Models of Host Immune Response, and the(co)Evolution of Virulence: *limited and preliminary extensions on Gilchrist-Sasaki*

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Introduction

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- Reinfection of already infected hosts (to deal with issues like super-infection.
- Variability of hosts *(not genetically determined)*.

Models for virus-immune system, 1

- P pathogen load
- I specific immunity level

$$\begin{cases} P' &= rP - cIP \\ I' &= aIP \end{cases}$$

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Infection grows (if $r > cI_0$) and then is cleared by immune system.

Some computations are easier since it is Kermack-McKendrick model disguised. Hence one obtains

$$P = \Phi(I) := \frac{r}{a}\log(I) - I + I_0 + P_0.$$

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Equations can be solved to have

$$P(t) = P_0 \exp\left\{ rt + \frac{cI_0}{\beta}(1 - e^{\beta t}) \right\}.$$

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If an infection can occur ($r > c\frac{h}{\delta}$), then system always goes to an equilibrium, generally after several infection cycles.

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m level (activity) of aspecific immunity.
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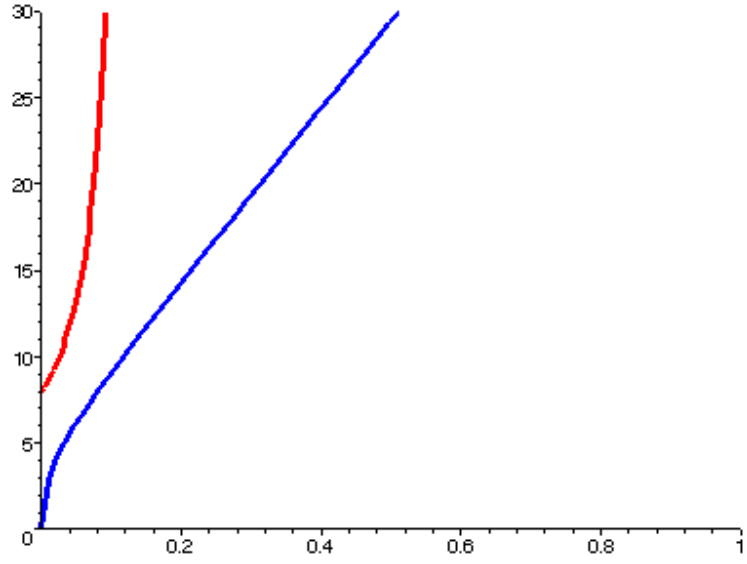

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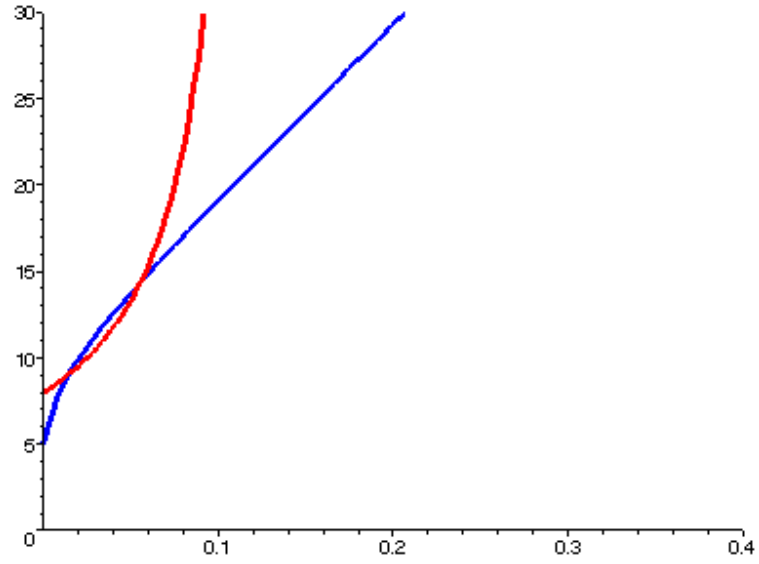

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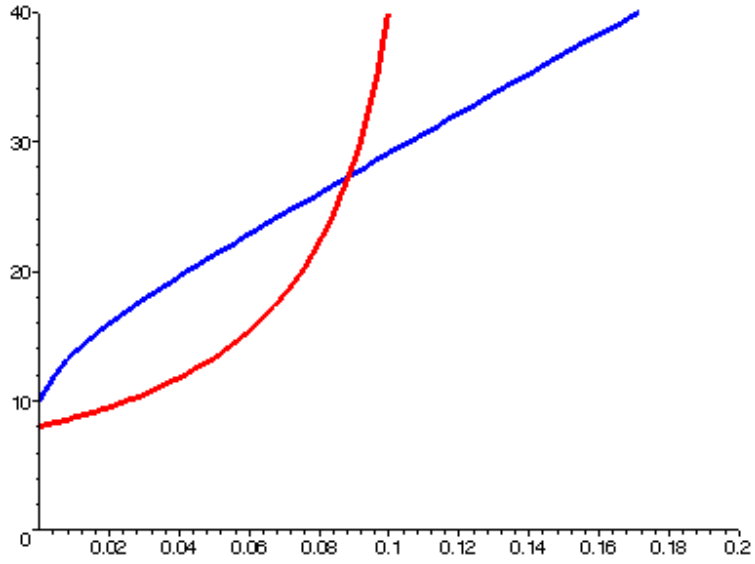

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Moreover, for $r + \delta > a/k_a$, solutions may diverge to infinity

(immune system does not control infection)

Question

Into which qualitative regime will the parameters (especially the replication rate r) evolve?

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where

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and

$$\begin{aligned} S'(t) &= \Lambda - (\mu + \lambda(t))S(t) \\ aP_0 i(t, 1) &= \lambda(t)S(t) \\ \lambda(t) &= \beta \int P i(t, P, I)\, dP\, dI \\ \alpha(P, I) &= k_1 a I P + k_2 r P \end{aligned}$$

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This system is in the class considered by Thieme and Castillo-Chavez for AIDS.

R_0

The behaviour of the system is mainly determined by R_0:

$$R_0 = \frac{\Lambda}{\mu} \beta \int_0^\infty P(\theta) \times \exp\left\{ -(\mu\theta + k_1 \int_0^\theta k_1 a I(s) P(s) + k_2 r P(s)\, ds \right\} d\theta.$$

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Pathogen level at time θ since infection

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Survival probability to time θ

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Population at disease-free equilibrium

