Within-Host Dynamics of Influenza Drug-Resistance

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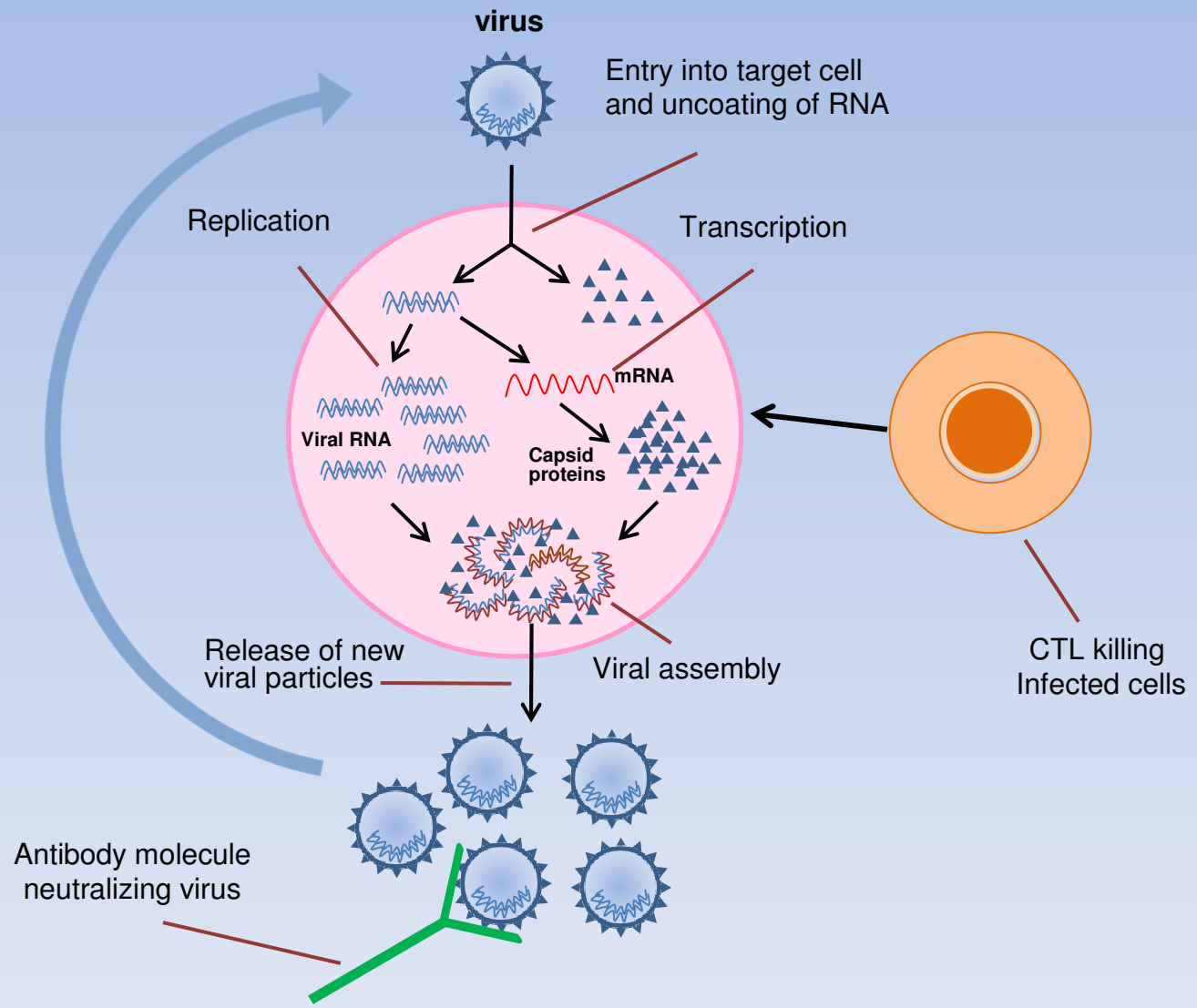
Outline

