Understanding the Homeostasis Hypothesis for Hepatitis C

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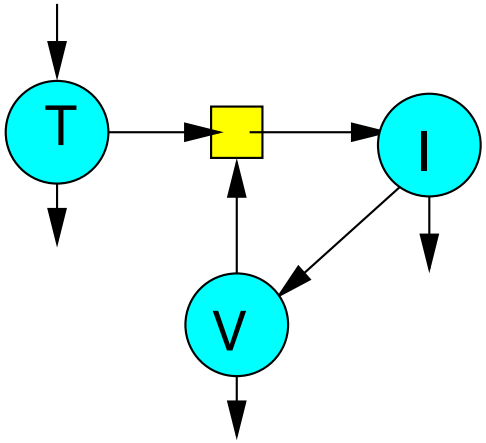
July 21, 2010

Hepatitis C Virus (HCV)

- 3.2×10^6 chronically in the US. Around 2×10^4 new infections per year in the US Primarily transmitted by injection drug use.
- 75 % of infections are chronic
- 20 % of chronic infections get cirrhosis
- 1% - 5% of those die from chronic liver disease
- 6 Identified genotypes of HCV, with many substrains.
- Treatment with combination pegylated interferon-α and ribavirin produces sustained responses in 50 % of patients.

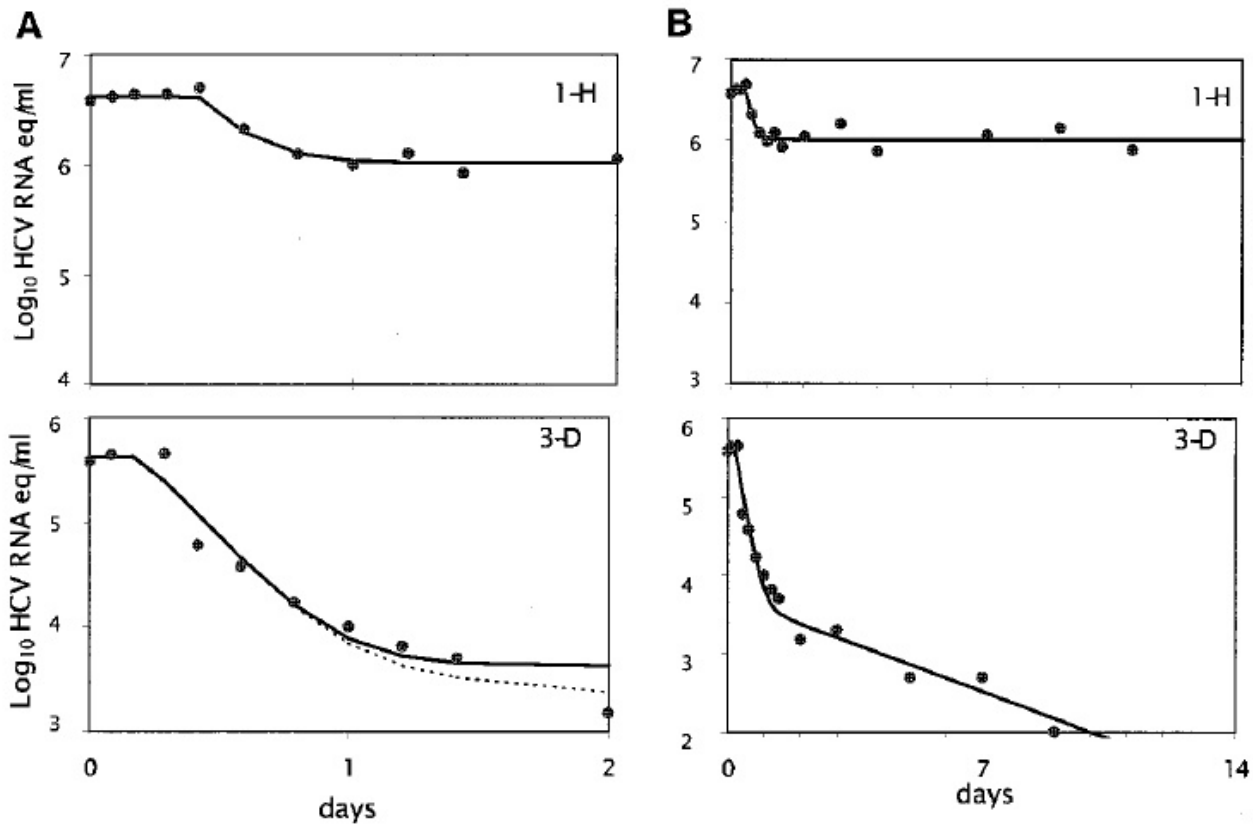
Within-Host Viral Dynamics[Neumann et al., 1998]



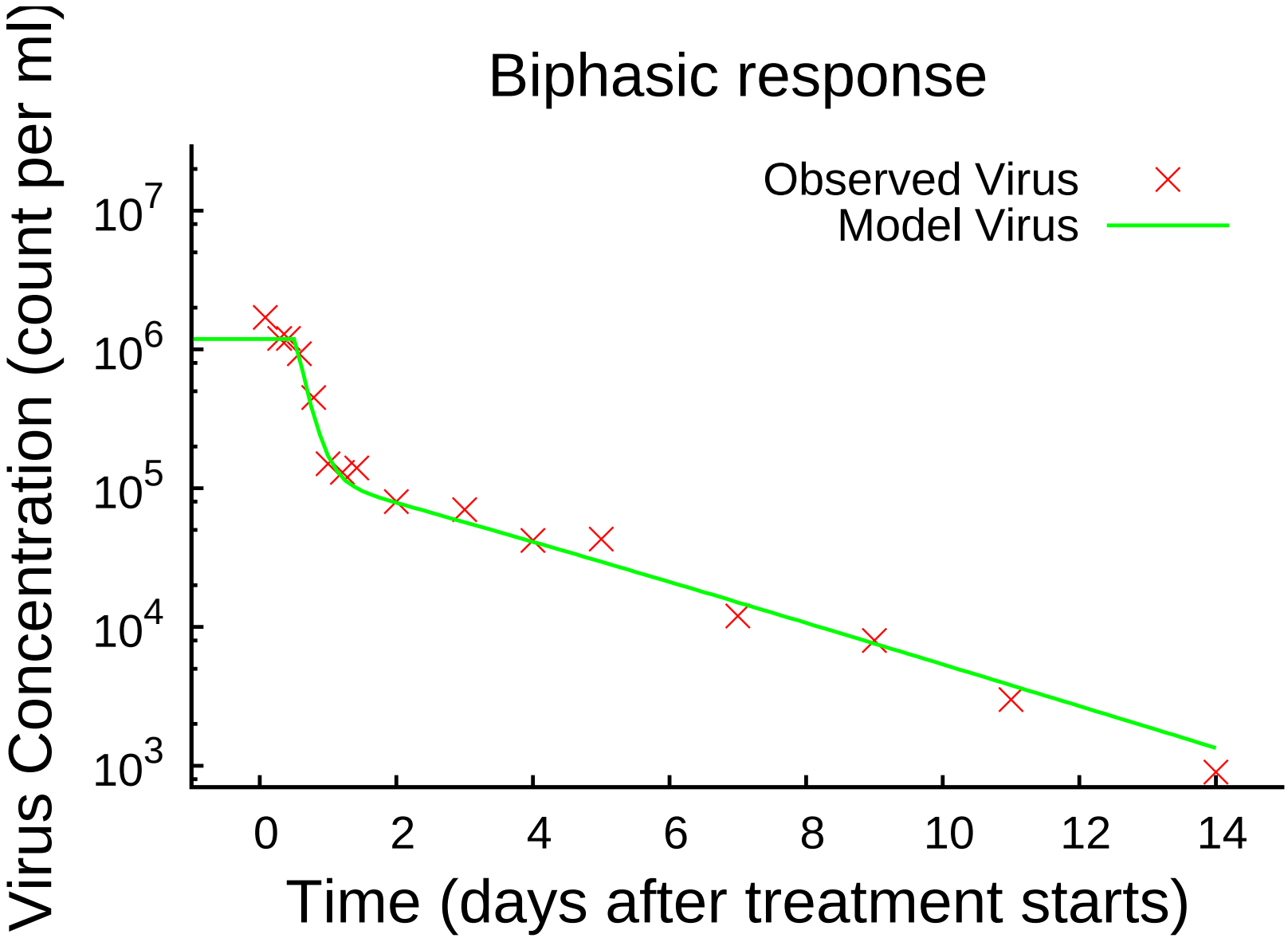
$$\dot{T} = \hat{s} - (1-\eta)\beta V T - d_T T \qquad (1a)$$