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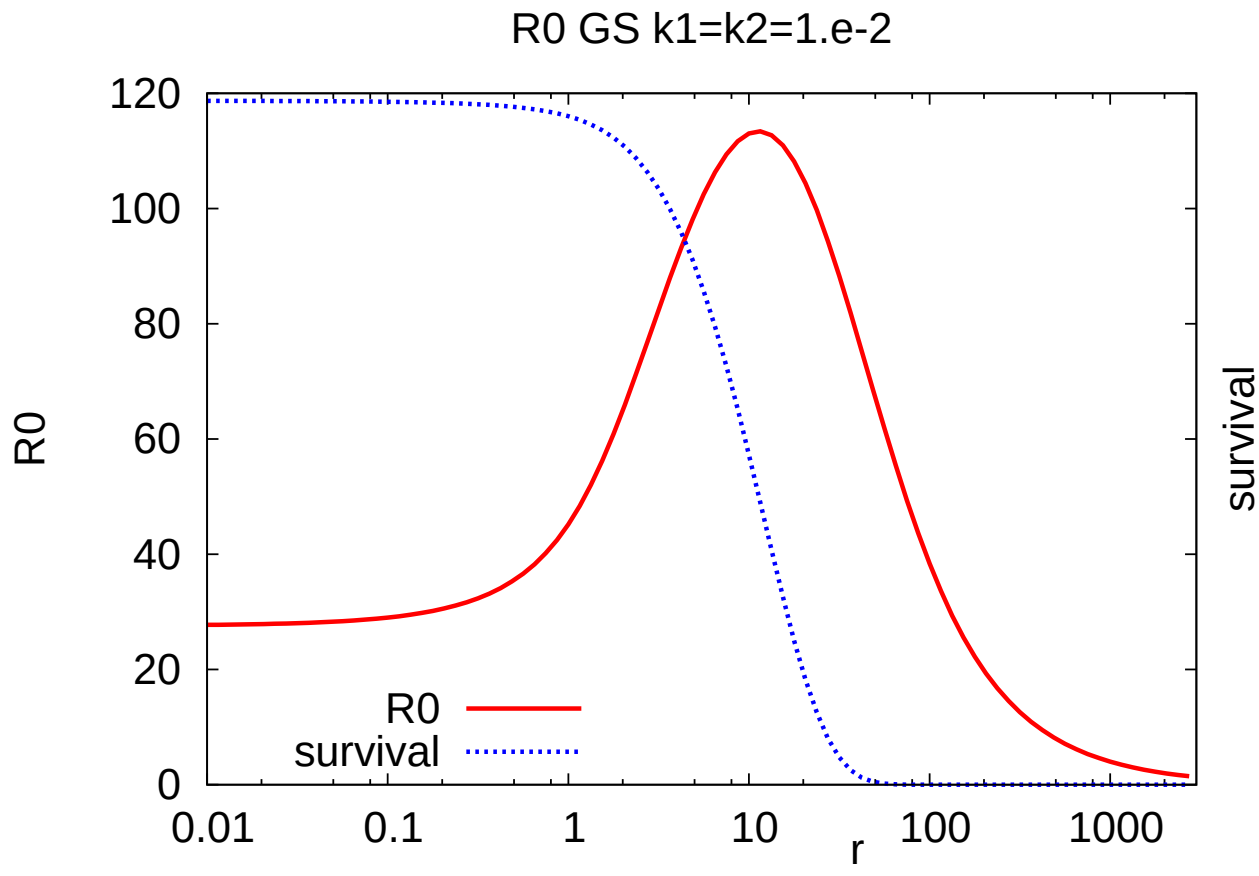
- If two strains compete, with complete cross-immunity, the strain with the highest R_0 outcompetes the other (Bremermann-Thieme, 1989).

Graph of R_0


R0 GS k1=k2=1.e-2
R0
survival
r
120
100
80
60
40
20
0
0.01
0.1
1
10
100
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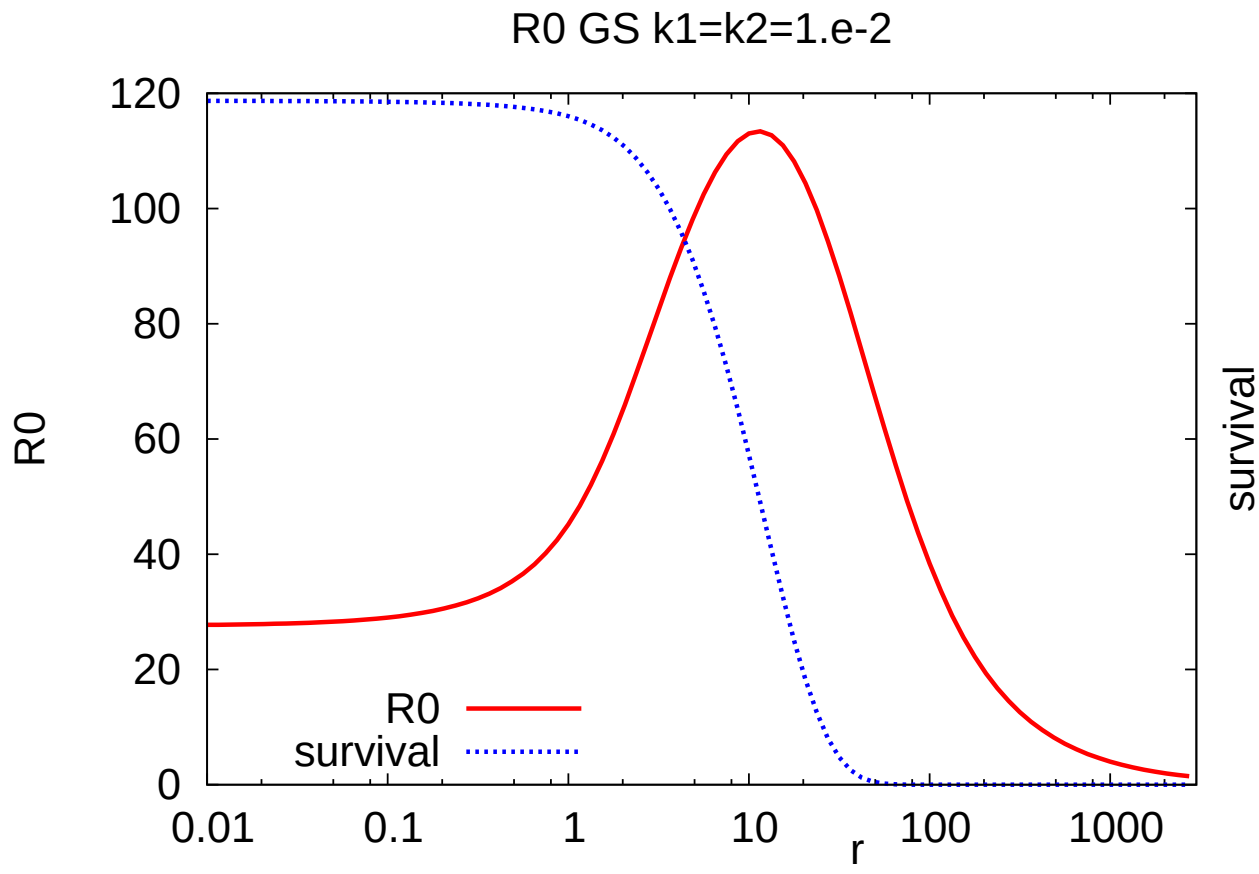
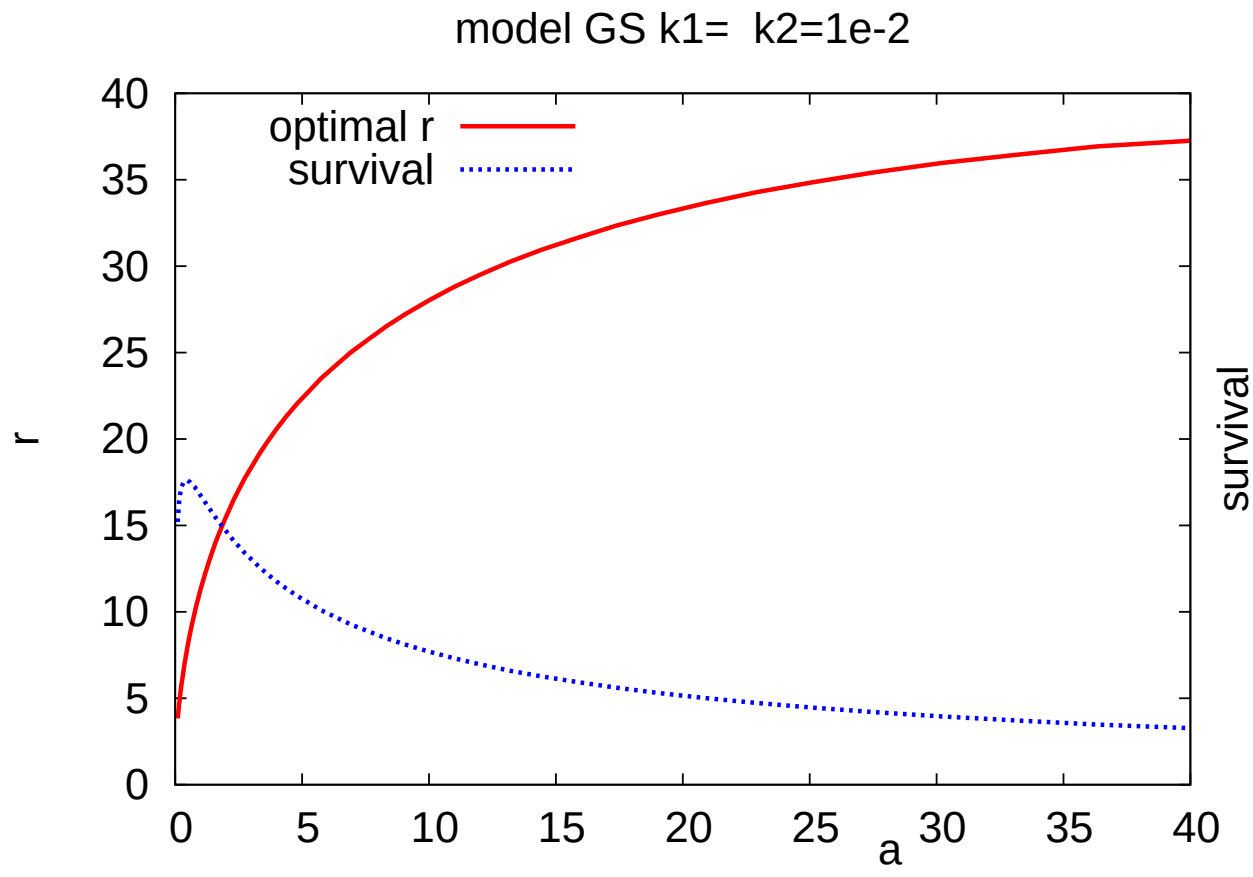


