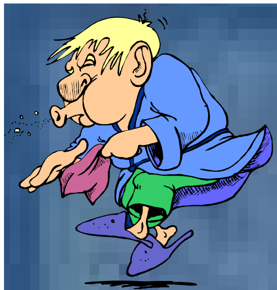
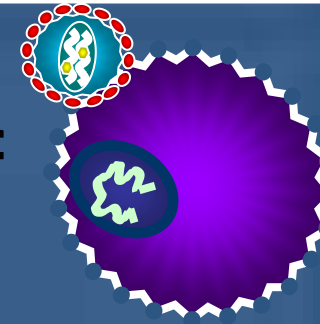
Influence of backward bifurcation in HBV or HCV infection.

Jane Heffernan
York University
Work with Redouane Qesmi and Jianhong Wu



Mathematical Modelling of Infectious Diseases



- Epidemiology
  - Spread of disease in a population
- Immunology
  - Spread of an infection in a host

HIV

Measles

Hepatitis B, C

Influenza

Herpes

Hepatitis

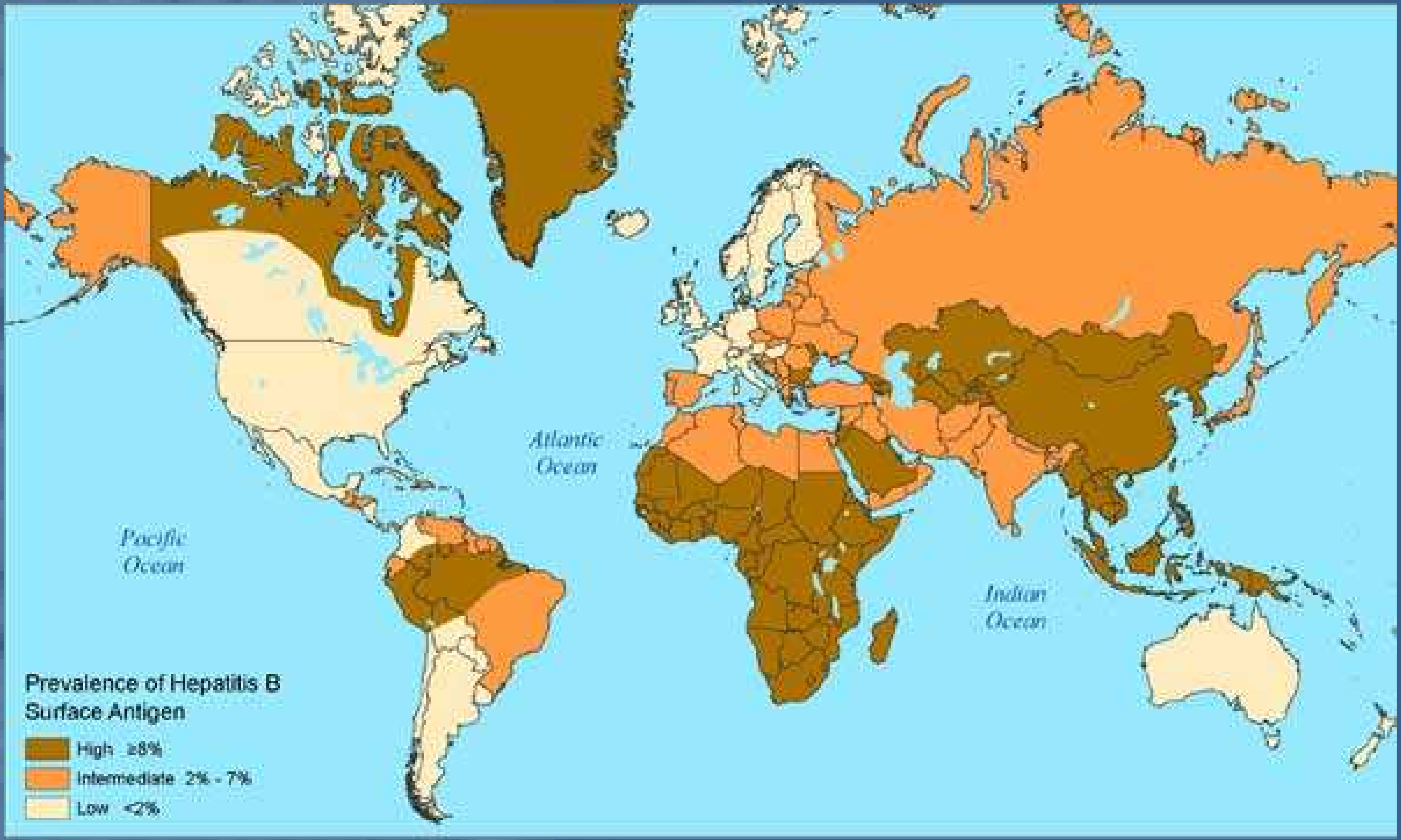
- Hepatitis refers to inflammation of the liver
- Can be caused by alcohol, certain medications and chemical, or by viral infection
- Hepatitis B virus and Hepatitis C virus are two such pathogens

Normal Liver, Fatty Liver, and Cirrhosis

Hepatitis B Virus

- DNA virus that infects liver cells and leads to acute or chronic infection.
- Acute disease for approx 1 year
  - Experience severe symptoms for up to a year, including jaundice, extreme fatigue, nausea, vomiting and abdominal pain.
- Chronic infection leads to cirrhosis or hepatocellular carcinoma.
  - About 25% of chronic carriers die from liver cancer induced by the virus.
  - 350 million of chronic HBV infections worldwide