$$\dot{I} = (1-\eta)\beta V T - d_I I \qquad (1b)$$

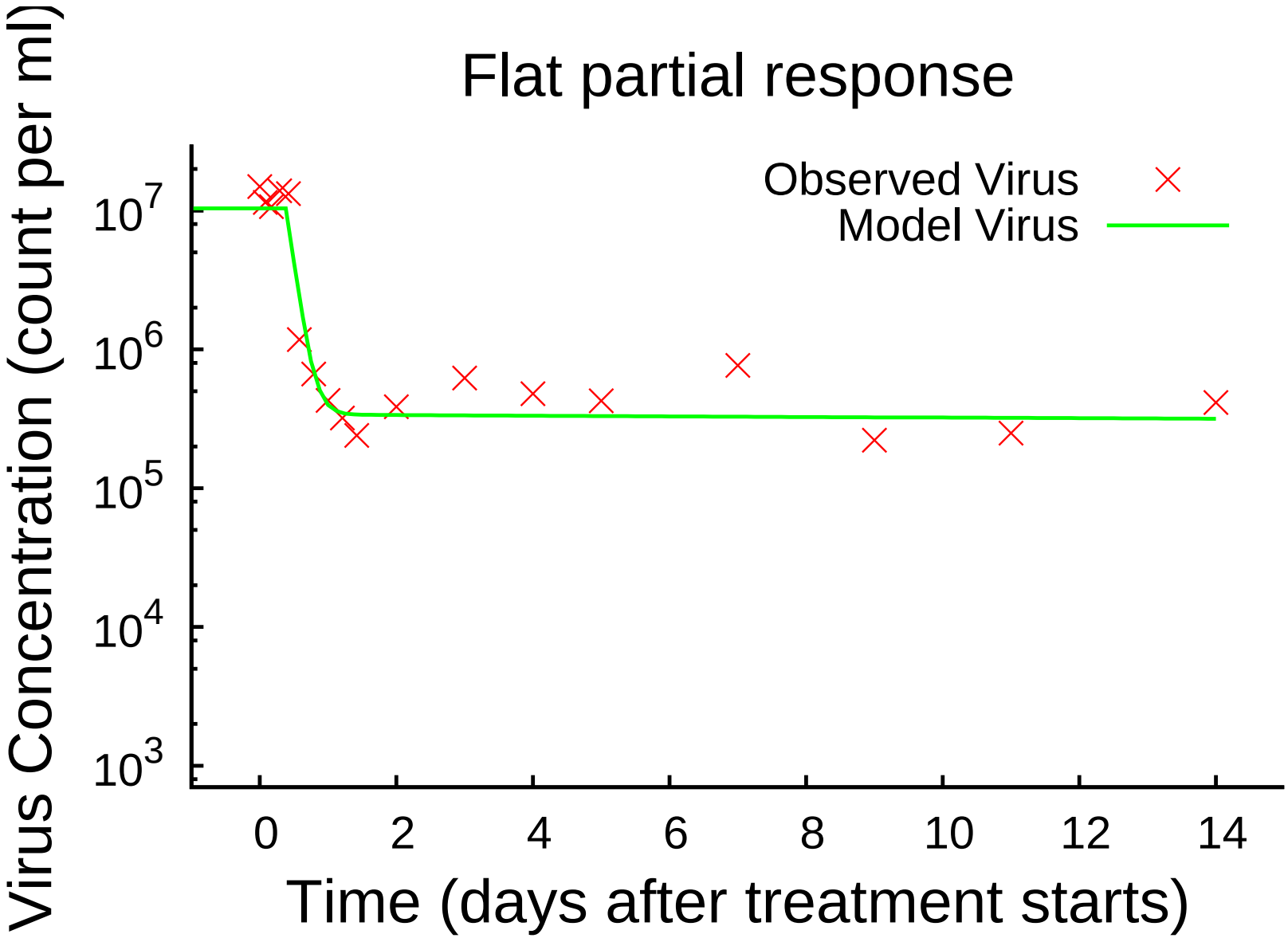
$$\dot{V} = (1-\epsilon) p I - c V, \qquad (1c)$$



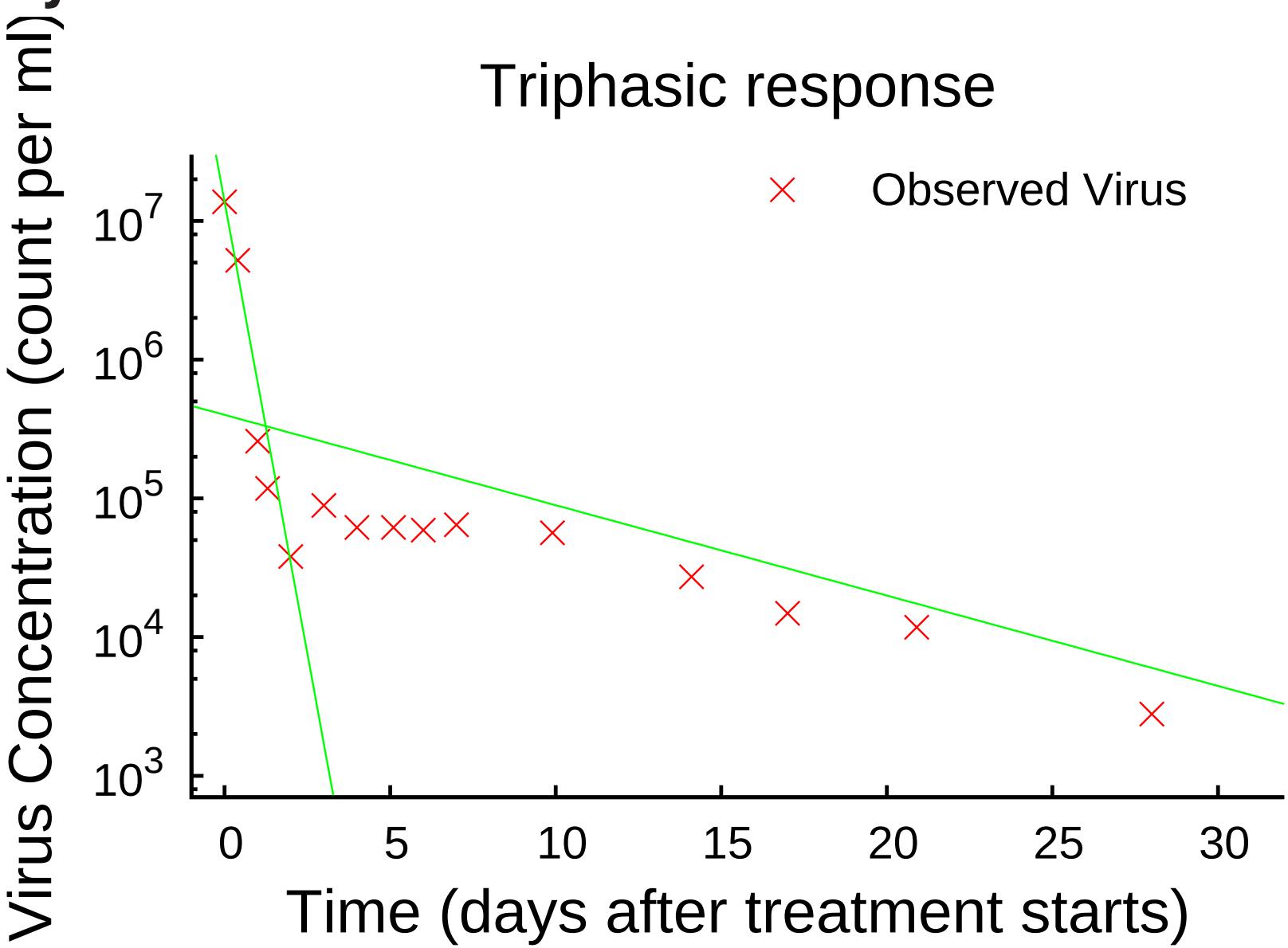
Dynamics under successful treatment



Dynamics when treatment failures



Lucky not to have treatment fail?