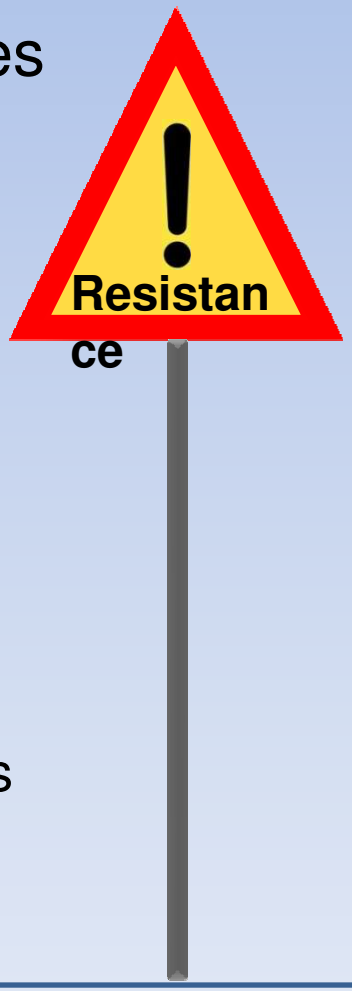
- Within-Host Infection Mechanisms:
  - Viral Replication and Mutation
  - Adaptive Immune Response
  - Infection in the Presence of Immune Memory
- Antiviral Treatment:
  - Compensatory Mutations
  - Emergence of Drug-Resistance
- Modelling Viral-Immune Dynamics:
  - Drug Efficacy and Timing of Treatment
- Conclusions and Future Direction
  - Need for Improved Experimental Work

Viral Replication and Inhibition

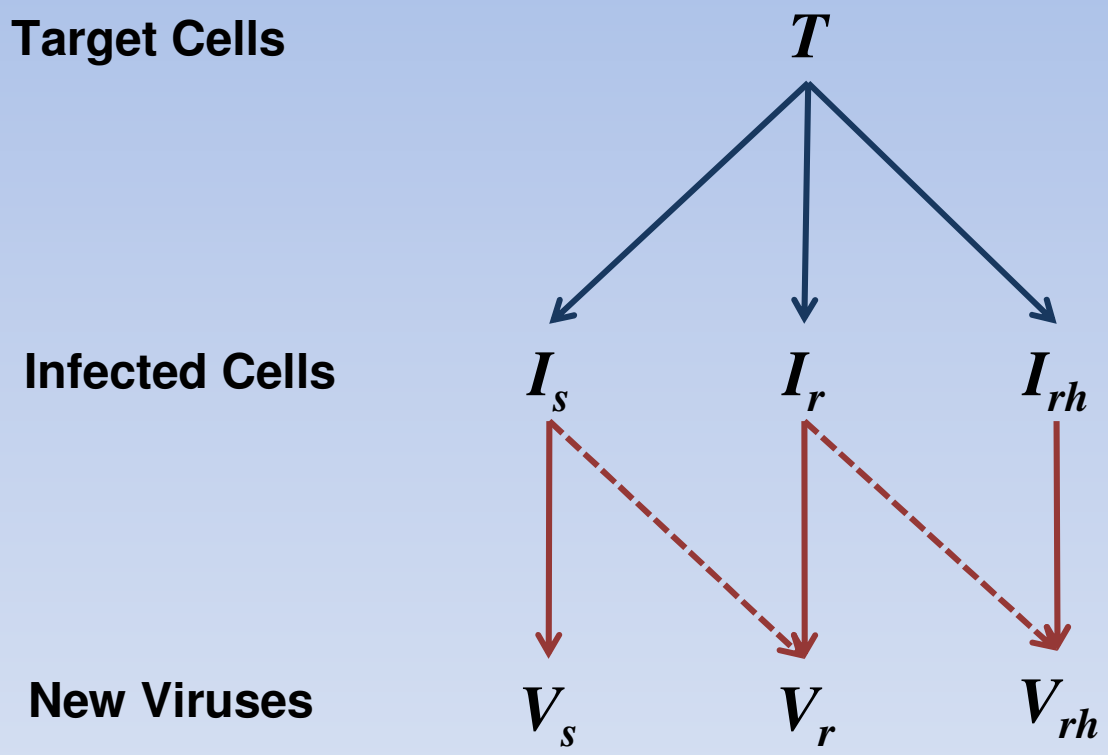


Drug Treatment and Resistance

- Early treatment is crucial in primary infection
  - Rapid infection of target cells between 2 and 3 days post exposure
- Treatment inhibits replication of sensitive viruses
  - Risk of treatment: development of resistance
- Fitness: replicative adaptability of an organism to its environment
  - E. Domingo, J.J. Holland, *Annu. Rev. Microbiol.* 1997
- Fitness cost:
  - Survival involves evolutionary responses: mutation
  - Mutations may reduce replicative adaptability
- Fitness gain:
  - Compensatory mutations can restore impaired fitness
  - Competitive advantage in growth and transmissibility