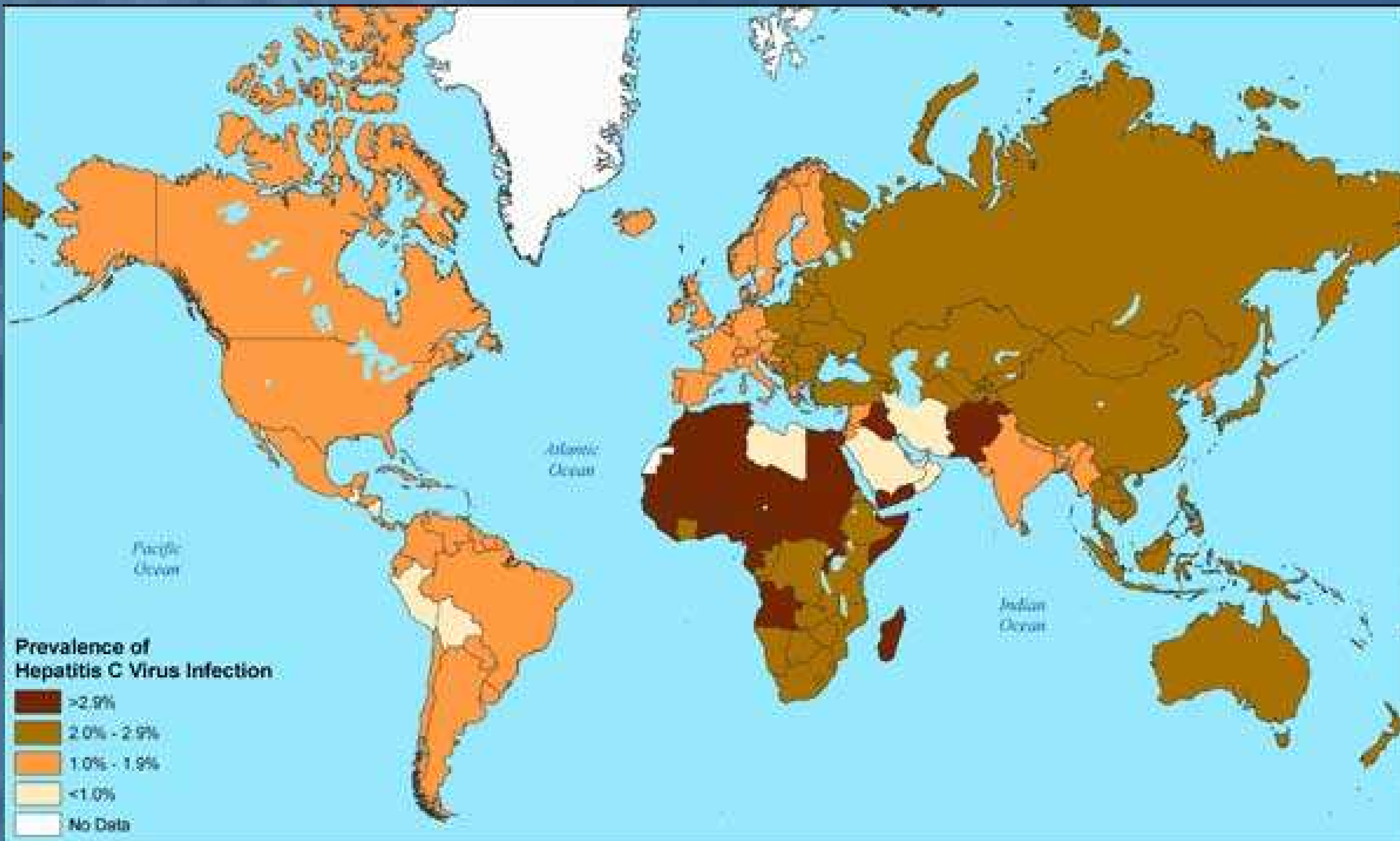
Hepatitis B Virus



Hepatitis C Virus

- RNA virus that infects liver cells and leads to acute or chronic infection.
- Acute disease for approx 6 months
  - May experience symptoms including decreased appetite, fatique, abdominal pain, jaundice, itching and flu-like symptoms.
- Chronic infection leads to cirrhosis or hepatocellular carcinoma.
  - One third of chronic carriers develop cirrhosis of the liver.
  - 170 million of chronic HCV infections worldwide.

Hepatitis C Virus



Treatment

- Drug therapy
  - HCV – Peginterferon ACRibavirin
  - HBV – lamivudine and entecavir
  - Ineffective in eliminating the virus

- Liver transplantation
  - Thought that this would cure patients since liver is primary source of infection
  - New liver is reinfected
    - Rapidly progressing

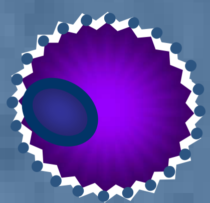
Standard of care

- The current standard of care (SOC) for HCV involves 48–72 weeks of treatment with pegylated interferon and ribavirin.
- Approximately 40–60% of the patients treated with SOC achieve a sustained viral response (SVR) after this treatment.

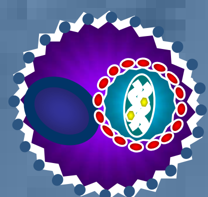
Compartments of infection

- The fact that reinfection of the liver after transplantation occurs, suggests that virus is present in other reservoirs
- The virus can be circulating in the blood which ultimately reinfects the liver if drug therapies cannot clear it
- We build on the basic model of in-host dynamics to include a second compartment of infection

Basic Model



$$\frac{dx}{dt} = \lambda - d_x x - \beta x v$$



$$\frac{dy}{dt} = \beta x v - d_y y$$

$$\frac{dv}{dt} = k y - d_v v$$

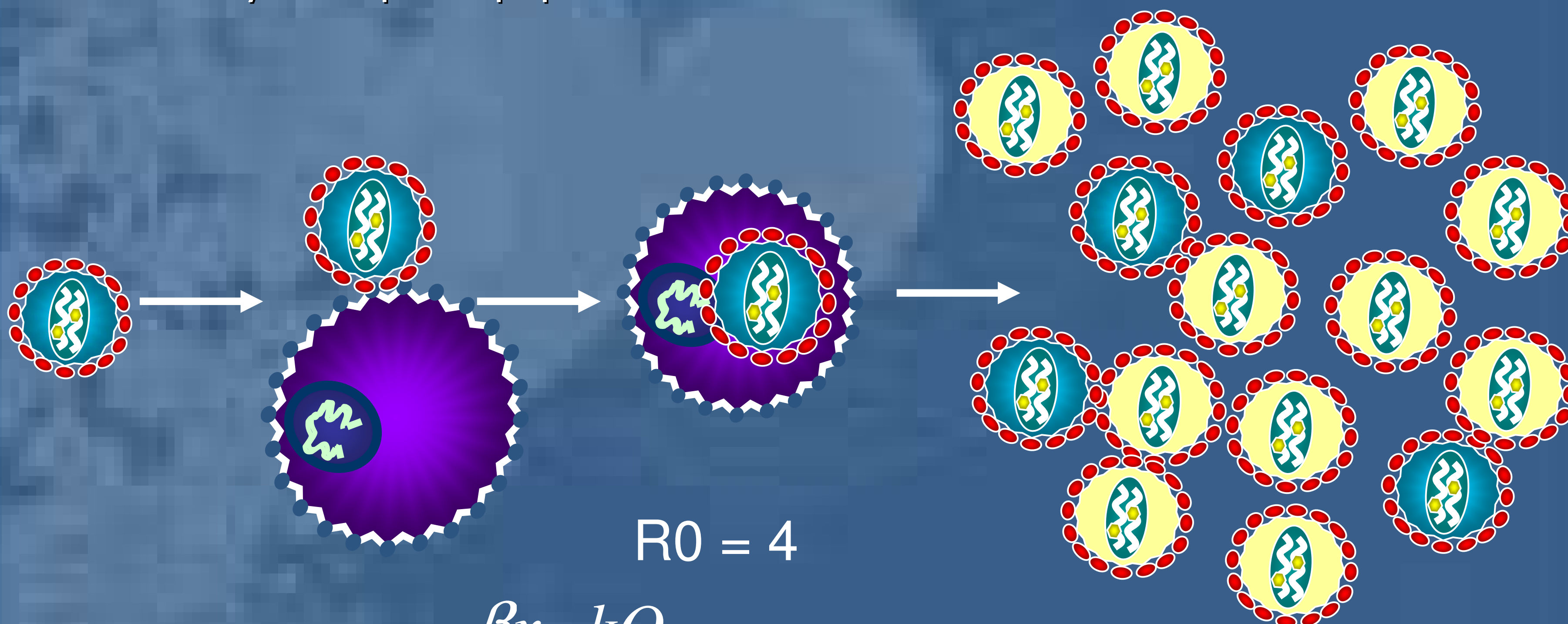
- x - uninfected cells
- y - infected cells
- v - free virus

- λ, k - production rate
- β - efficacy of infection
- d_x, d_y, d_v - death rates/ clearance time

Nowak, M.A. and R.M. May, Virus Dynamics

In-host Model

- Basic reproductive ratio
  - The number of secondary infections produced by an initial infective in a totally susceptible population