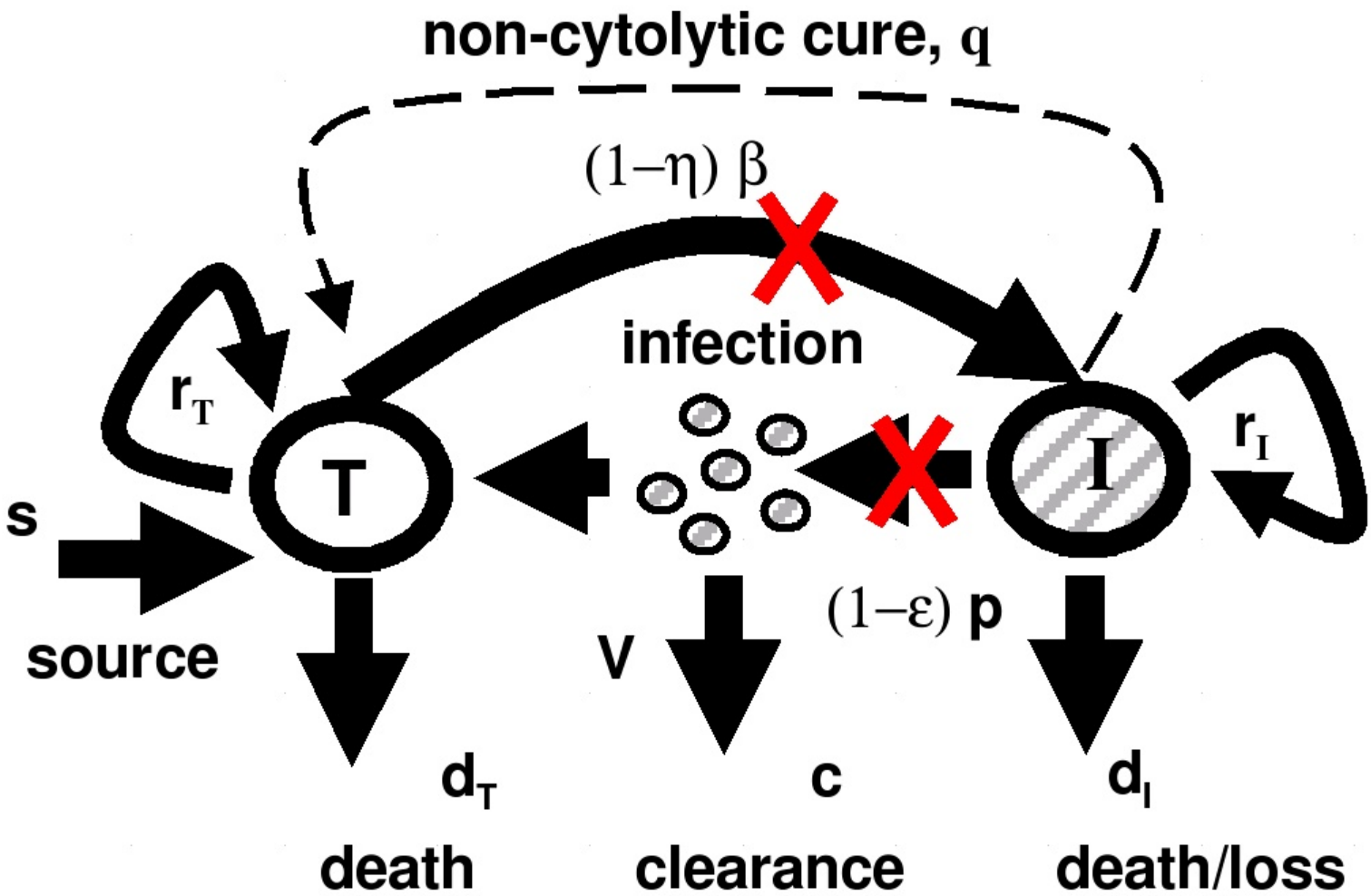
A Homeostasis/Vertical Transmission Hypothesis

Conjecture 1. *In addition to the action of free virus, HCV infection can spread by vertical transmission of hepatocytes that proliferate homeostatically.*

Because HCV is very efficient, almost all target hepatocytes are infected in the absence of treatment. Removed cells are thus most likely to be replaced by proliferation of neighboring cells that are already infected themselves.

We think this may explain the delayed responses to treatment sometimes seen in patients.

A Hypothesis: Homeostasis and Vertical Transmission



HCV with hepatocyte homeostasis and vertical transmission

$$\dot{T} = \hat{s} + r_T T \left(1 - \frac{T+I}{T_{\text{max}}}\right) - d_T T - (1-\eta)\beta V T + \hat{q} I \tag{2a}$$

$$\dot{I} = r_I I \left(1 - \frac{T+I}{T_{\text{max}}}\right) + (1-\eta)\beta V T - d_I I - \hat{q} I \tag{2b}$$

$$\dot{V} = (1-\epsilon) p I - c V, \tag{2c}$$

where

- T is the concentration of uninfected hepatocytes.
- I is the concentration of infected hepatocytes.
- V is the concentration of virus.

HCV Parameters

Parameters are uncertain and differ between patients, but we can get some ranges.

Symbol	Minimum	Maximum	Units
β	10^{-8}	10^{-6}	virus^{-1} ml day^{-1}
T_{max}	4×10^{6}	1.3×10^{7}	cells ml^{-1}
p	0.1	44	virus cell^{-1} day^{-1}
$\hat{s}$	1	1.82×10^{5}	cells ml^{-1} day^{-1}
$\hat{q}$	0	1	day^{-1}
c	0.8	22.2	day^{-1}
d_T	10^{-3}	1.4×10^{-2}	day^{-1}
d_I	10^{-2}	0.49	day^{-1}
r_T	2×10^{-3}	3.4	day^{-1}
r_I	Unknown	Unknown	day^{-1}

Removal of the fast virus time-scale

In numerical simulations, virus dynamics appear to be much faster than other dynamic processes. This suggests that viral dynamics can be decomposed into two time scales: a fast time scale where the number of infected hepatocytes, I, is relatively constant and

$$V(\hat{t}) \approx \frac{(1-\epsilon)p}{c} I(\hat{t}_0) + \left[V(\hat{t}_0) - \frac{(1-\epsilon)p}{c} I(\hat{t}_0) \right] e^{-c(\hat{t}-\hat{t}_0)}, \tag{3}$$

and a slow time scale where

$$V(\hat{t}) \approx \frac{(1-\epsilon)p}{c} I(\hat{t}). \tag{4}$$

A simplified model for dynamics without treatment

Under the quasi-steady state approximation, our model reduces to a dimensionless system. Data suggests that immigration and spontaneous clearance are slow, so on intermediate time scales, we can study

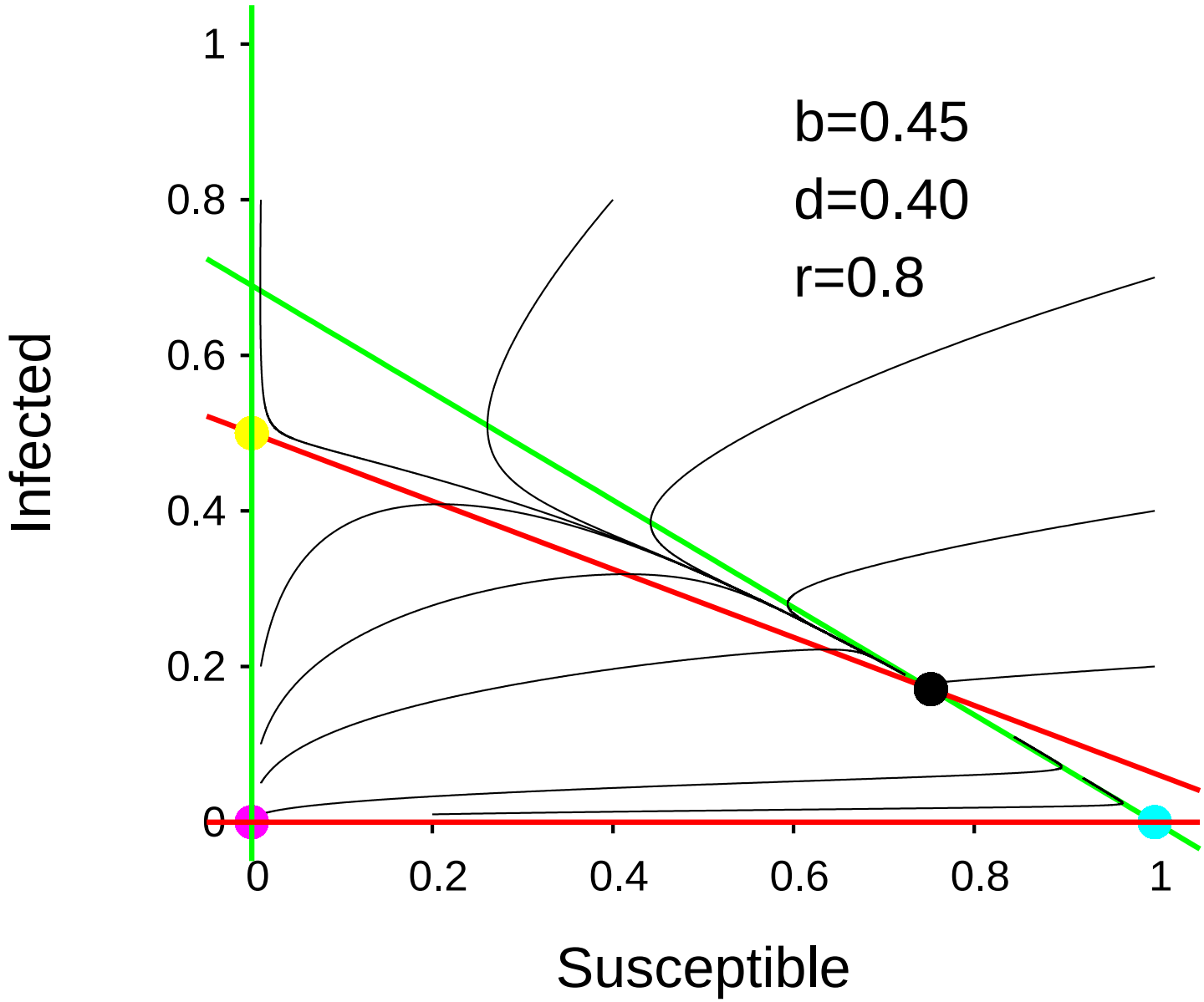
$$\dot{x} = x\,(1 - x - y) - byx, \tag{5a}$$

