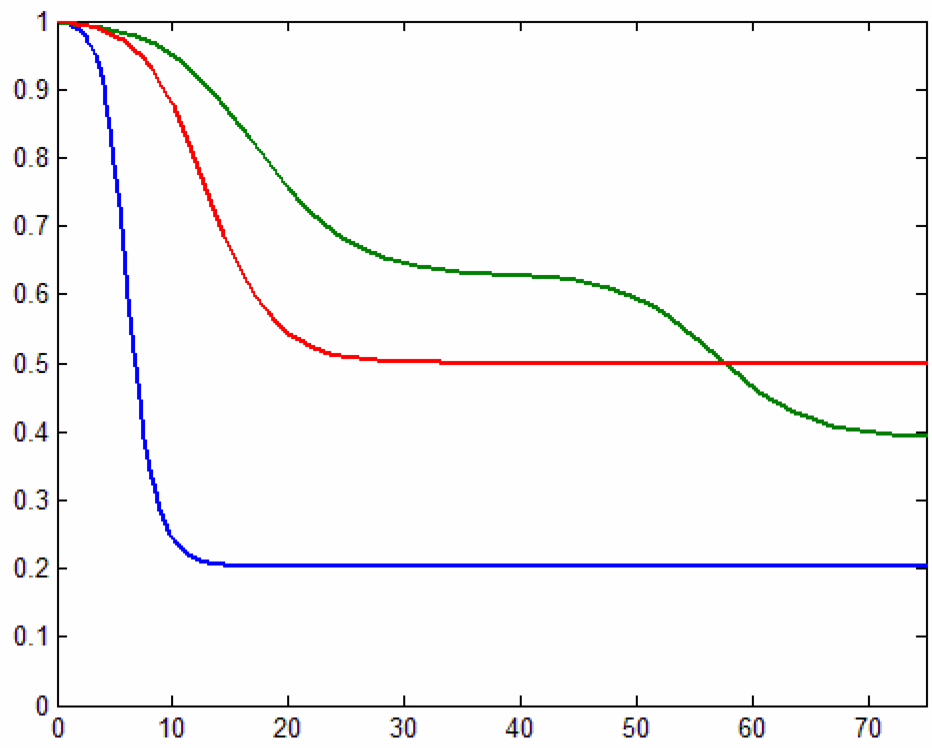
$$\gamma_c = \frac{\alpha_1\left(\hat{R}_1(0) - R_2\right)}{R_2 - \hat{R}_1(\infty)}$$

- If $\gamma < \gamma_c$, increasing treatment reduces total attack rate
- If γ is large, increasing treatment increases total attack rate
- In between, ?

Simulations for Simple Model



Why?



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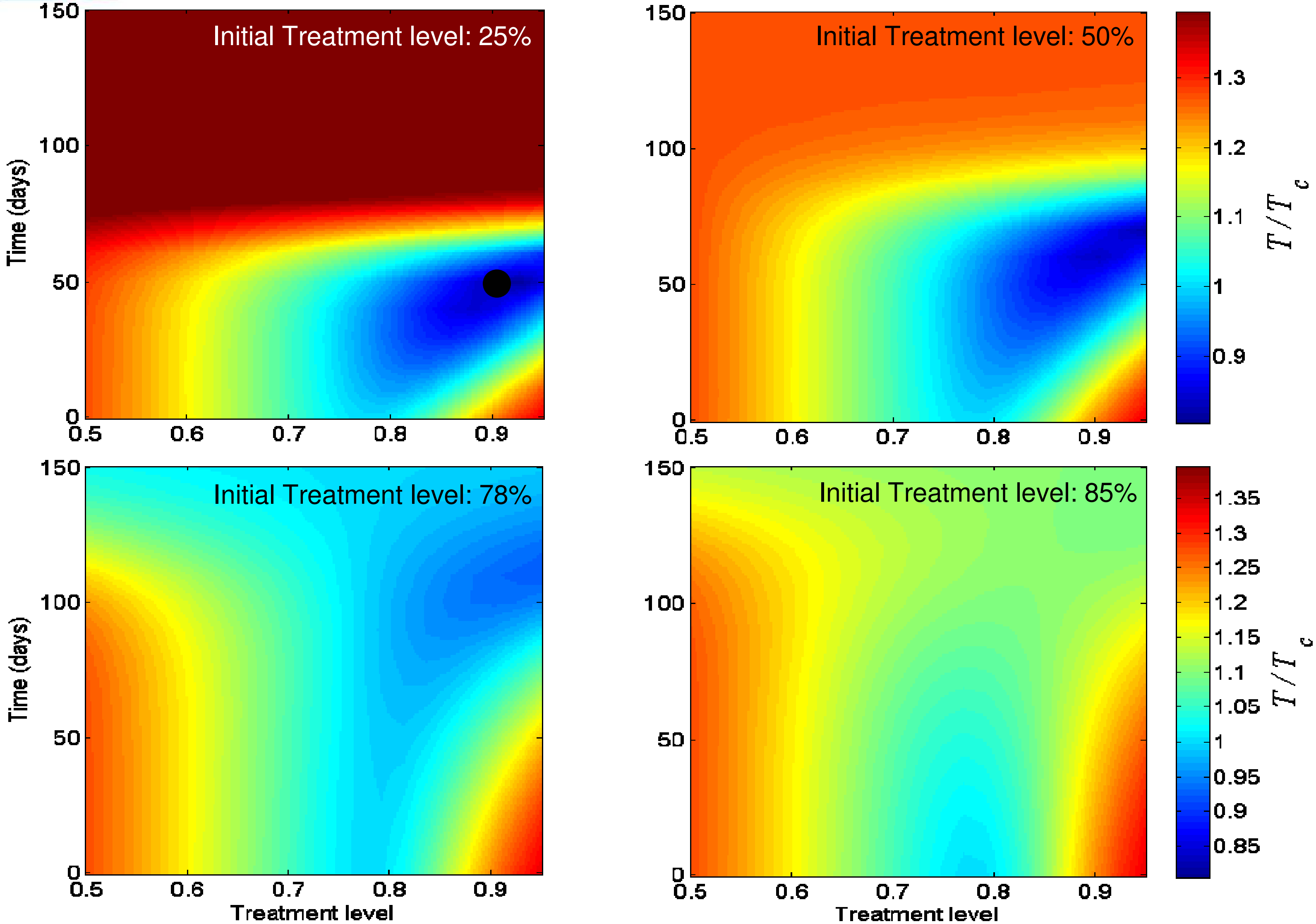
It’s a Race

- The wild type competes against the resistant strains for hosts
- Slowing spread of wild -> advantage to resistant
- Balance -> interference -> lower total attack rate
- Can this be used to our advantage?

Time varying treatment

- Constant treatment -> optimum
- Other treatment strategies:
  - Hit hard early
    - Stop if resistance observed
  - Delay onset of aggressive antiviral use
    - Moghadas, Bowman, Rost and Wu, PLoS ONE (2008)

Time varying treatment



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