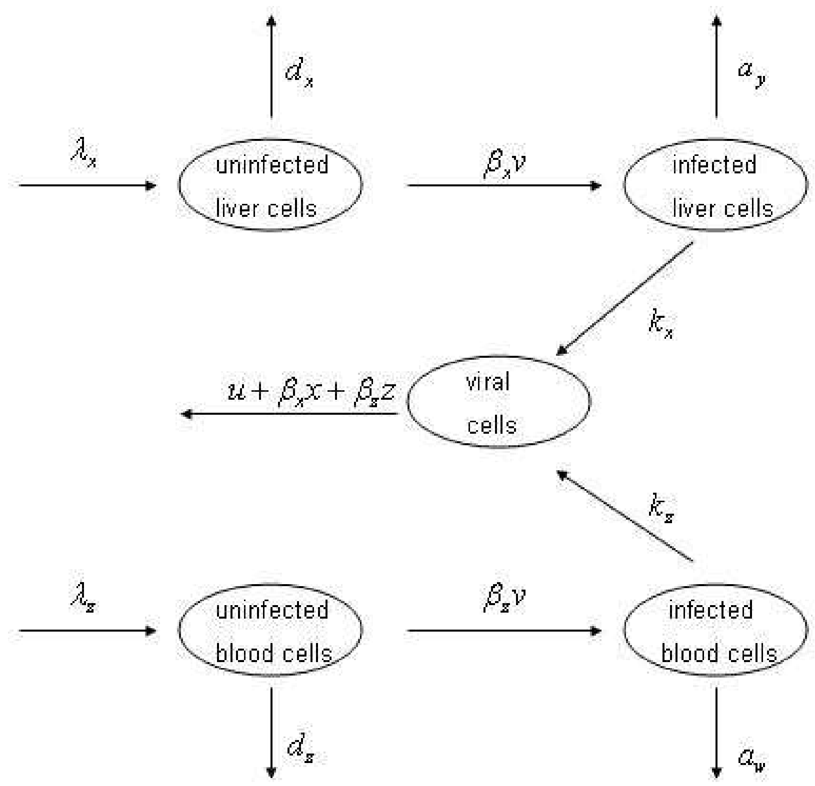
$$R_0 = \frac{\beta x_0}{u}\frac{kQ}{d_y}$$

Basic Model

- Model doesn't show persistence of virus after transplantation, but virus does persist
- We add another compartment of infection
  - Blood
    - Peripheral blood mononuclear cells and various organs likely contribute to the high rate of re-infection

Hepatitis B/C

- Model



Qesmi, Wu, Wu, Heffernan, Math Biosci, 224, 118-125

Hepatitis B/C

- Liver-blood-virus model

$$\frac{dx}{dt} = \lambda_x - \beta_x xv - d_x x$$

$$\frac{dy}{dt} = \beta_x xv - a_y y$$

$$\frac{dv}{dt} = k_x y + k_z w - uv - \beta_x xv - \beta_z zv$$

$$\frac{dz}{dt} = \lambda_z - \beta_z zv - d_z z$$

$$\frac{dw}{dt} = \beta_z zv - a_w w$$

Qesmi, Wu, Wu, Heffernan, Math Biosci, 224, 118-125

Hepatitis B/C

$$R_0 = \frac{k_x}{a_y}\frac{\beta_x \bar{x}_0}{\beta_x \bar{x}_0 + \beta_z \bar{z}_0 + u} + \frac{k_z}{a_w}\frac{\beta_z \bar{z}_0}{\beta_x \bar{x}_0 + \beta_z \bar{z}_0 + u}$$

- Find disease-free and endemic equilibria
- Stability does not only depend on R0

Qesmi, Wu, Wu, Heffernan, Math Biosci, 224, 118-125

Hepatitis B/C

- Liver-blood-virus model
  - Uninfected and infected equilibrium

x	$\dfrac{\lambda_x}{d_x}$	$\dfrac{\lambda_x}{\beta_x \bar{v} + d_x}$
y	0	$\dfrac{\beta_x \lambda_x \bar{v}}{(\beta_x \bar{v} + d_x) a_y}$
v	0	$\bar{v}$
z	$\dfrac{\lambda_z}{d_z}$	$\dfrac{\lambda_z}{\beta_z \bar{v} + d_z}$
w	0	$\dfrac{\beta_z \lambda_z \bar{v}}{(\beta_z \bar{v} + d_z) a_w}$

Qesmi, Wu, Wu, Heffernan, Math Biosci, 224, 118-125

Hepatitis B/C

- Infected equilibrium

$$A\bar{v}^2 + B\bar{v} + C = 0$$

$$A = u\beta_x\beta_z$$

$$B = ud_z\beta_x + ud_x\beta_z + \lambda_x\beta_x\beta_z\left(1-\frac{k_x}{a_y}\right) + \lambda_z\beta_x\beta_z\left(1-\frac{k_z}{a_w}\right)$$

$$C = ud_xd_z + \lambda_x\beta_xd_z\left(1-\frac{k_x}{a_y}\right) + \lambda_z\beta_zd_x\left(1-\frac{k_z}{a_w}\right)$$