Maximum at an intermediate r. All graphs look like this (no proof!).

Optimal r for fixed a



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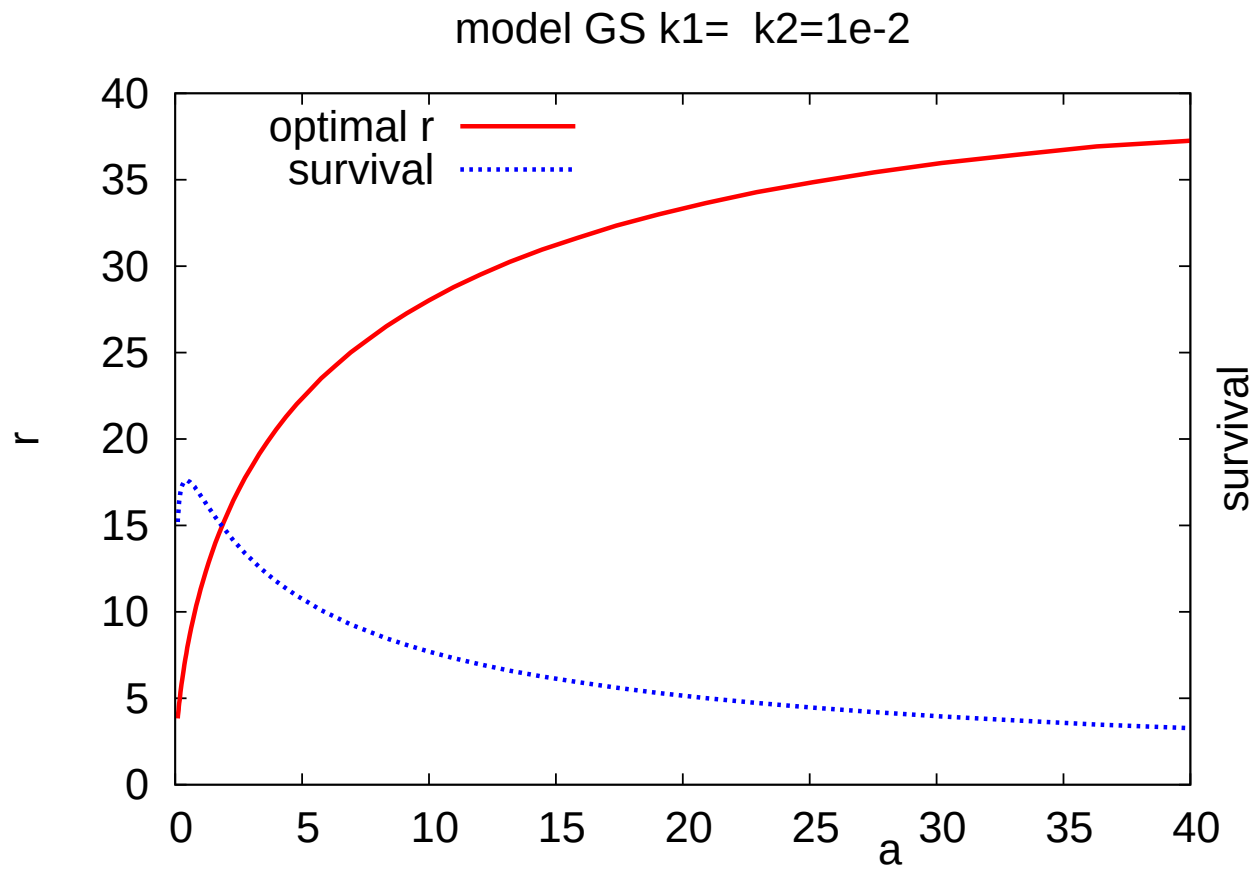
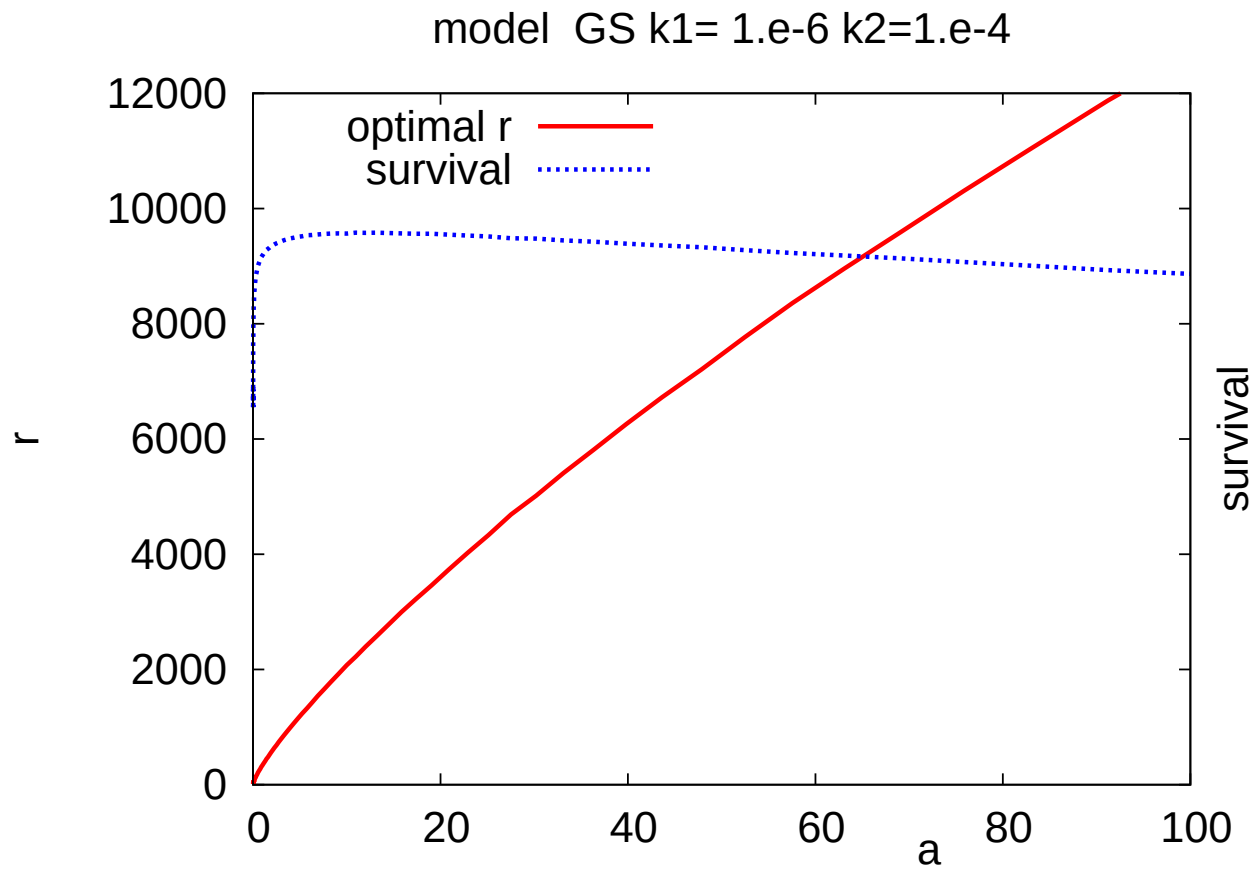