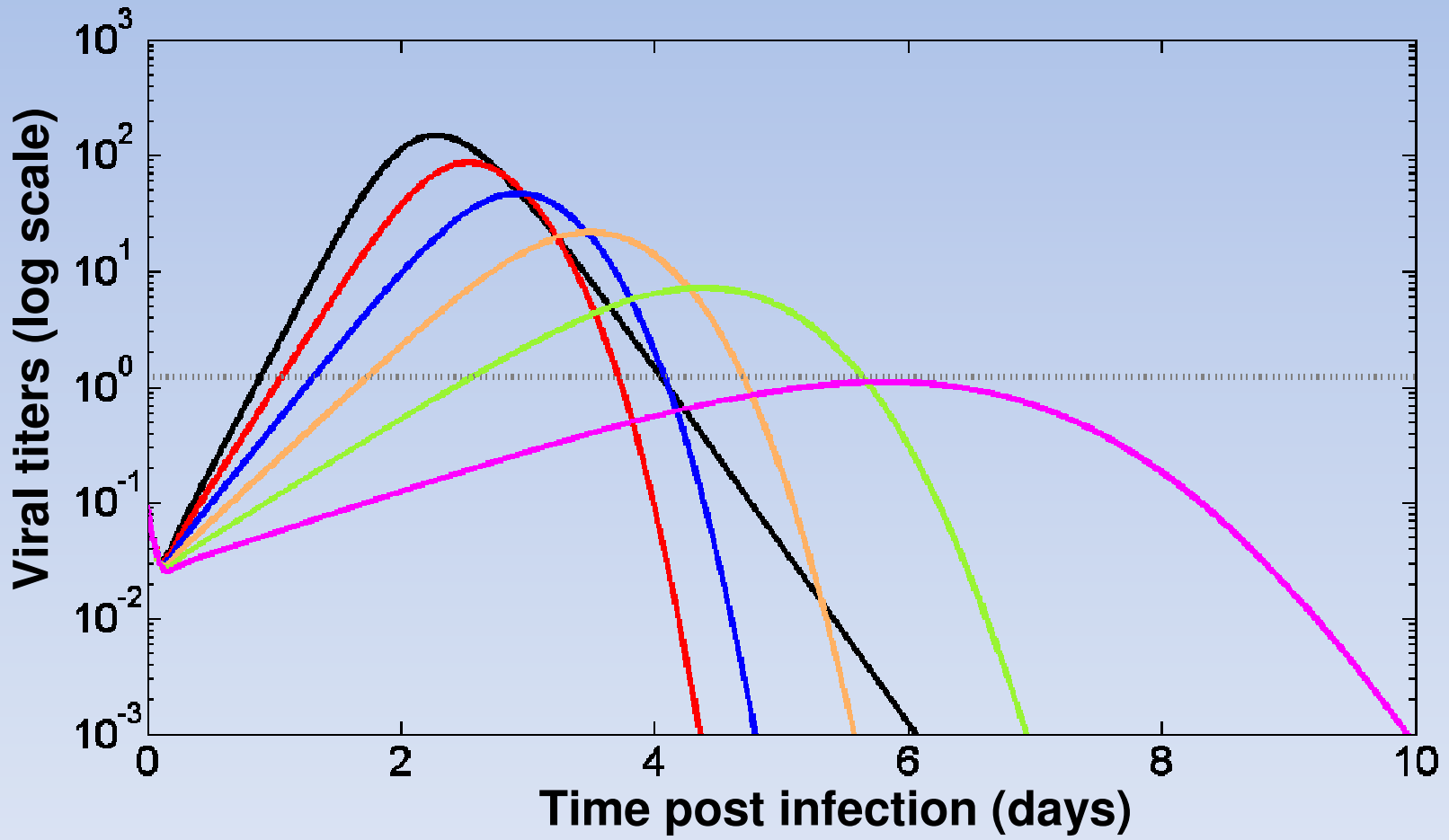
Modelling Viral-Immune Dynamics



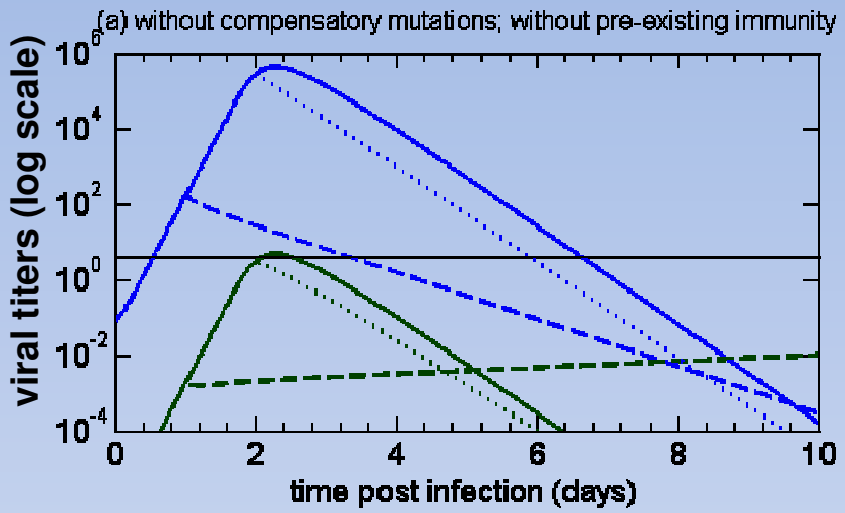
Modelling Viral-Immune Dynamics

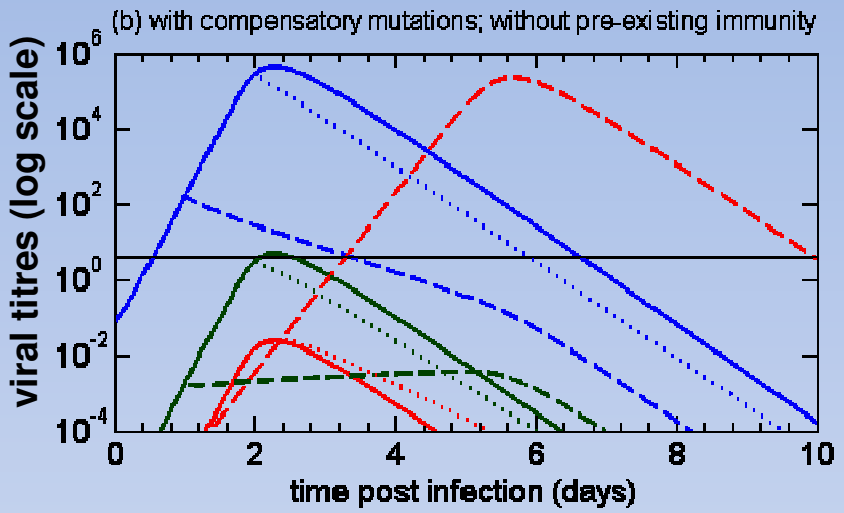
$$T' = -\beta(V_s + V_r + V_{rh})T$$
$$I_s' = \beta V_s T - (d + \gamma_1 C) I_s$$
$$I_r' = \beta V_r T - (d + \gamma_1 C) I_r$$
$$I_{rh}' = \beta V_{rh} T - (d + \gamma_1 C) I_{rh}$$
$$V_s' = (1-\alpha)(1-\kappa_r)\, p I_s - (\mu + \gamma_2 A) V_s$$
$$V_r' = (1-\alpha)\kappa_r\, p I_s + (1-c_r)(1-\kappa_{rh})\, p I_r - (\mu + \gamma_2 A) V_r$$
$$V_{rh}' = (1-c_{rh})\, p I_{rh} + (1-c_r)\kappa_{rh}\, p I_r - (\mu + \gamma_2 A) V_{rh}$$
$$C' = \delta(I_s + I_r + I_{rh})(C + C_m)$$
$$A' = \nu C - \gamma_2 (V_s + V_r + V_{rh}) A$$