- C<0 is equivalent to R0>1

Qesmi, Wu, Wu, Heffernan, Math Biosci, 224, 118-125

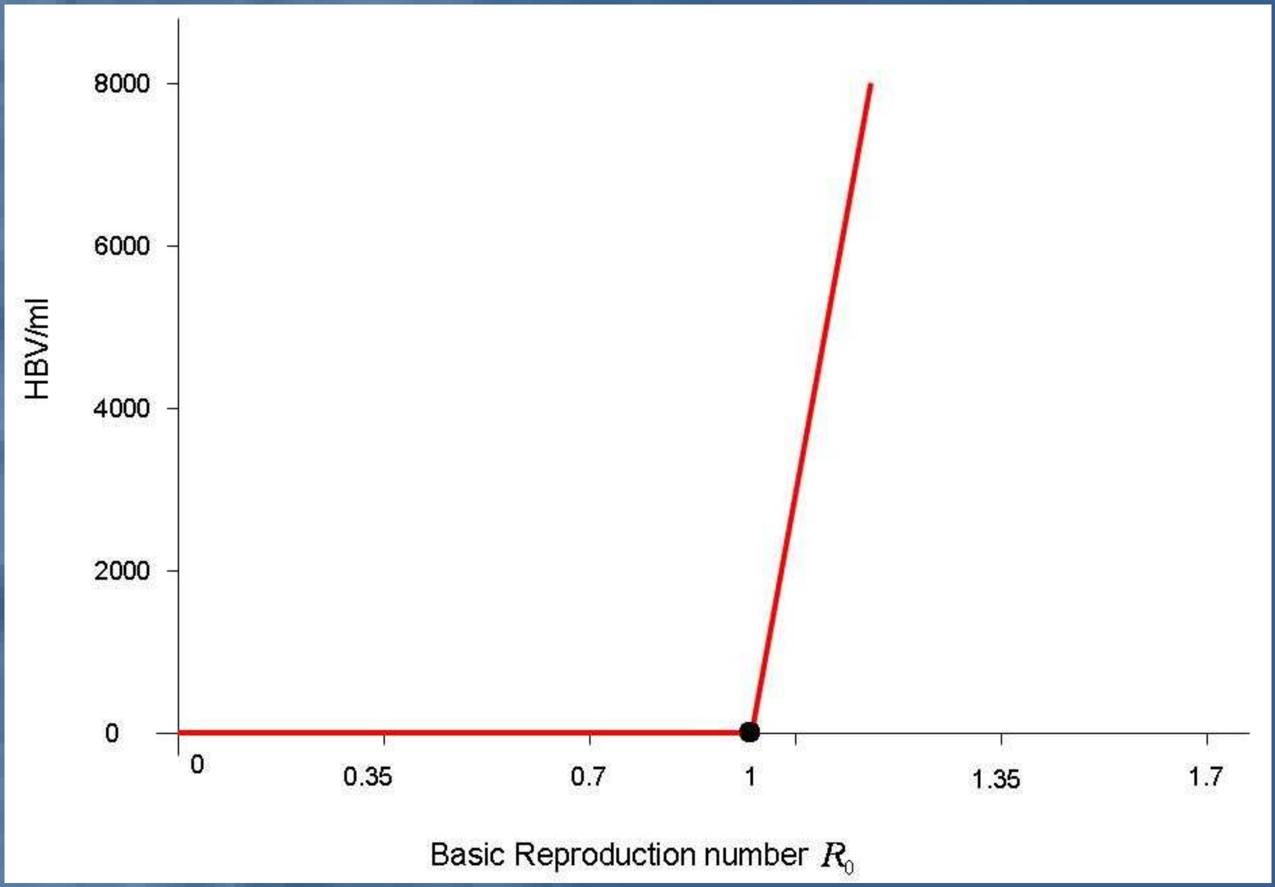
Hepatitis B/C

- Theorem
  i. A unique endemic equilibrium if $C<0$ ($R0>1$)
  ii. A unique endemic equilibrium if $B<0$ and $C=0$ or $B^2-4AC=0$
  iii. Two endemic equilibria if $C>0$, $B<0$ and $B^2-4AC>0$
  iv. No endemic equilibrium otherwise

Qesmi, Wu, Wu, Heffernan, Math Biosci, 224, 118-125

Hepatitis B/C

- Transcritical bifurcation $(k_z - a_w)(k_x - a_y) > 0$



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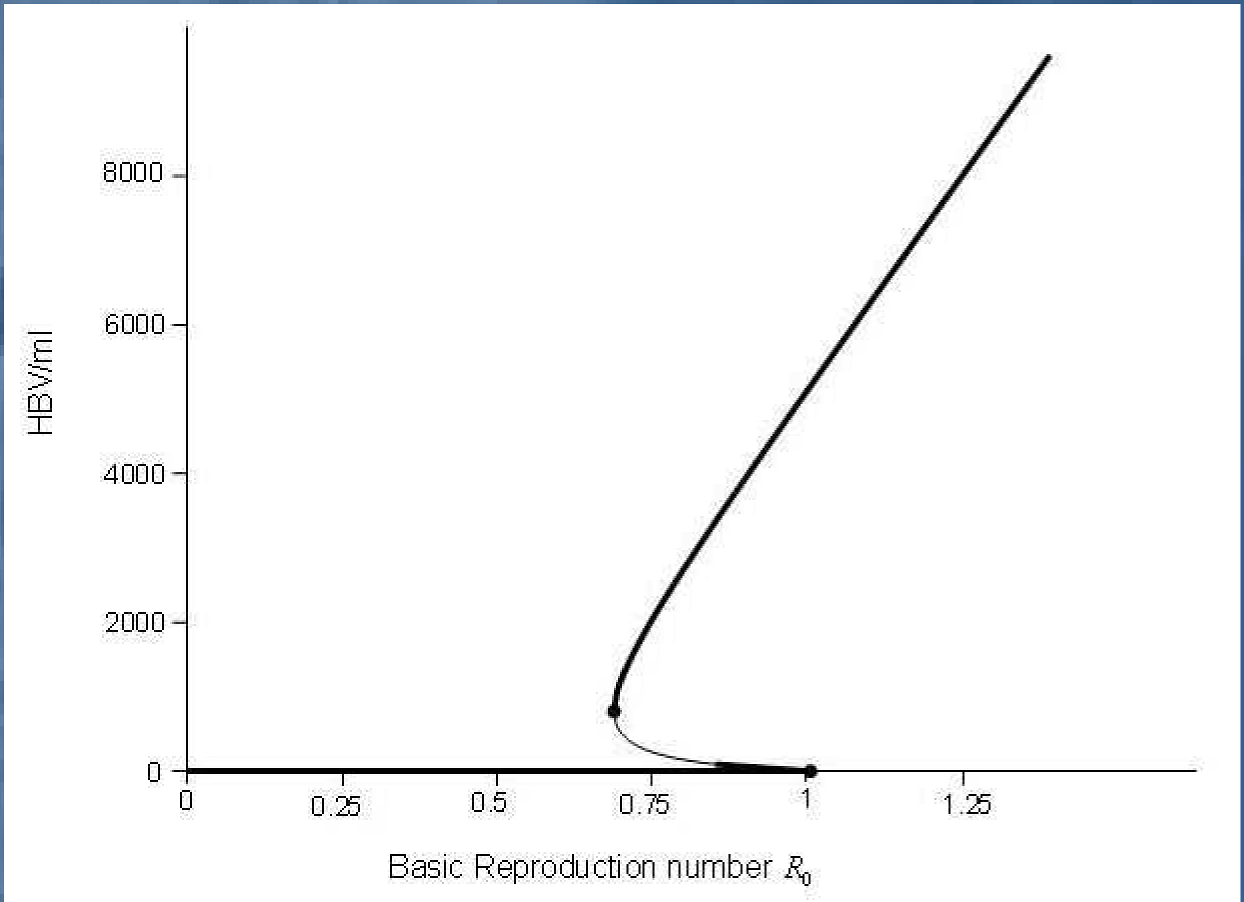
Hepatitis B/C

- Backward bifurcation

$$(k_z - a_w)(k_x - a_y) < 0$$



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Hepatitis B/C

- Change model assumptions to closer reflect the biology of the system
- $k(a)$
  - The proliferation rate of the virus depends on the age of infection, starts low and ramps up to a maximum production rate
- $\delta(a)$
  - The mortality rate of an infected cell depends on its age

Hepatitis B/C

$$
\begin{aligned}
\frac{dx}{dt} &= \lambda_x - \beta_x x v - d_x x \\
\frac{dy}{dt} + \frac{dy}{da} &= -\delta_y(a) y(a,t) \\
\frac{dv}{dt} &= \int_0^\infty k_y(a) y(a,t)\,da + \int_0^\infty k_w(a) w(a,t)\,da - uv - \beta_x x v - \beta_z z v \\
\frac{dz}{dt} &= \lambda_z - \beta_z z v - d_z z \\
\frac{dw}{dt} + \frac{dw}{da} &= -\delta_w(a) w(a,t)
\end{aligned}
$$