If host evolution of a is slower than pathogen's, move along the red curve to the maximum of the blue.

Lower costs of immune response



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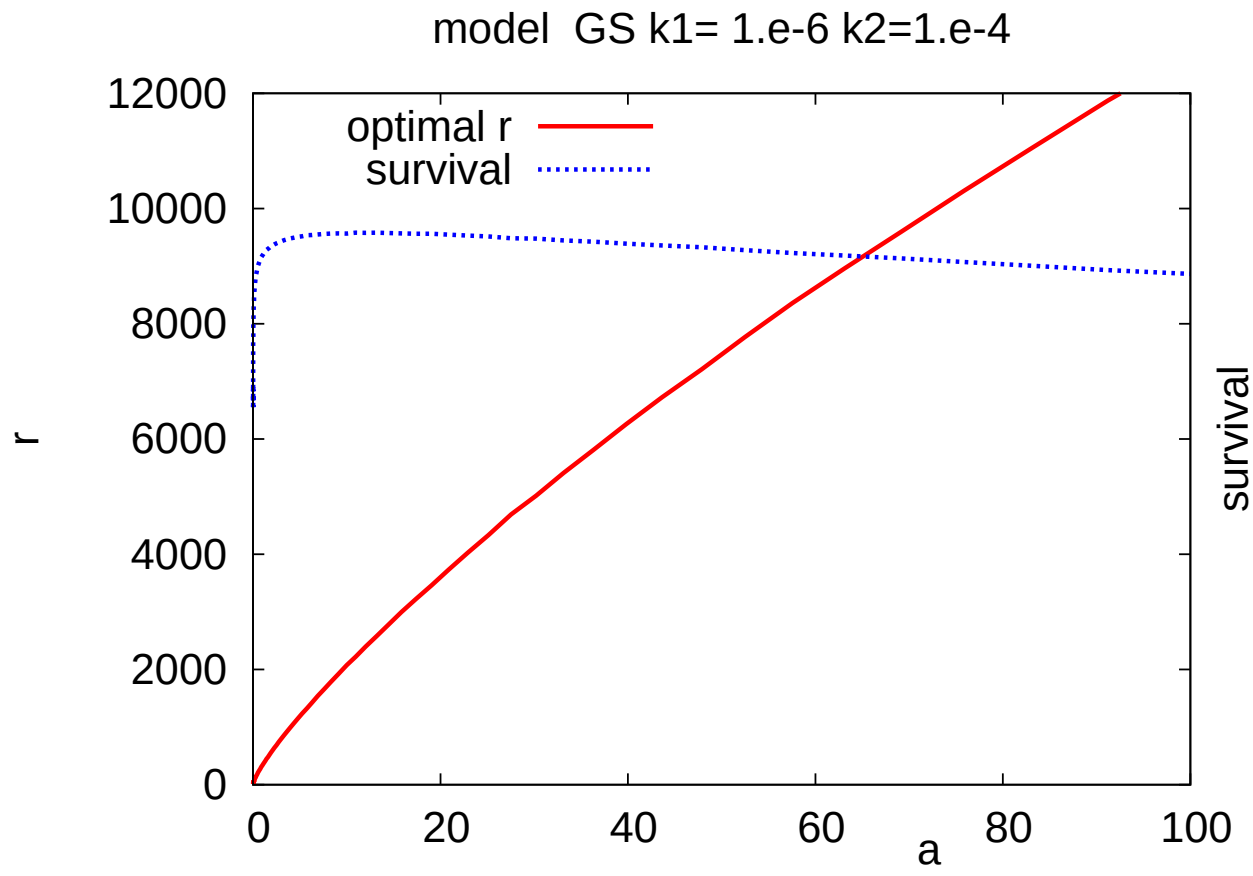
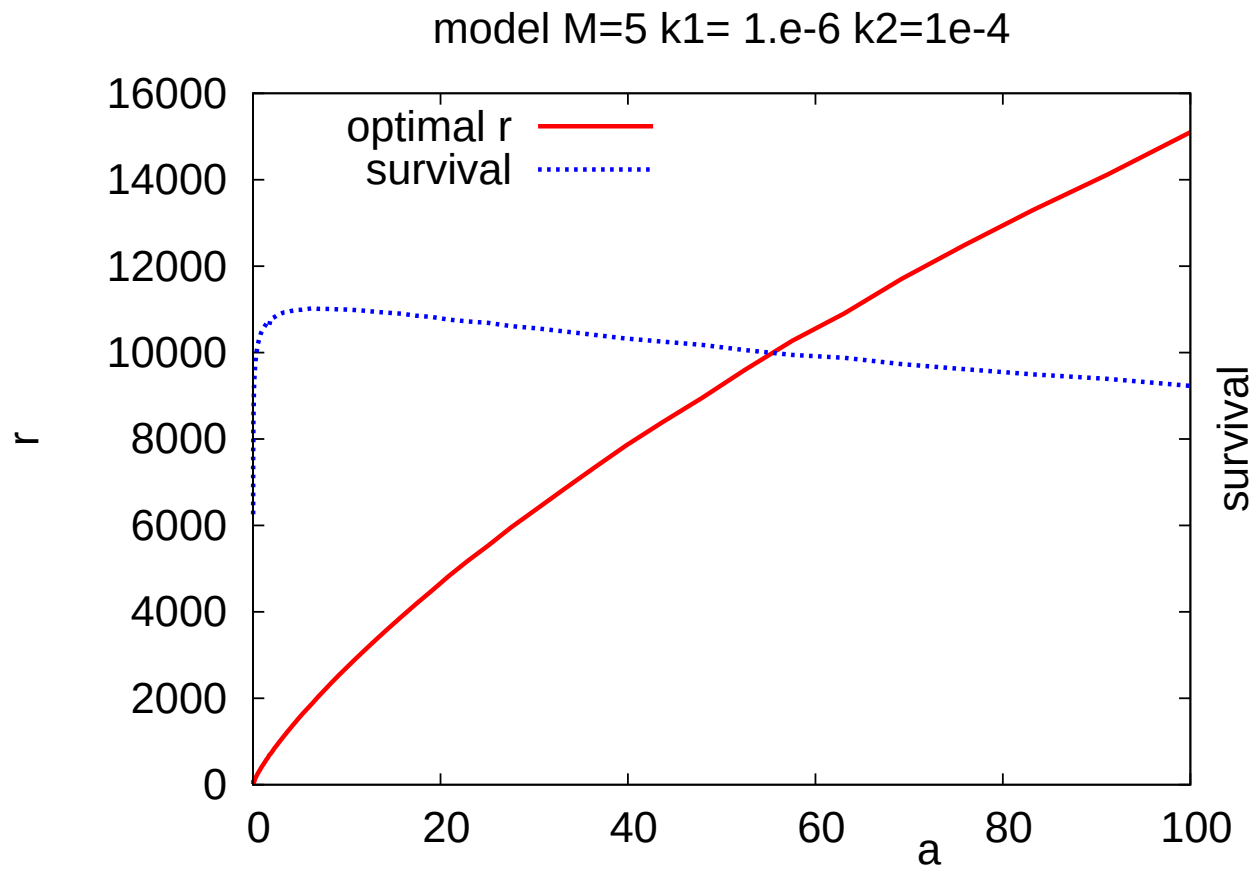