$$\dot{y} = ry\,(1 - x - y) + byx - dy. \tag{5b}$$

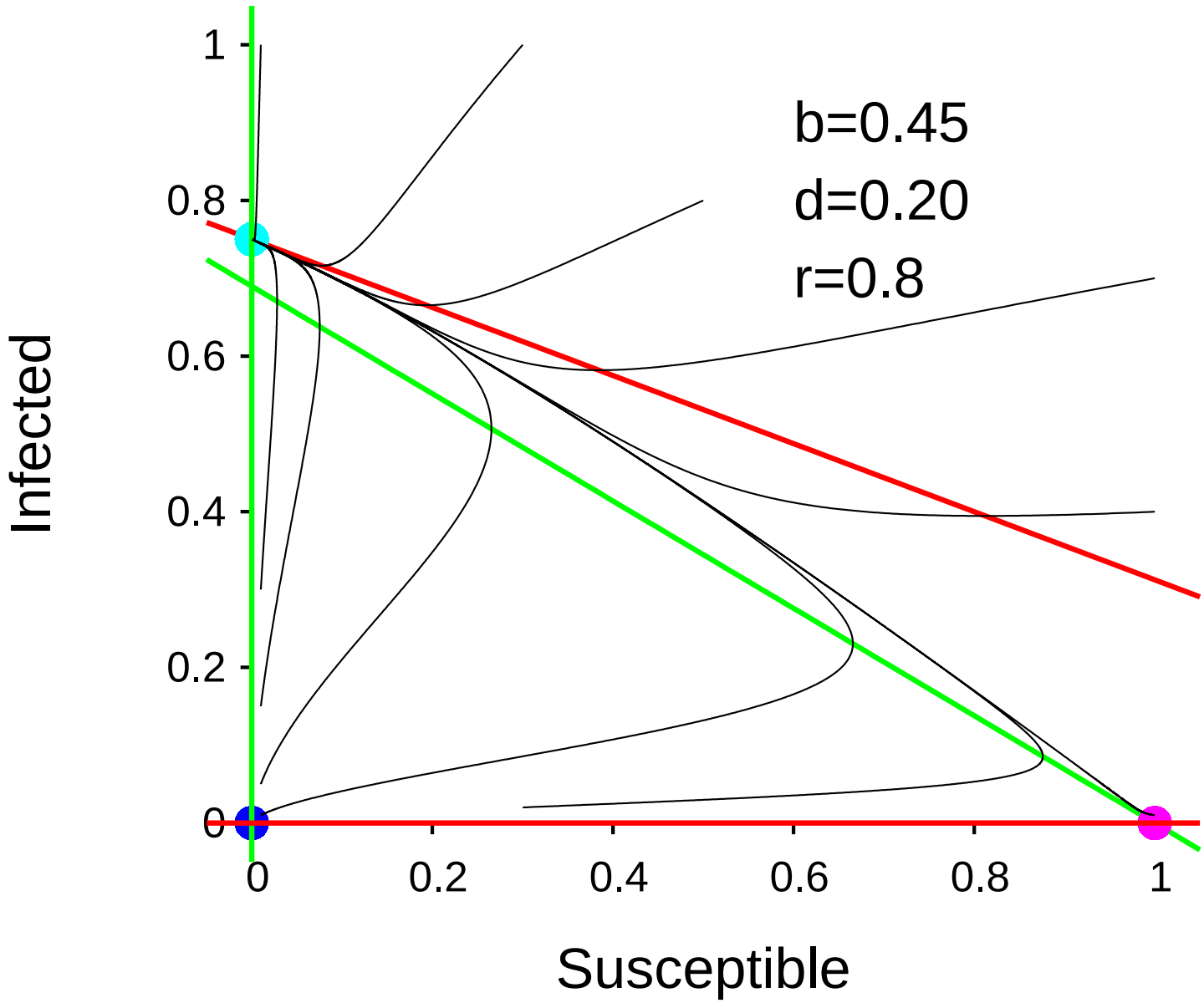
- b is the transmission rate
- d is the excess death of infected cells
- r is the relative homeostatic proliferation of infected cells.

Most of the parameter ranges are captured by allowing $b \in [10^{-2}, 10^{3}]$ and $d \in [10^{-3}, 10^{2}]$.