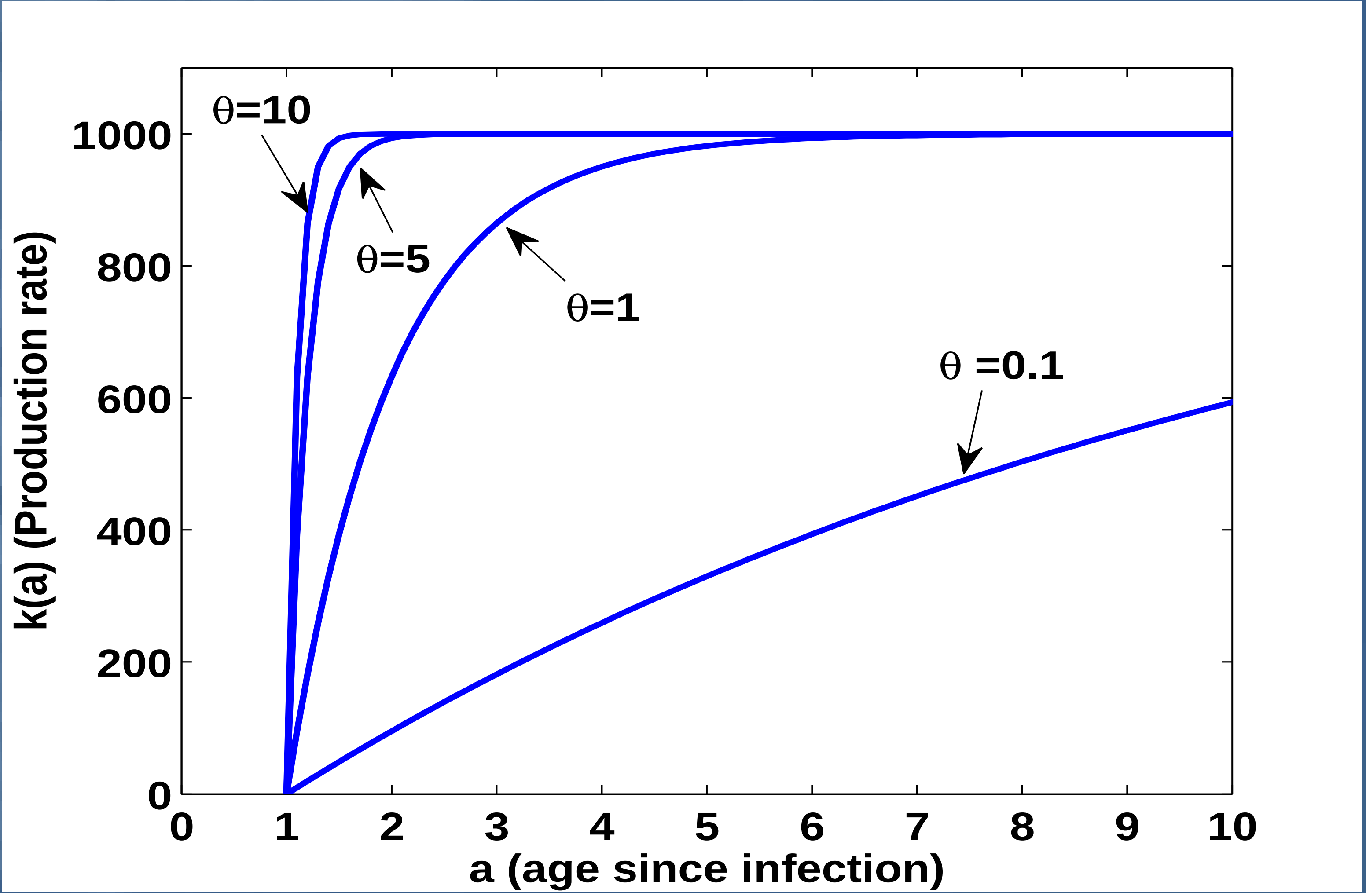
$$
y(0,t) = \beta_x x(t) v(t) \qquad w(0,t) = \beta_z z(t) v(t)
$$

$$
y(a,0) = 0 \qquad w(a,0) = 0
$$

Qesmi, El-Saddany, Heffernan, Wu, submitted

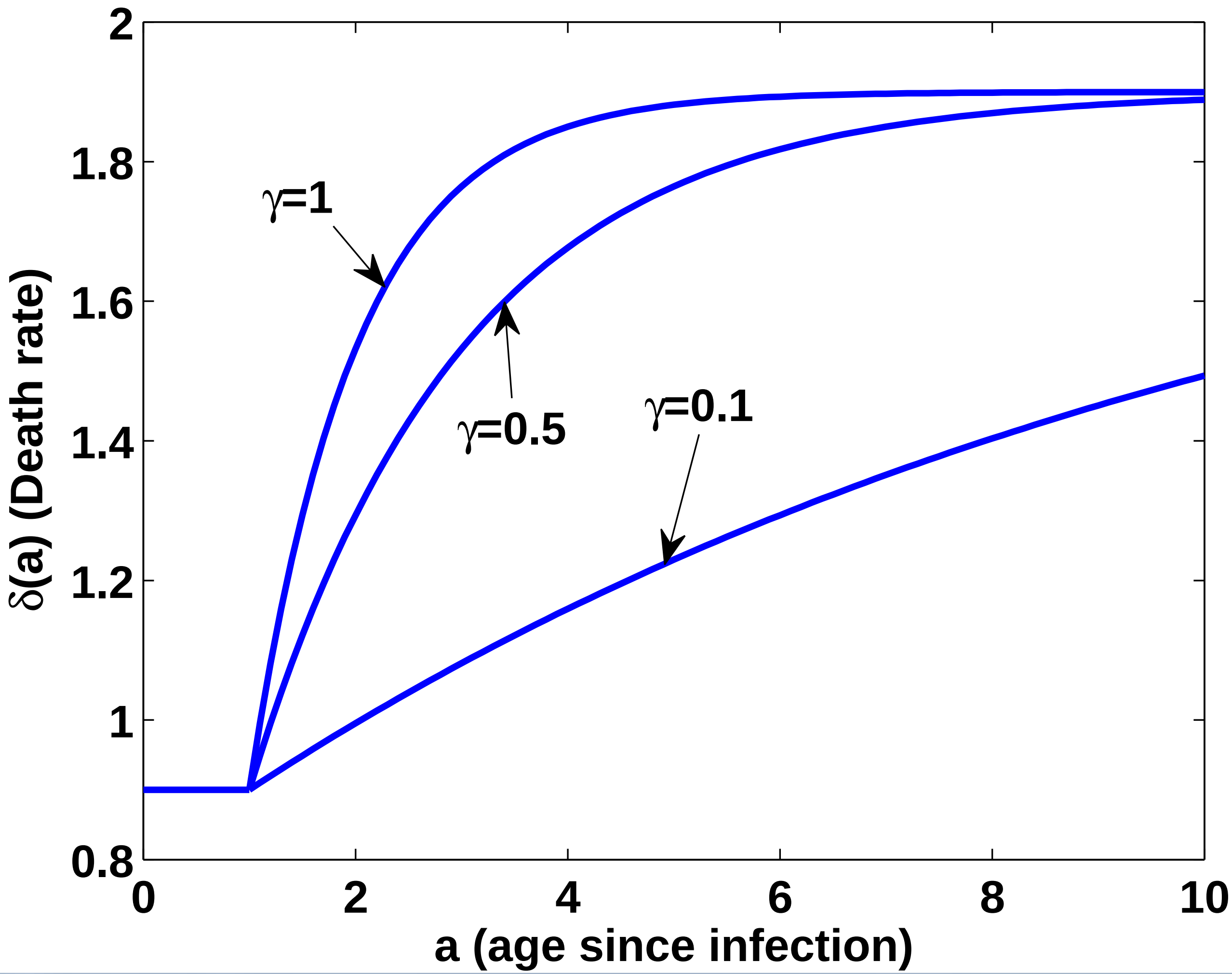
Production rate

$$k(a) = k_{\max}(1 - e^{-\theta(a-a_1)}), \quad a \geq a_1 \text{ and } 0 \text{ else}$$



Death rate

$$\delta(a) = \delta_0 \text{ if } a < a_2 \text{ and } \delta_0 + \delta_m(1 - e^{-\gamma(a - a_2)}) \text{ if } a \geq a_2$$



Hepatitis B/C

$$R_0 = N_y \frac{\beta_x \bar{x}}{\beta_x \bar{x} + \beta_z \bar{z} + u} + N_w \frac{\beta_z \bar{z}}{\beta_x \bar{x} + \beta_z \bar{z} + u}$$

- where

$$N_y = \int_0^\infty k_y(a) e^{-\int_0^a \delta_y(s)ds} da$$

$$N_w = \int_0^\infty k_w(a) e^{-\int_0^a \delta_w(s)ds} da$$

Qesmi, elSaadany, Heffernan, Wu, submitted

Hepatitis B/C

$$\frac{dx}{dt} = \lambda_x - \beta_x x v - d_x x$$

$$\frac{dz}{dt} = \lambda_z - \beta_z z v - d_z z$$

$$\frac{dv}{dt} = \beta_x \int_0^\infty k_y(a)\sigma_y(a)v(t-a)x(t-a)da + \beta_z \int_0^\infty k_w(a)\sigma_w(a)v(t-a)z(t-a)da$$

$$-uv - \beta_x x v - \beta_z z v$$

$$\sigma_y(a) = e^{-\int_0^a \delta_y(s)ds}$$

$$\sigma_w(a) = e^{-\int_0^a \delta_w(s)ds}$$

Qesmi, El-Saddany, Heffernan, Wu, submitted

Hepatitis B/C

- If R0 < 1 then the DFE is locally asymptotically stable

- If R0 > 1 then the DFE is unstable

- If R0 ≤ 1 and (Ny – 1) (Nw – 1) ≥ 0 then the DFE of the system is GAS.