Higher survival, but still a rather lethal infection.

Effect of innate immunity



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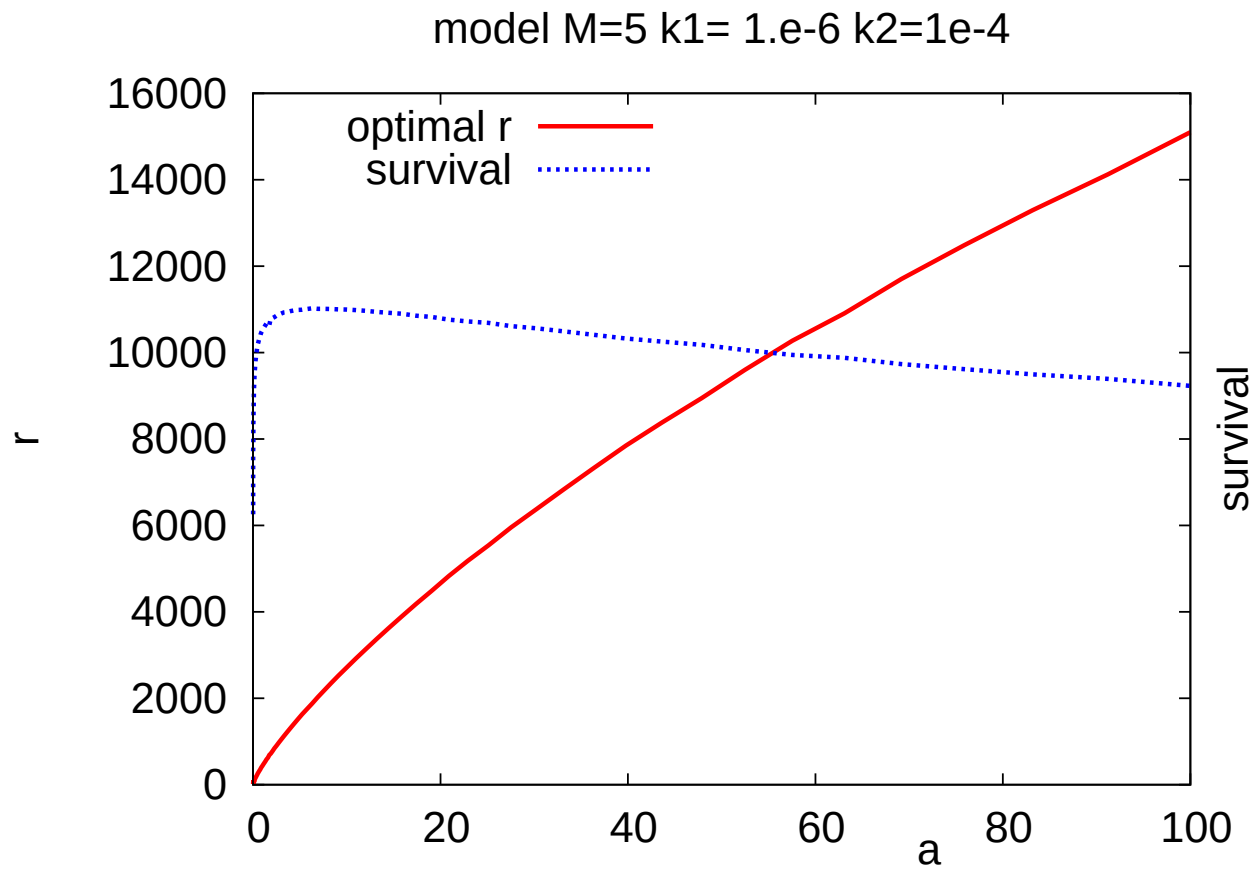

Survival lower than without.

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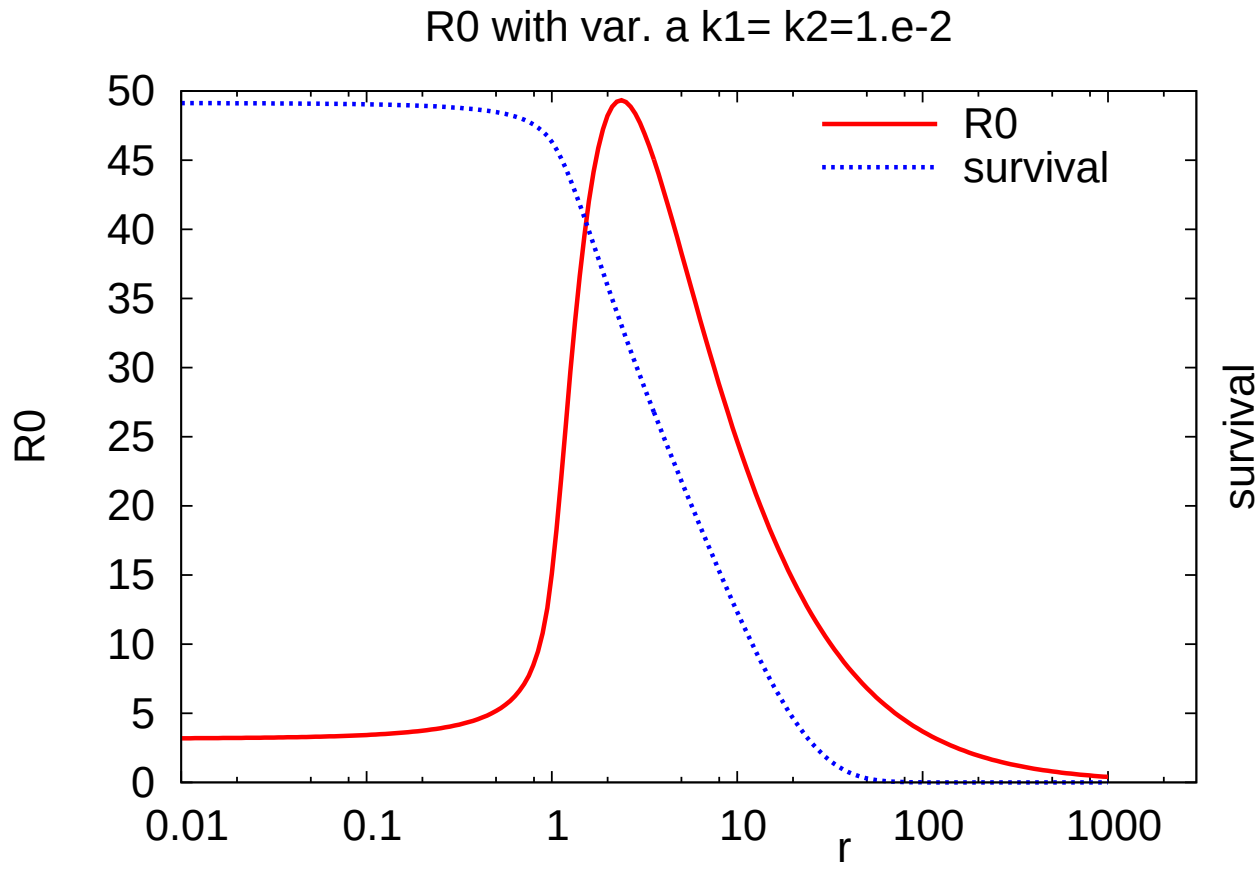