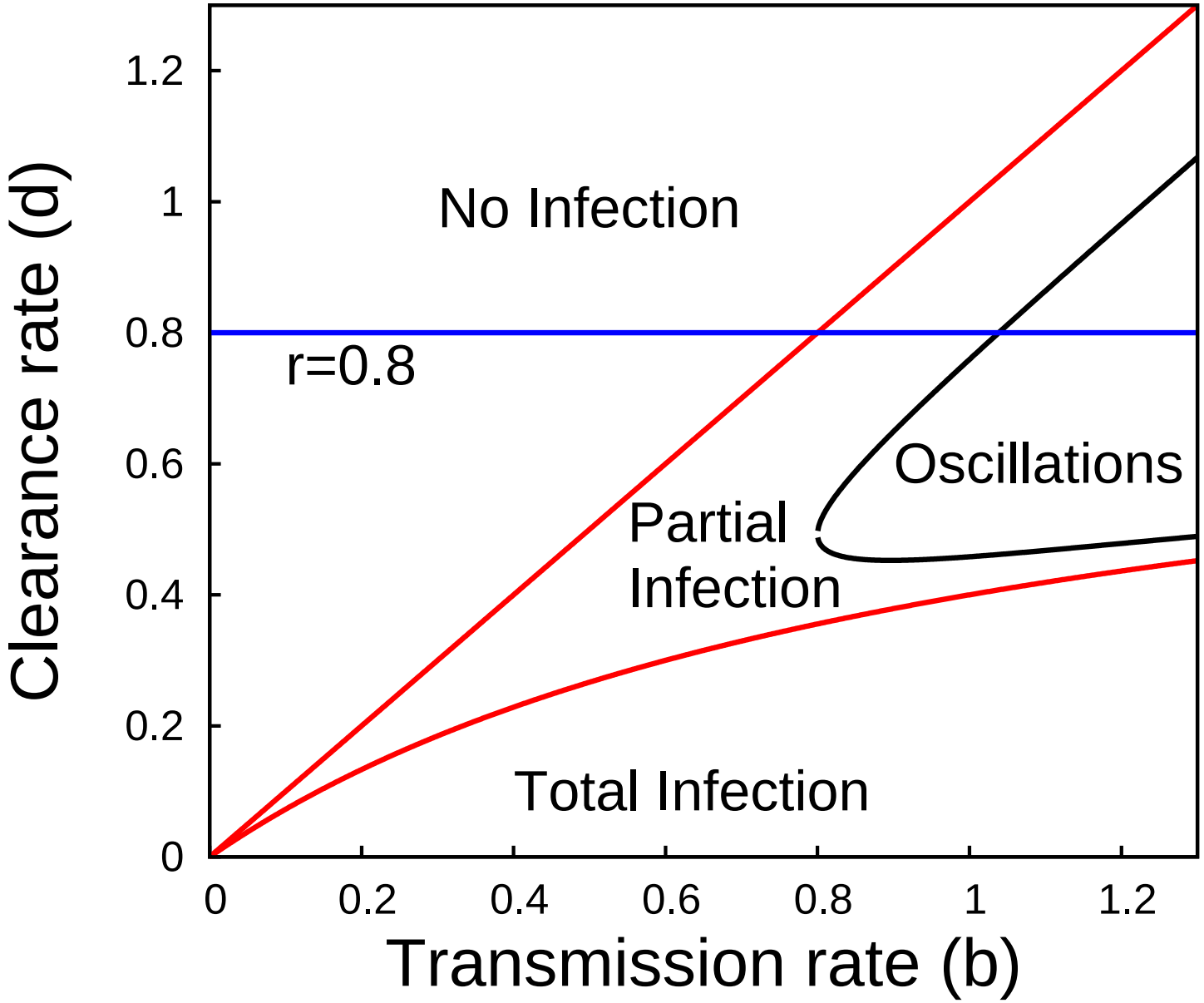
Phaseplane for an infected patient



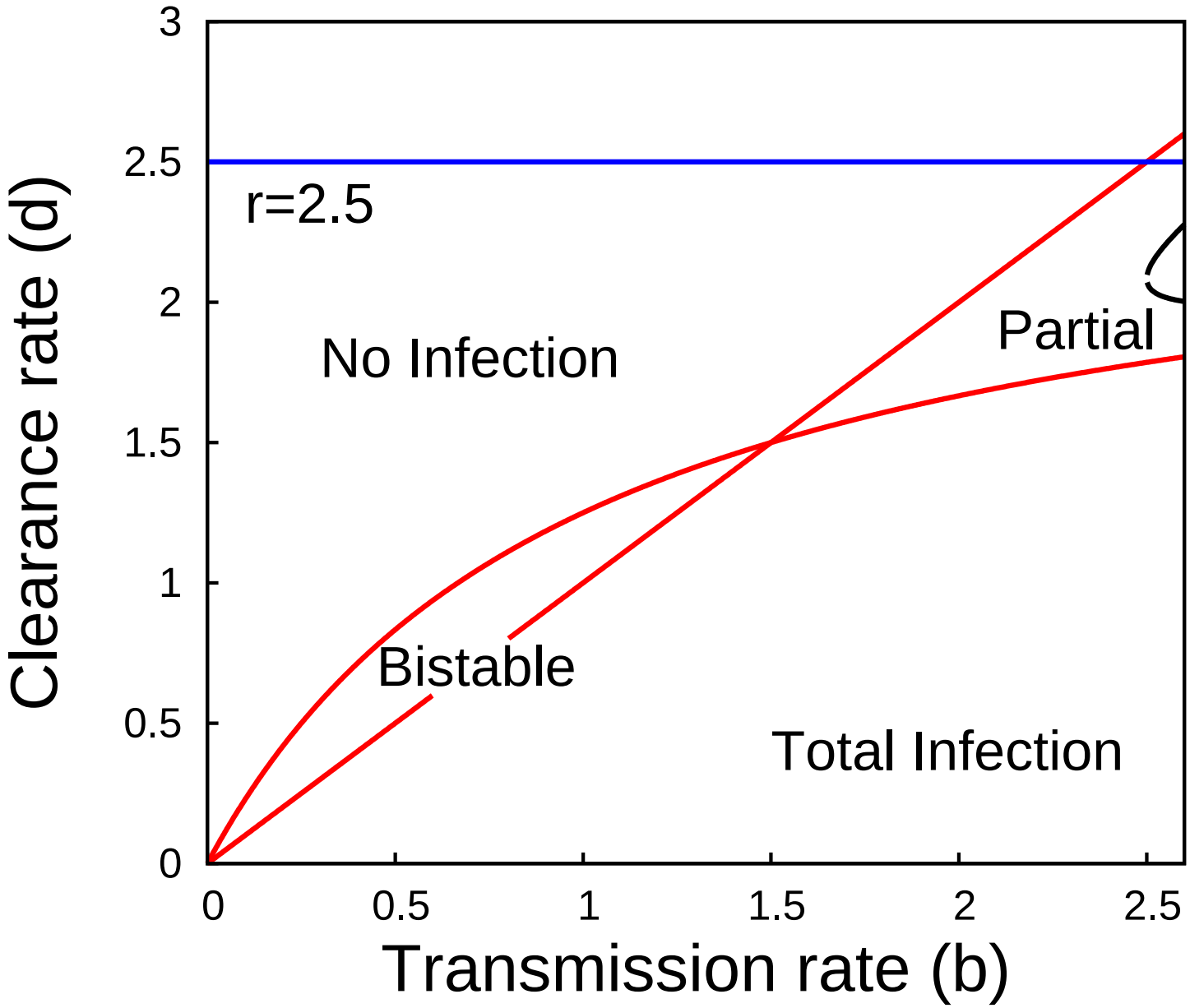
Strong proliferation of infected cells can lead to total infection of the hepatocyte population



Bifurcation structure from parameters



Proliferation of infected cells can create bistability



Immigration and cure

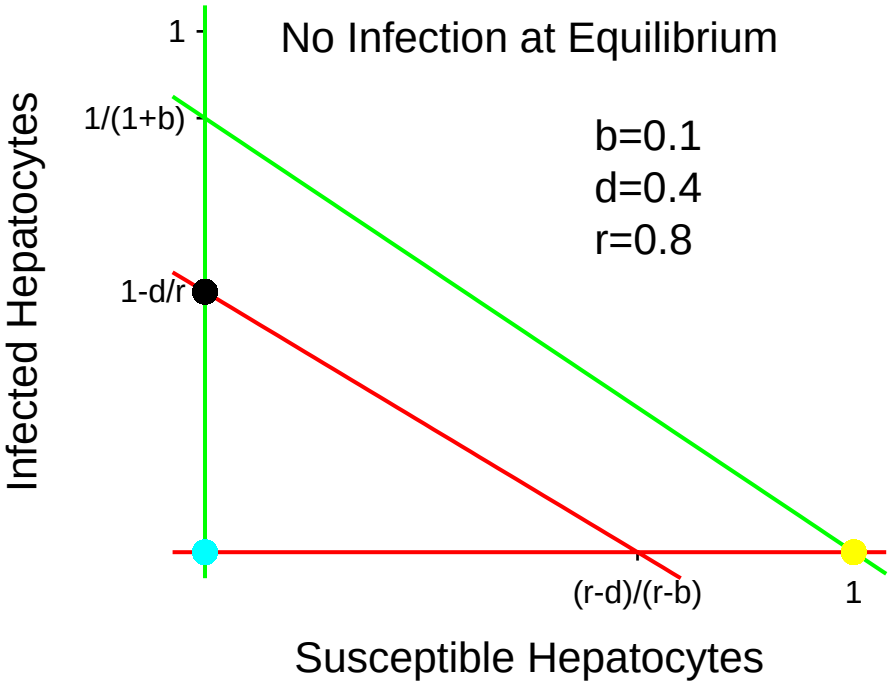
There is also evidence suggesting that infected hepatocytes may be cured of virus at a small rate, and that there is continuous immigration of uninfected hepatocytes. Adding these terms to our model,

$$\dot{x} = x\,(1 - x - y) - byx + qy + s, \tag{6a}$$

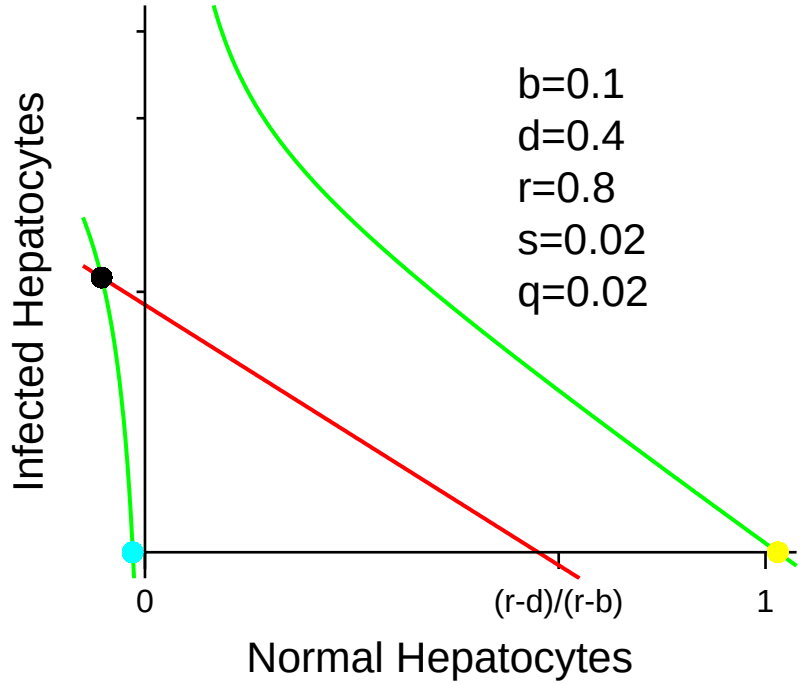
$$\dot{y} = ry\,(1 - x - y) + byx - dy - qy. \tag{6b}$$

- s is the immigration rate of uninfected cells
- q is the rate that infected cells are cured

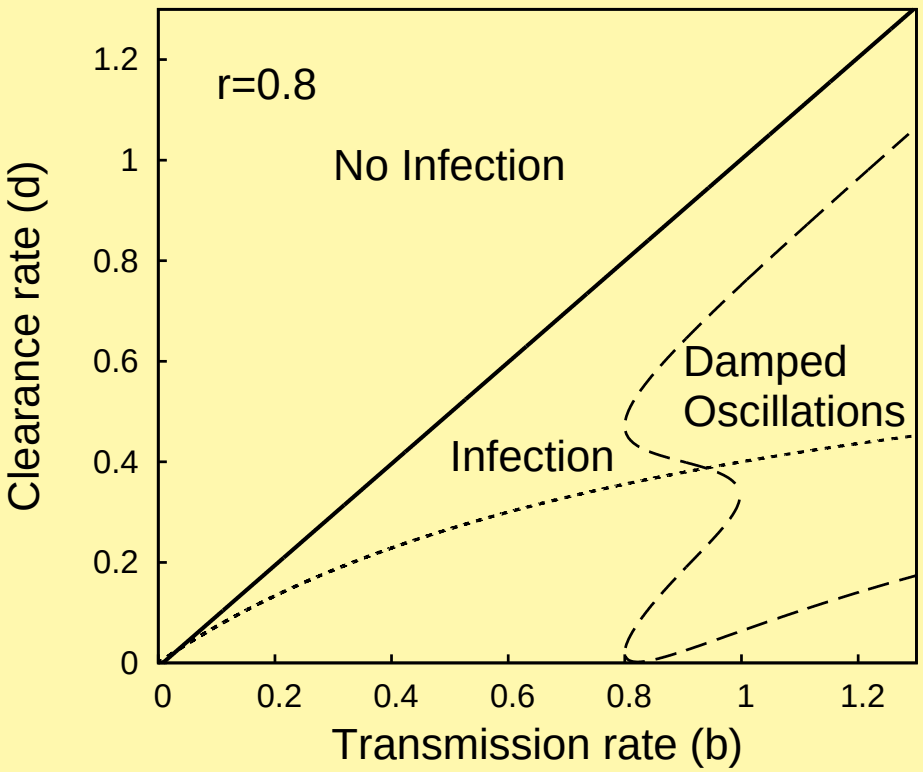
How do immigration or cure change things?