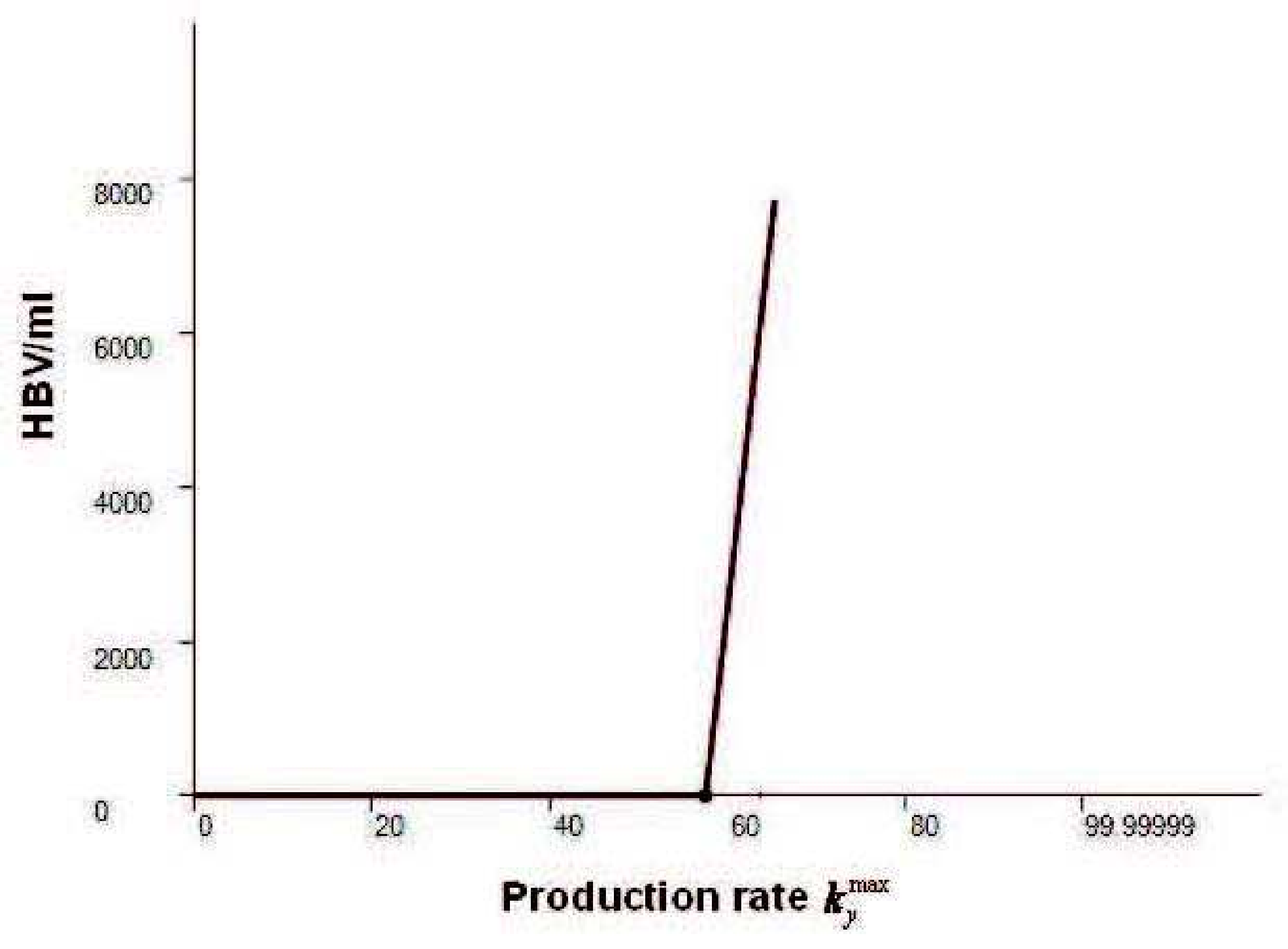
$$R_0 = N_y \frac{\beta_x \bar{x}}{\beta_x \bar{x} + \beta_z \bar{z} + u} + N_w \frac{\beta_z \bar{z}}{\beta_x \bar{x} + \beta_z \bar{z} + u}$$

Transcritical bifurcation

- $(Ny - 1)(Nw - 1) \geq 0$
- The endemic state undergoes a Transcritical bifurcation:
  - For $R0 > 1$, $R0$ close to 1, the EE is LAS and the DFE is unstable.
    - The HBV disease persists
  - For $R0 \leq 1$, the DFE is GAS.
    - The HBV disease dies out

Hepatitis B/C

- Transcritical bifurcation



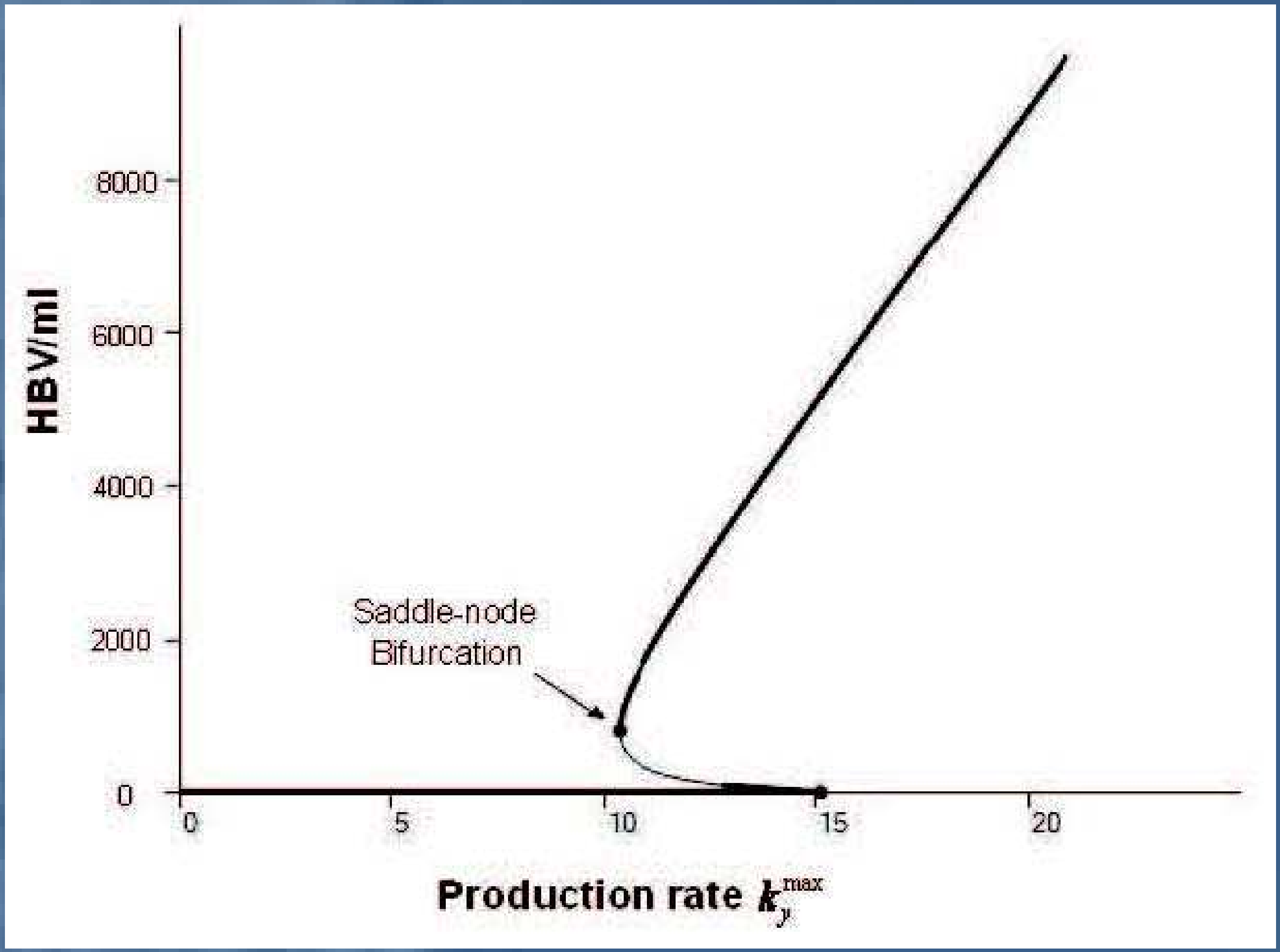
Qesmi, ElSaadany, Heffernan, Wu, submitted