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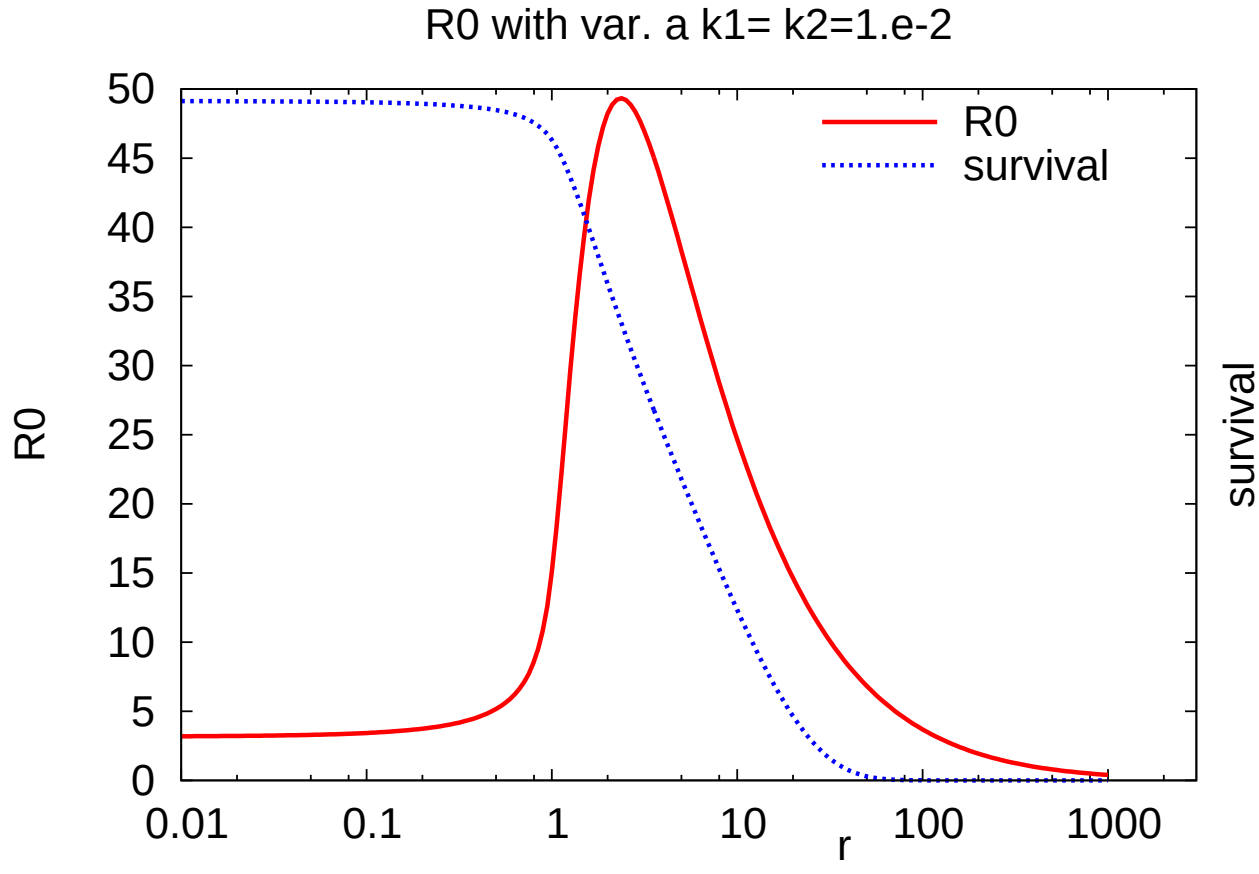
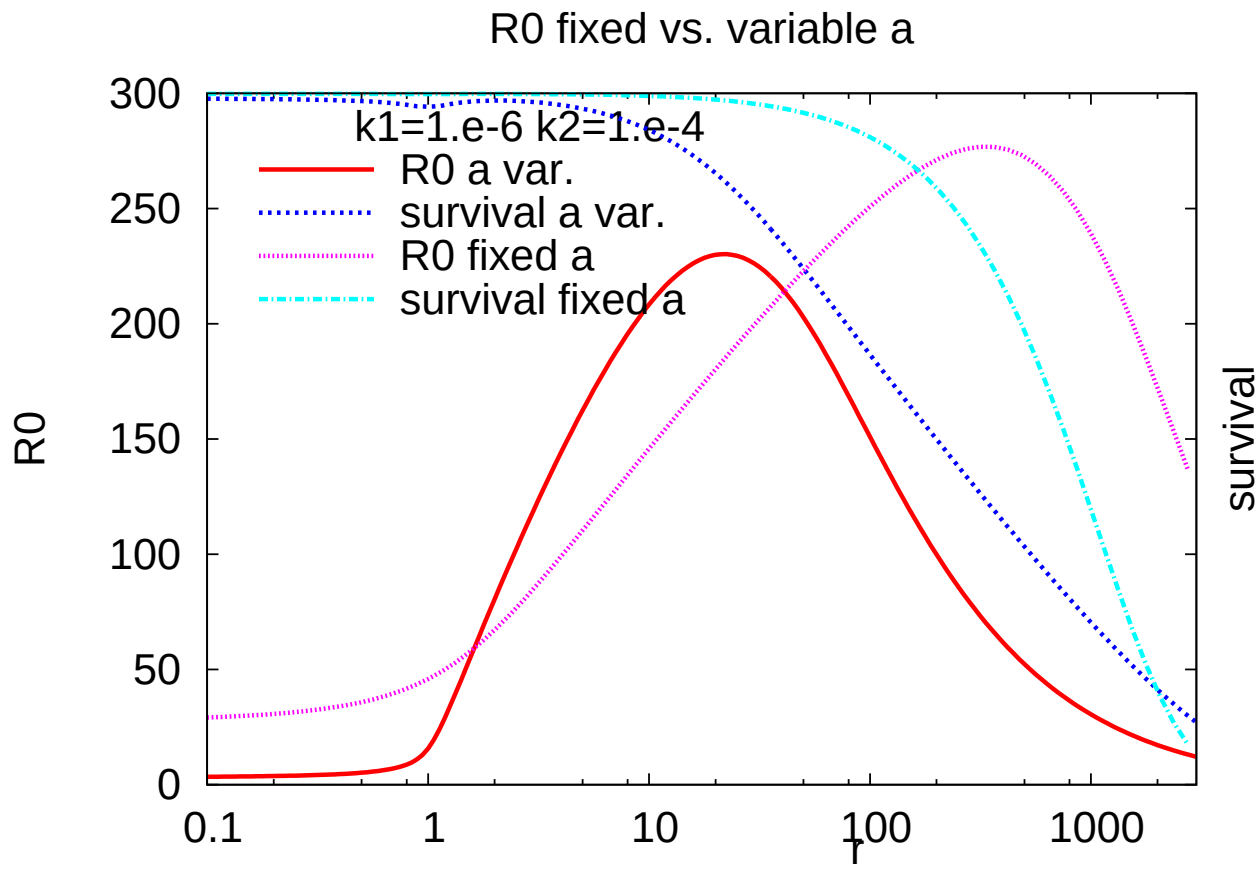


How does it compare with fixed a?