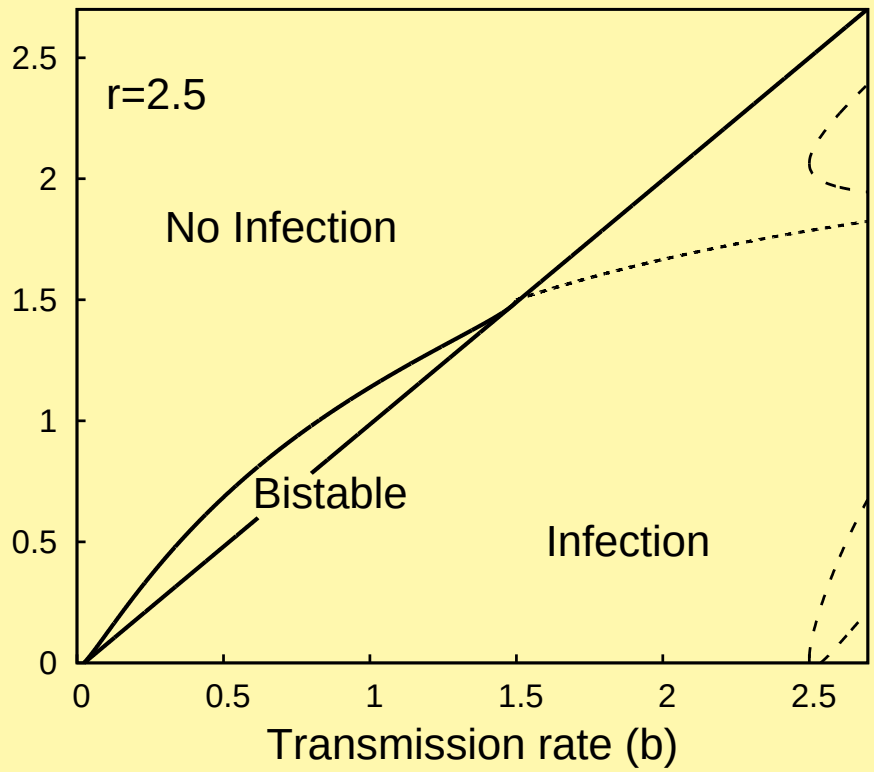


With immigration and cure



Bifurcations with immigration and cure of uninfected hepatocytes





Incorporating Treatment, Immigration, and Cell Cure

Treatment enters into the model by modifying the rates of transmission and virus production. In the standardized model,

$$\dot{x} = x\,(1 - x - y) - (1 - \theta)byx, \tag{7a}$$

$$\dot{y} = ry\,(1 - x - y) + (1 - \theta)byx - dy. \tag{7b}$$

where θ is the treatment efficacy.

With both immigration of uninfected hepatocytes and cure of infected hepatocytes,

$$\dot{x} = x\,(1 - x - y) - (1 - \theta)byx + qy + s, \tag{8a}$$

$$\dot{y} = ry\,(1 - x - y) + (1 - \theta)byx - dy - qy. \tag{8b}$$

Treatment Thresholds

When treatment is introduced, there are two threshold values for efficacy θ that can be used to understand the treatment response:

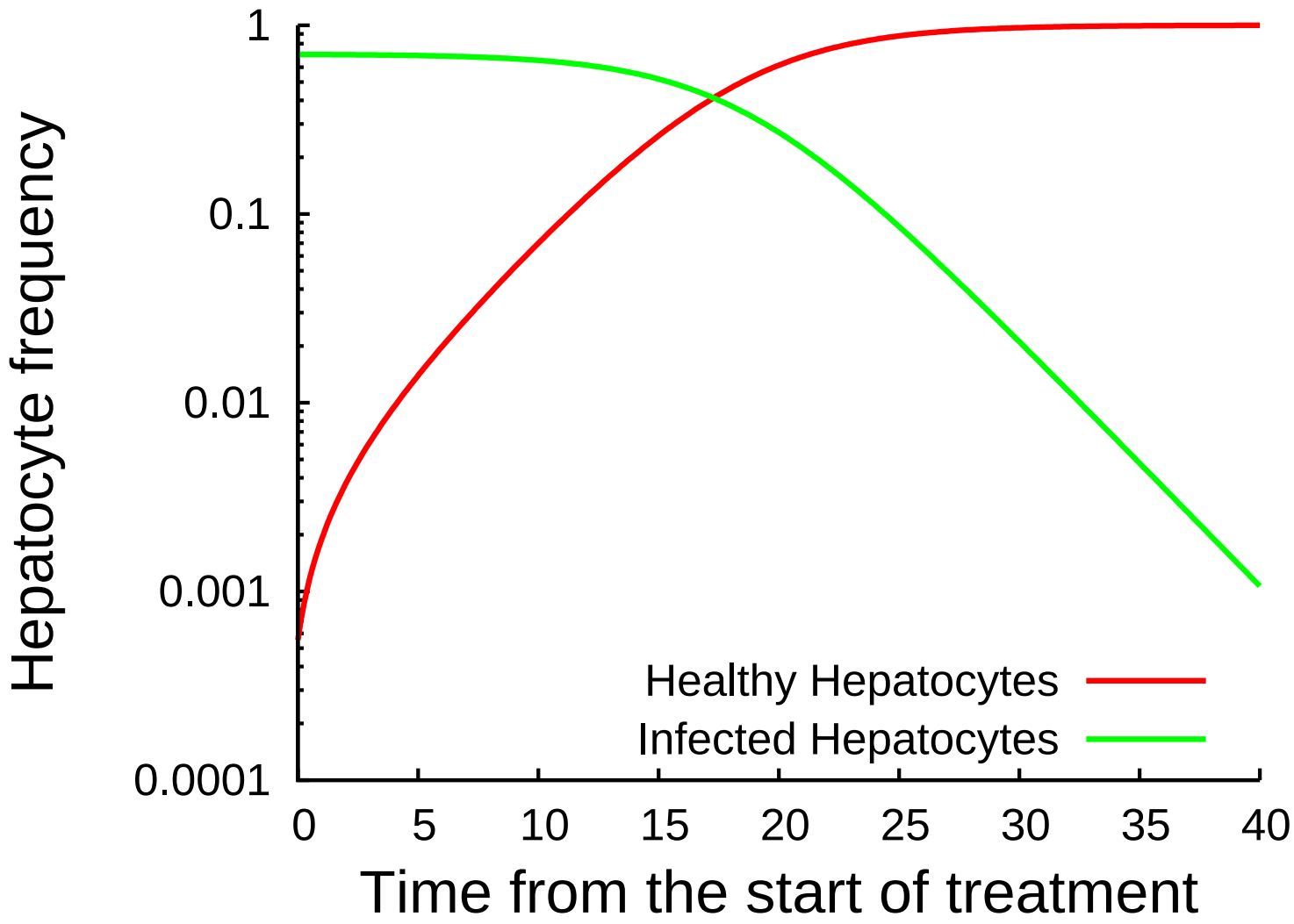
- Partial efficacy threshold needed to get a response in a patient -

$$\theta_p \approx \begin{cases} 0 & \text{if} \quad r < d + d/b. \\ 1 - \frac{d}{(r-d)b} & \text{if} \quad d + d/b < r < d + 1, \\ 1 - \frac{d+q+rs}{(1+s)b} & \text{if} \quad r > d + 1, \end{cases} \tag{9}$$

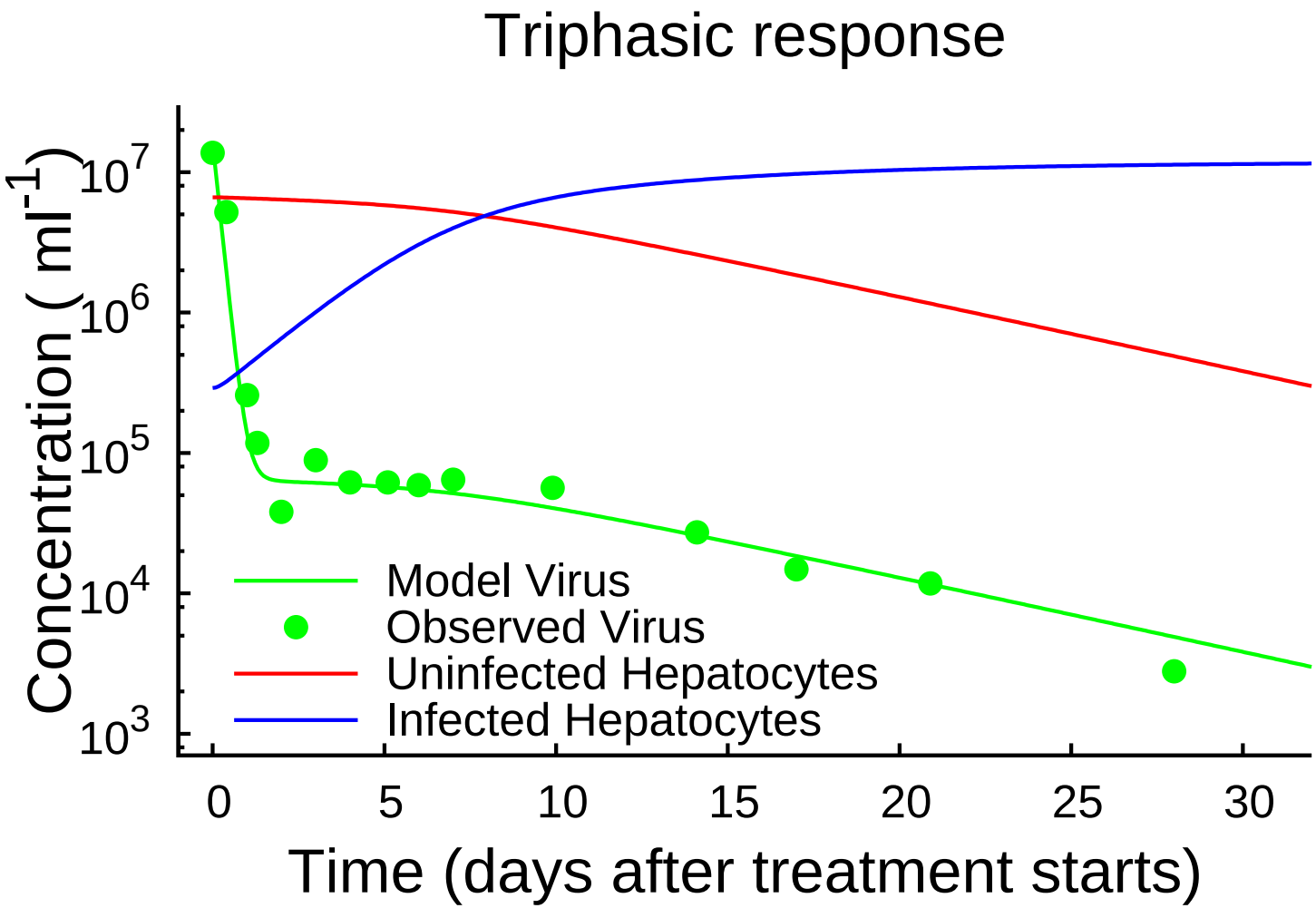
- Critical efficacy threshold to cure a patient -