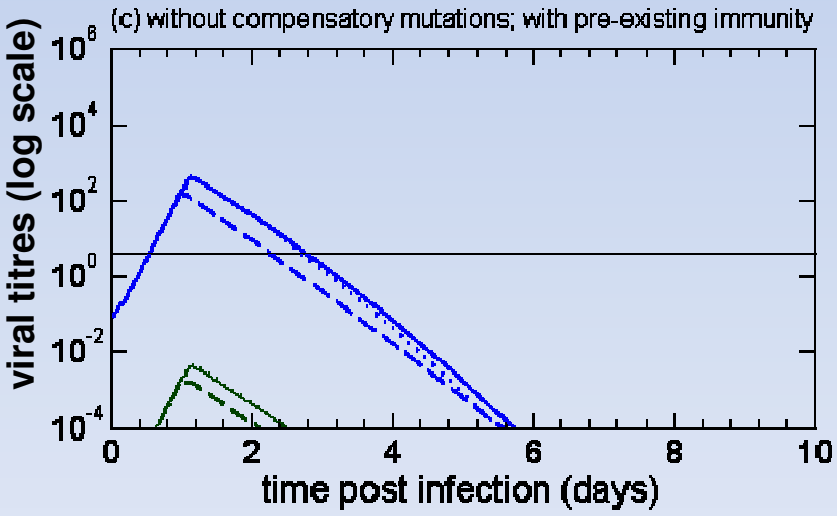
Infection in the Presence of Immunity

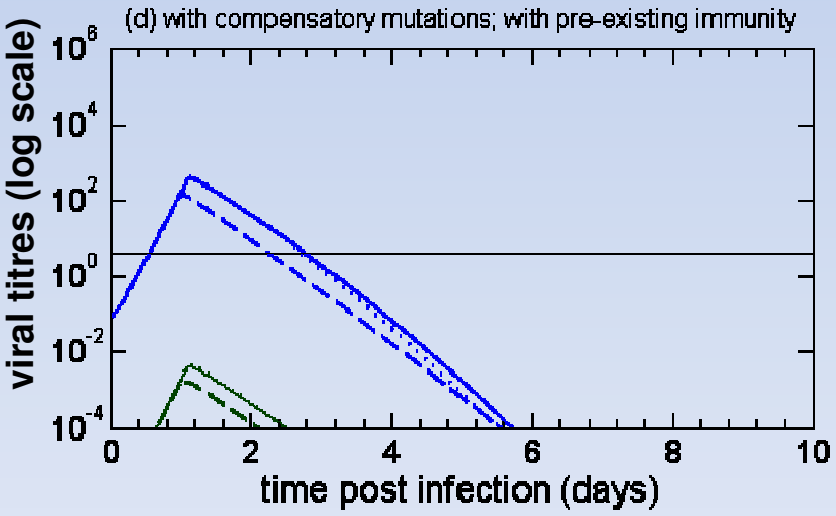


Time Lines of Infection



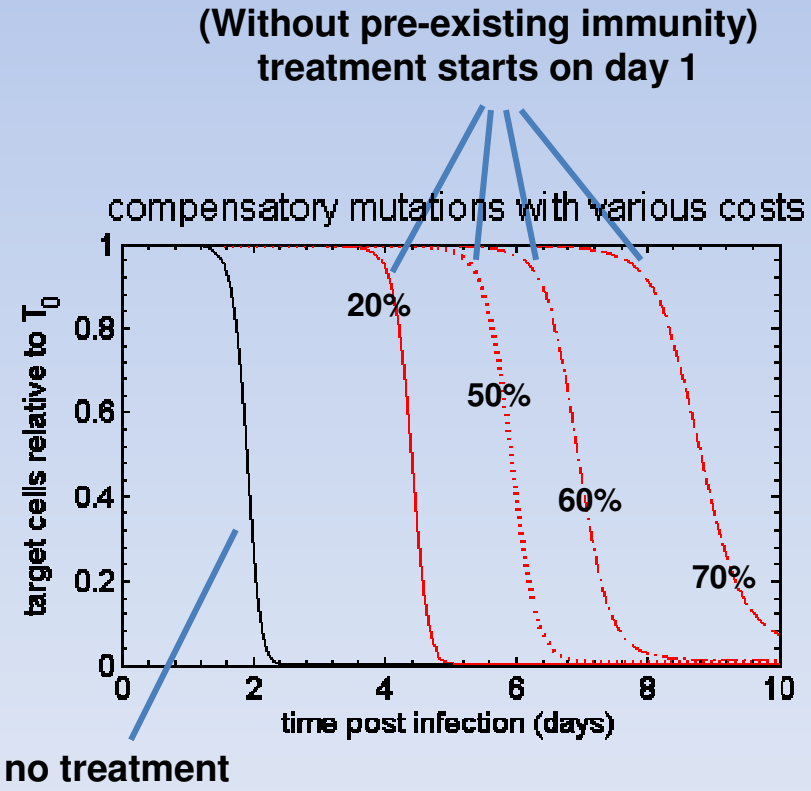






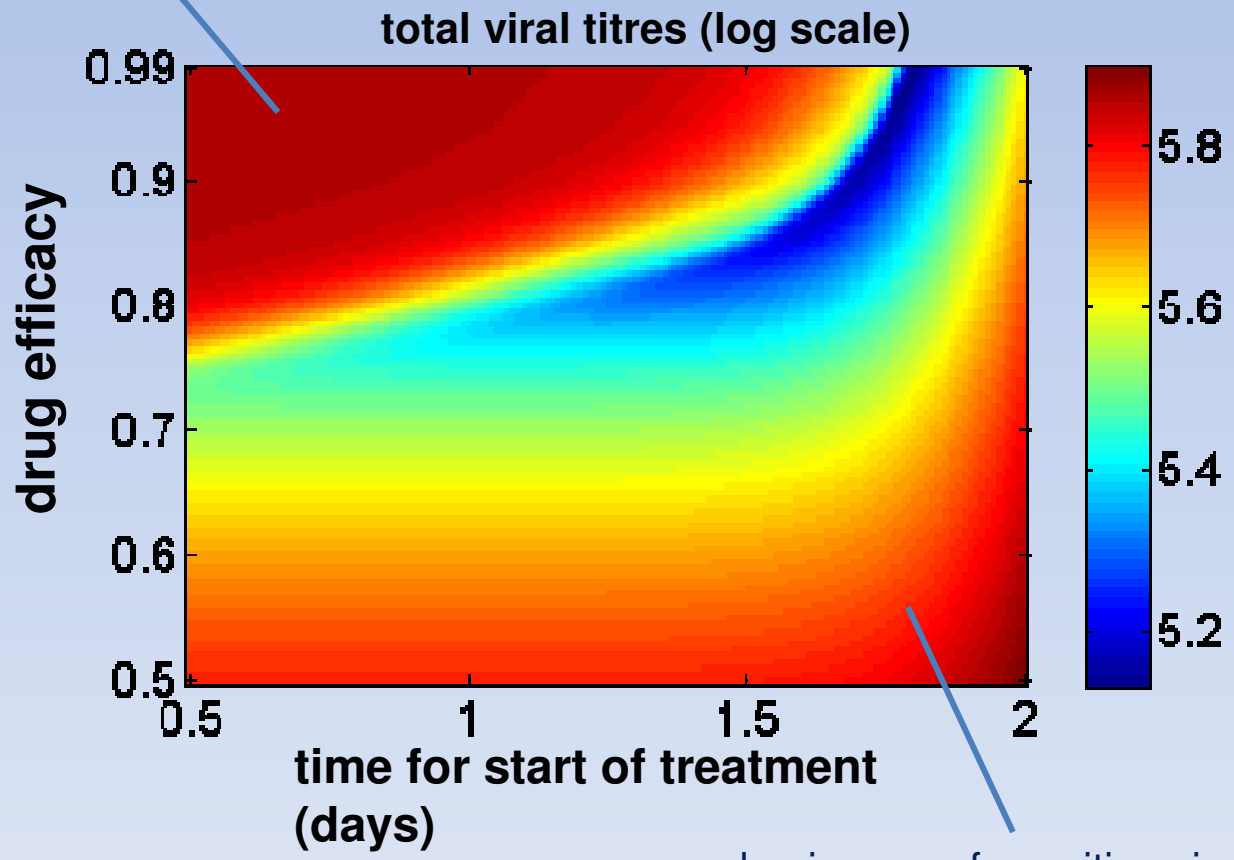
Cost of Resistance and Fitness Enhancement

- Treatment may fail if compensatory mutations arise
- Further delay in infection process with higher cost of resistance



Timing and Efficacy of Treatment

dominance of resistant viruses



dominance of sensitive viruses

Summary

- In the absence of pre-existing immunity:
  - Invasion of resistance if fitness cost is sufficiently low
  - Drug efficacy and timing of treatment are crucial
- In the presence of pre-existing immunity:
  - Infection process is suppressed / delayed
  - Resistance is unlikely to emerge
- Immune memory may be a key factor:
  - Preventing development of clinical disease
  - Preventing lethal consequences despite infection

Limitations and Future Work

- Simplifying assumptions in model development:
  - Proportionality of T cell expansion to the total number of infected cells
  - Simplification of mechanisms of adaptive immune response
  - Exclusion of innate immunity
  - Absence of delay between cell infection and virus release
- Extension of the model to include:
  - Mechanisms of innate immunity
  - Antigen presentation and clonal expansion of T and B cells
- Need for improved experimental work:
  - Provide more accurate estimates of *in vivo* parameters
- What can we say about:
  - Re-emergence of drug sensitive strains in the presence of compensatory mutations