Comparison of fixed vs. distributed a



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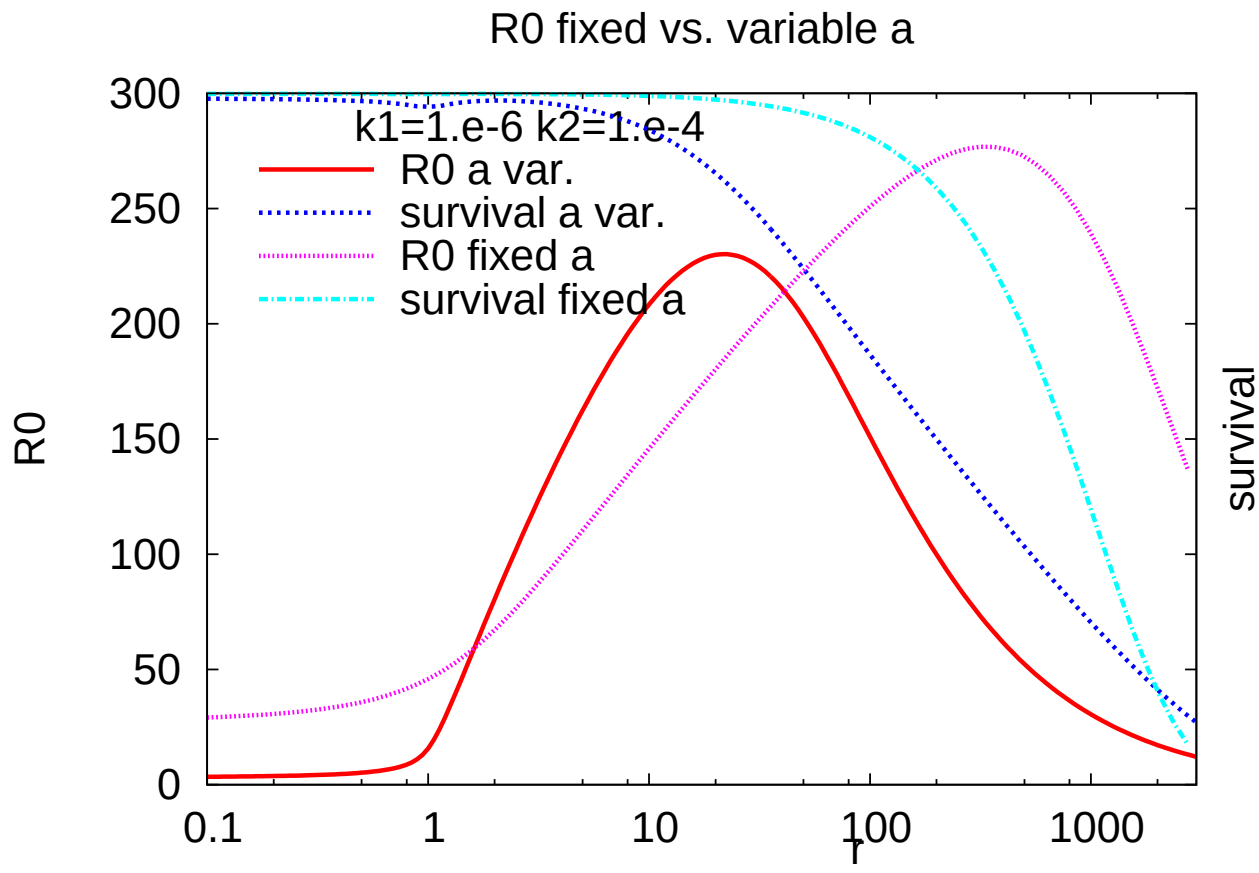
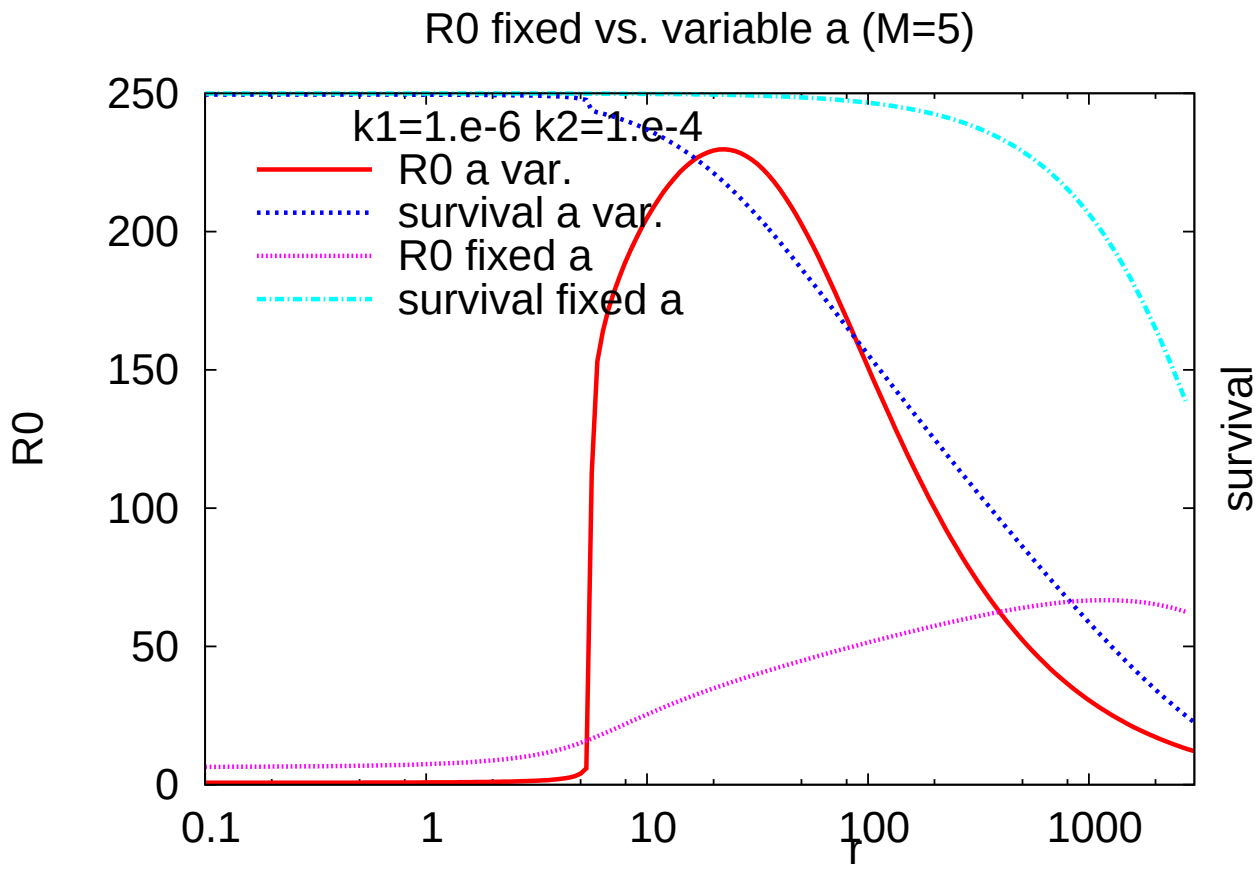