$$\theta_c \approx \begin{cases} 1 - \frac{d+q+rs}{(1+s)b} & \text{if} \quad r < d + 1, \\ 1 - \frac{d}{(r-d)b} & \text{if} \quad r > d + 1. \end{cases} \tag{10}$$

Example of Treatment Delay in the Simplified Model



Fitted Time Series with Shoulder Phase



What controls the delay duration?

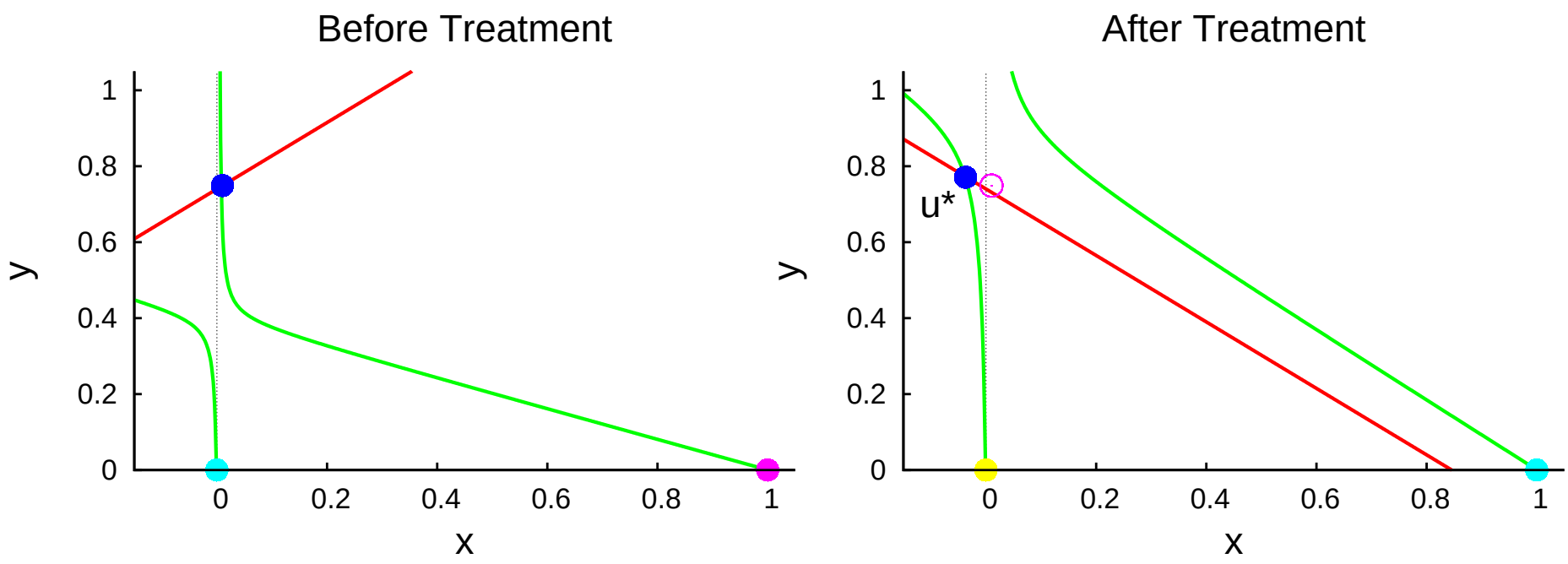
This model provides two hypotheses for why re-establishment of the healthy hepatocyte population following the start of treatment may be delayed.

- The healthy hepatocyte pool is initially small, and takes time to be restored.
- A bottleneck near the fold bifurcation can slow restoration of the healthy hepatocyte population.

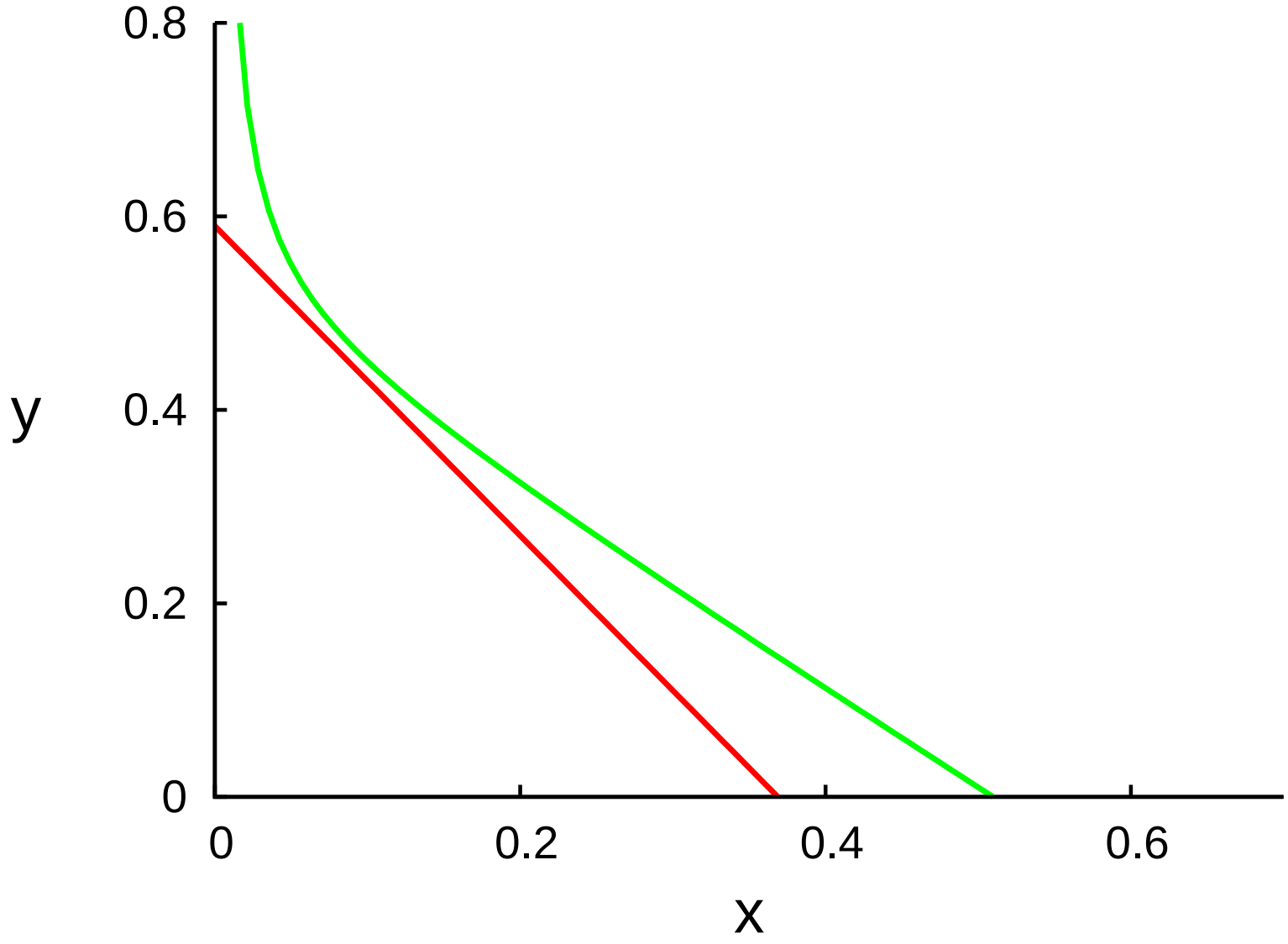
Both effects can appear in our model, although for different parameter values. The relative importance of these two mechanisms can have important consequences for treatment.

The effect of a small initial population

If almost all target hepatocytes are infected before treatment starts, then at the start of treatment, the healthy hepatocyte pool is initially very small and takes time to return to normal.