Backward bifurcation

- (Ny – 1) (Nw – 1) < 0
- When R0 = 1, the LVB system undergoes a backward bifurcation
  - For Rc < R0 < 1, there is an endemic equilibrium which is LAS;
  - The DFE is LAS for R0 ≤ 1;
  - For R0 > 1, the DFE is unstable and an endemic equilibrium appears and is stable.

Hepatitis B/C

- Backward bifurcation



Qesmi, ElSaadany, Heffernan, Wu, submitted.

Conclusions and Future Work

- Drug therapy may be effective at reducing Nx < 1 in the liver, but may not be successful in reducing Nz < 1 and therefore, the virus can not be eradicated.

- CURRENT DEBATE
  - Are there virus producing cells in the blood?!!!!!!

  - Can use our model for liver transplantation studies
    - Compare to reate of reinfection data of the new liver
    - Give us an idea if virus and/or infected cells are needed for this to occur

Acknowledgements

- Dr. Redouane Qesmi (York)
- Dr. Jianhong Wu (York, CDM)
- Dr. Jun Wu (PHAC)
- Dr. Susie ElSaadany (PHAC)

- NSERC
- MITACS
- ERA

- Group:
- Undergrads:

  Alexandra Teslya, Naamah Jacobs, Ramnath Bagavath, Amir Razavi
- Grad

  Shannon Collinson, Yimin Du, Yan Wang, Navjot Singh, Roman Khaykin
- Post Doc

  Suma Ghosh, Redouane Qesmi, Venkata Duvuurri, Qian Wang, Vahid Anvari
- Collaborators

  Neal Madras, Jianhong Wu, Robert Smith?

Immune System

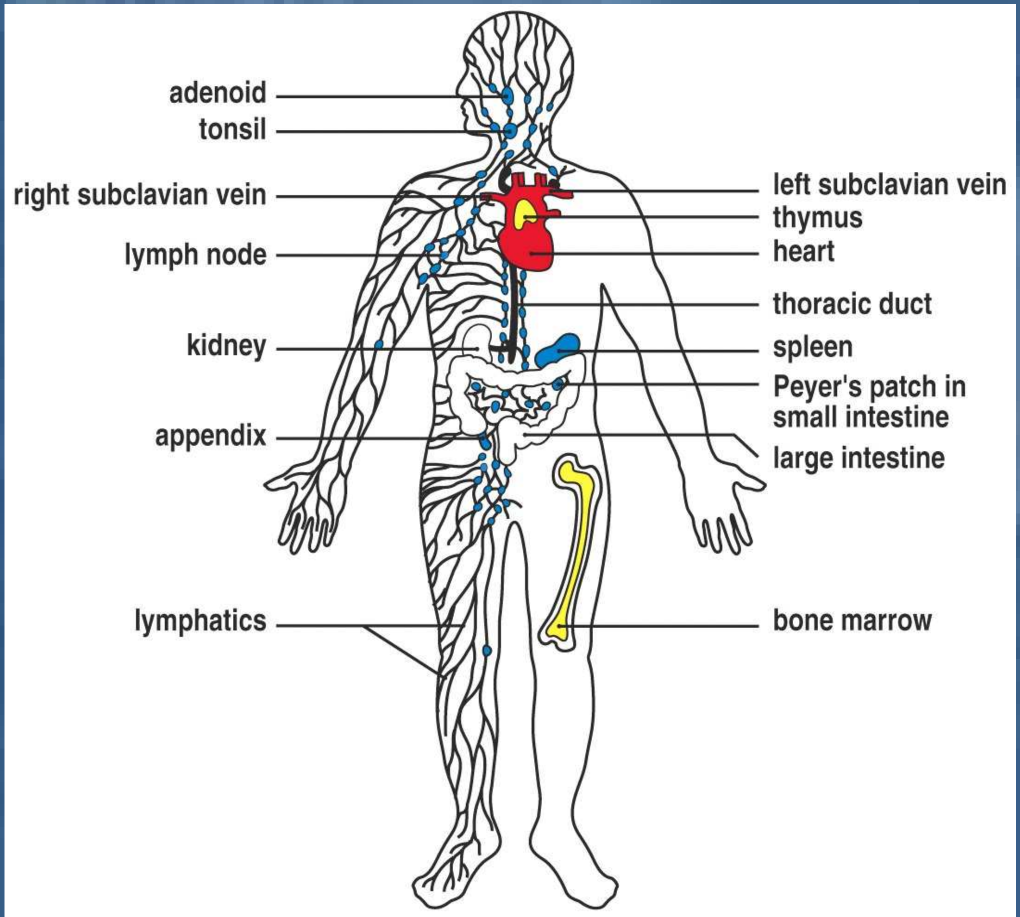


Figure 1-7 Immunobiology, 6/e. (© Garland Science 2005)