Selection for much lower r

Adding innate immunity



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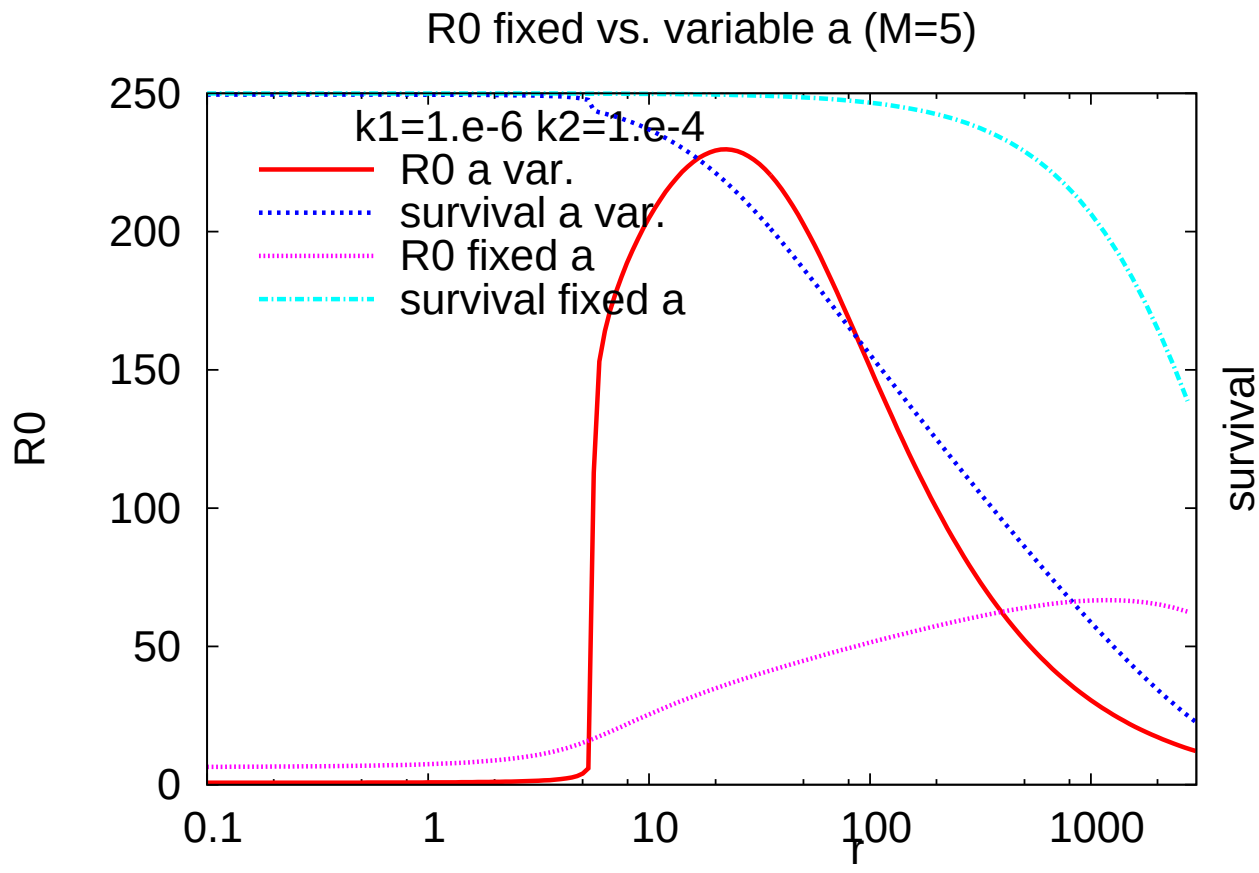

Similar picture

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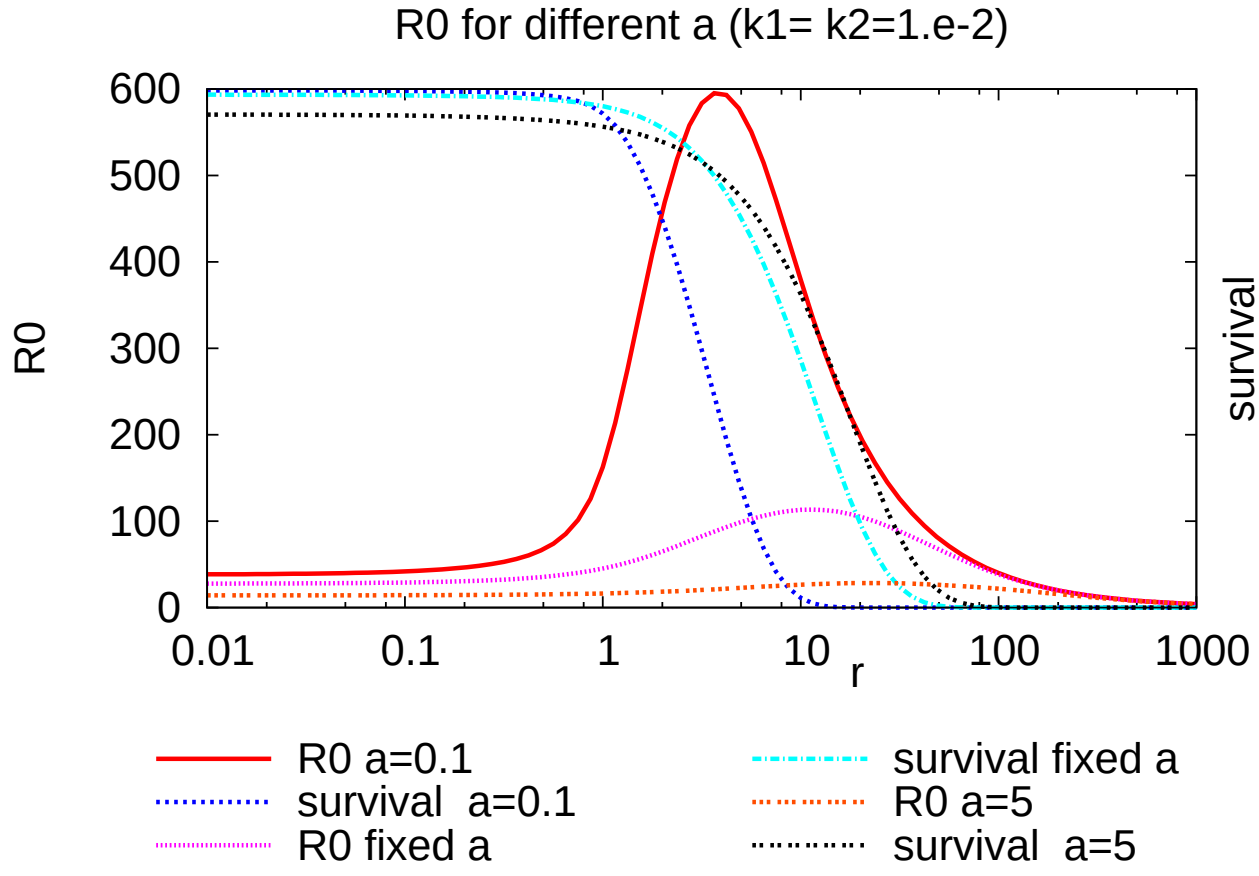

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Thanks

- The within-host model was set up and analysed with Alberto Gandolfi (IASI - Roma).
- Thanks to DIMACS for providing the support and the smooth organization for this workshop...
- ... and to you for your attention.