A nearby fold bifurcation can create a bottleneck with a slow transit time



A Toy Bottleneck Calculation

The normal form of a generic saddle-node bifurcation satisfies the first-order differential equation

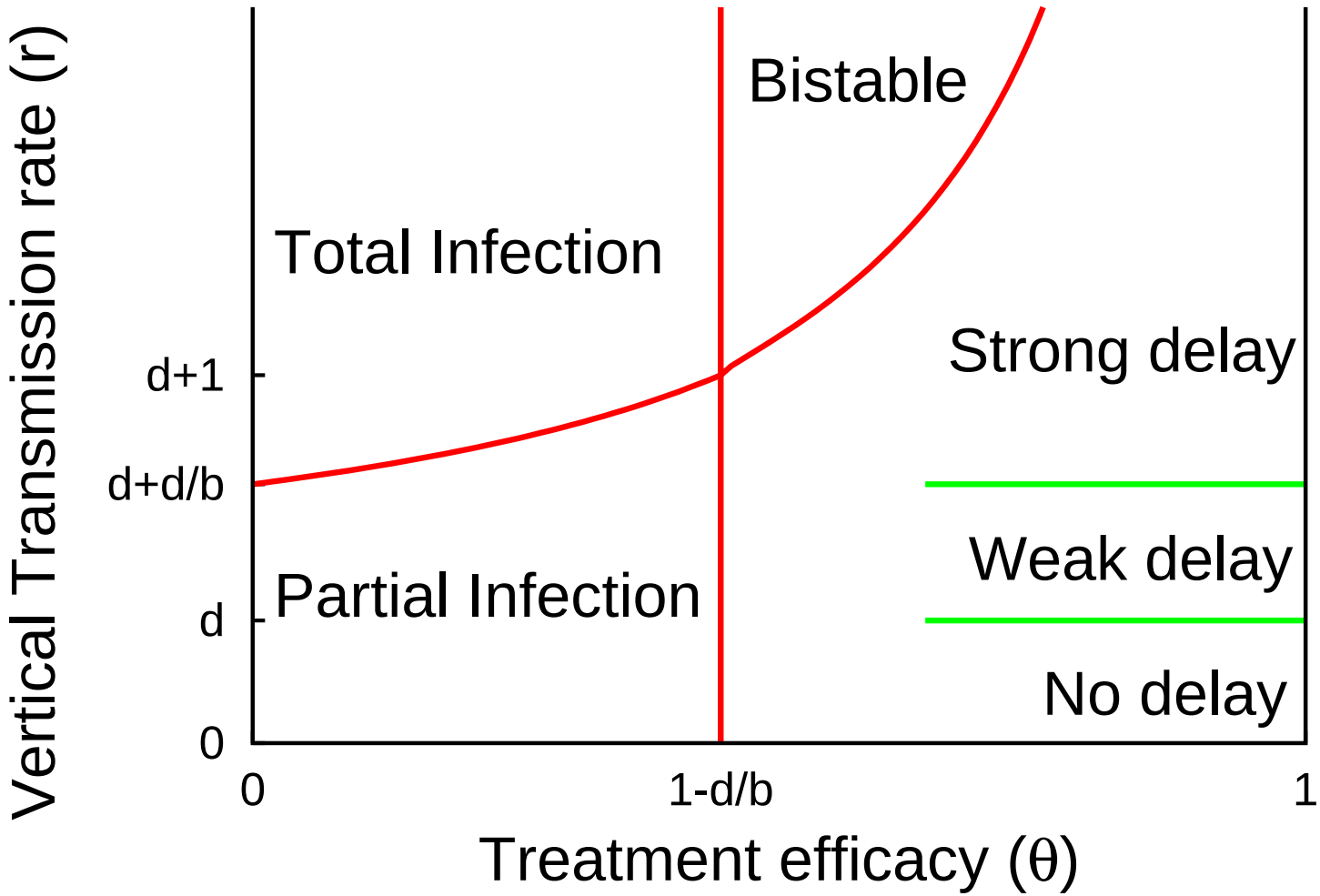
$$\dot{u} = a_0(r^* - r) + a_2 u^2, \quad \int_{-1}^{1} \frac{\mathrm{d}u}{a_0(r^* - r) + a_2 u^2} = t_d.$$

The transit-time across the bottle-neck scales according to

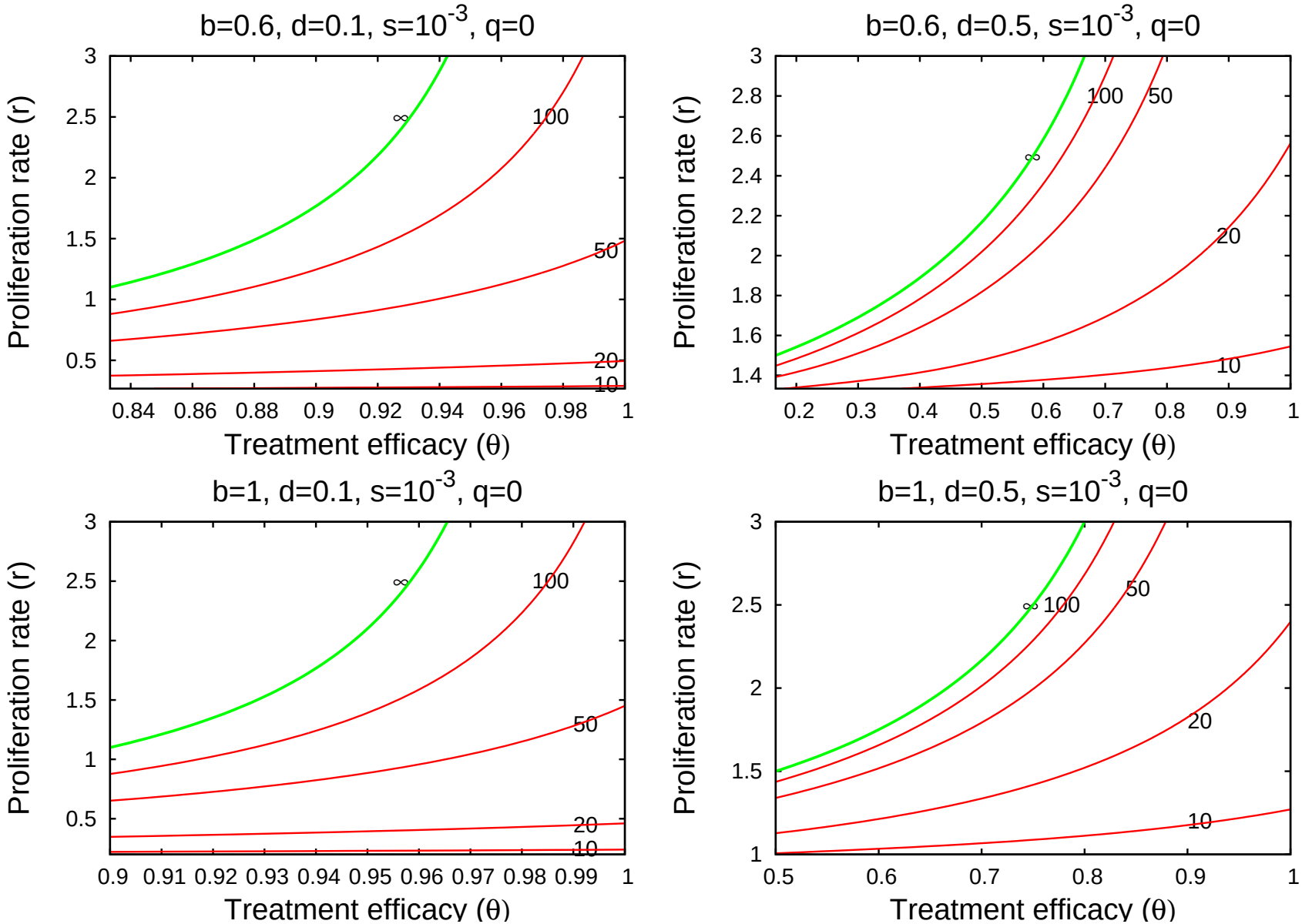
$$t_d \sim \frac{\pi}{\sqrt{a_0 a_2 (r^* - r)}}.$$

As r is increased toward r^*, the time becomes longer. If $r > r^*$, the time is infinite because solutions are trapped by an intermediate attracting state.

Bifurcations and Delayed Responses



Contour Plot of Delay durations



Recent Advances

- New drugs -- direct-acting antiviral agents targetting NS3 protease and RNA-dependent NS5B polymerase. Telaprevir, for instance, is a potent protease blocker.

- Genome wide association studies (GWAS) have discovered a SNP near the IL28B gene encoding interferon λ-3 is associated with 3x greater likelihood of HCV clearance.

Conclusions

- Homeostatic proliferation of infected hepatocytes and the associated vertical transmission can, in theory, explain delay seen in treatment response data.
- Large shocks may help some patients who do clear automatically.
- Experiments are needed to test the hypothesis.
- Alternative hypotheses would also be useful.

Acknowledgements

- Harel Dahari and Alan Perelson
- Published in SIAM Journal of Applied Mathematics, 2009

References

A. U. Neumann, N. P. Lam, H. Dahari, D. R. Gretch, T. E. Wiley, T. J. Layden, and A. S. Perelson. Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-alpha therapy. *Science*, 282(5386):103--107, 1998.