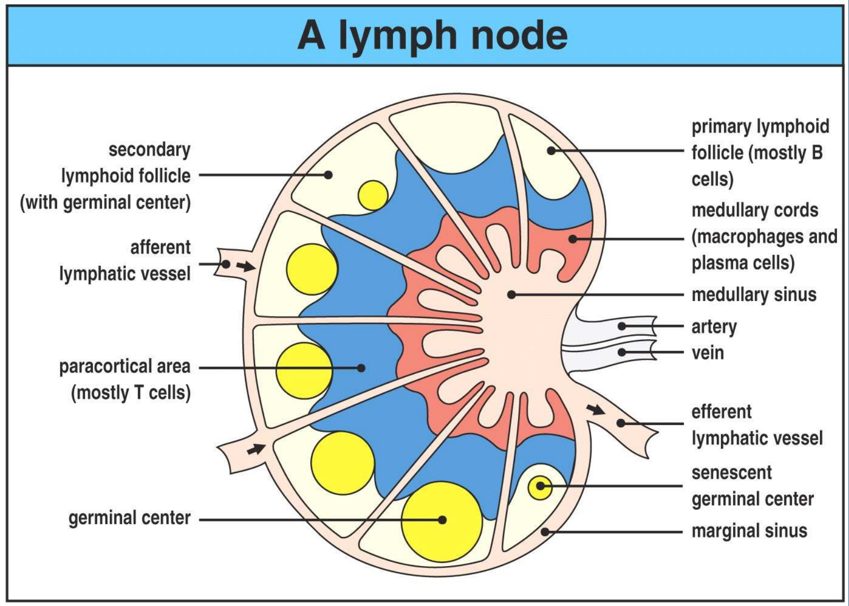


Figure 1-8 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

- Innate immunity
- Adaptive immunity
  - Humoral and cell mediated

Immune System

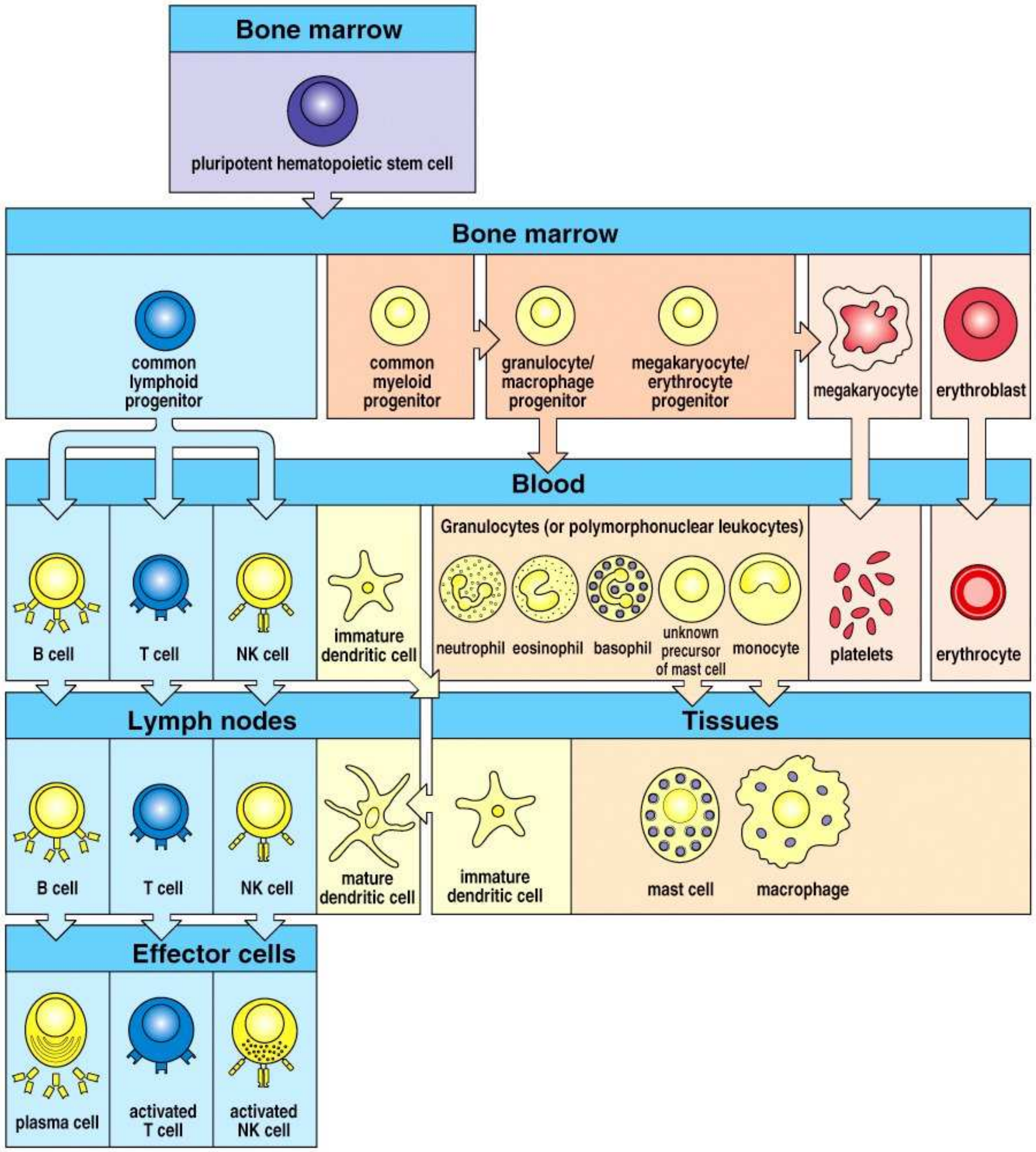


Figure 1-3 Immunobiology, 6/e. (© Garland Science 2005)

- Macrophages, Dendritic cells, etc
- Lymphocytes
  - T – produced by thymus
    - CD4
      - Helper T-cells
      - Activated by antigen presenting cells
      - Activate the rest of the immune response
    - CD8
      - Killer T-cells
  - B - produced in bone marrow
    - Mature in spleen
    - Plasma cells, antibodies
  - Naive, activated memory

Immune System

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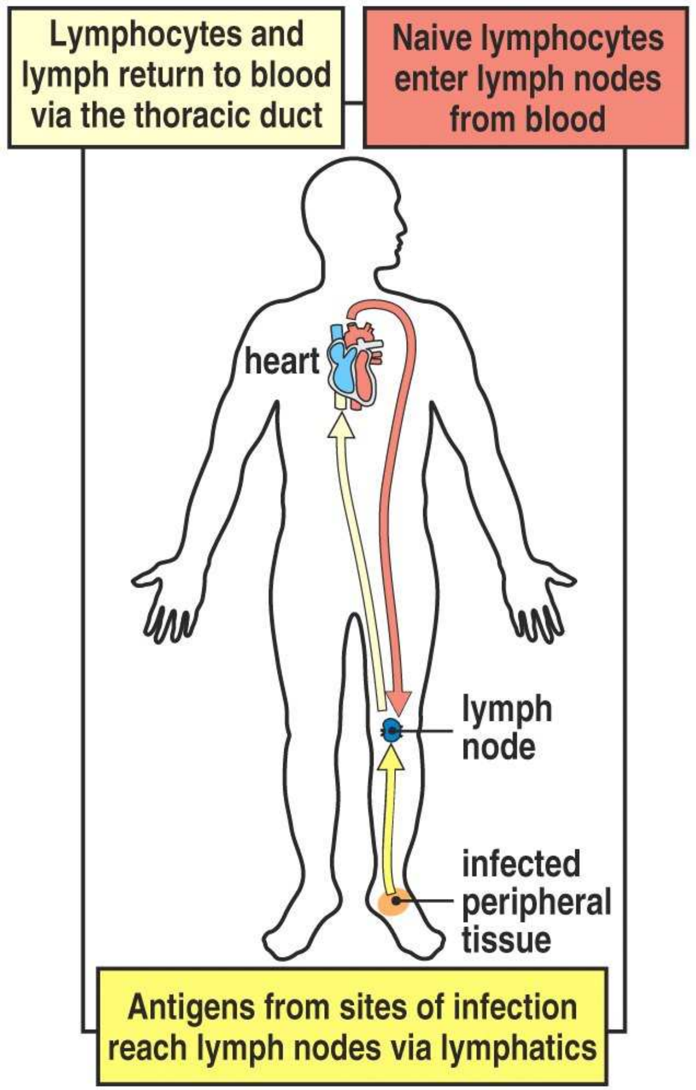

Figure 1-11 Immunobiology, 6/e. (© Garland Science 2005)

Basic Model

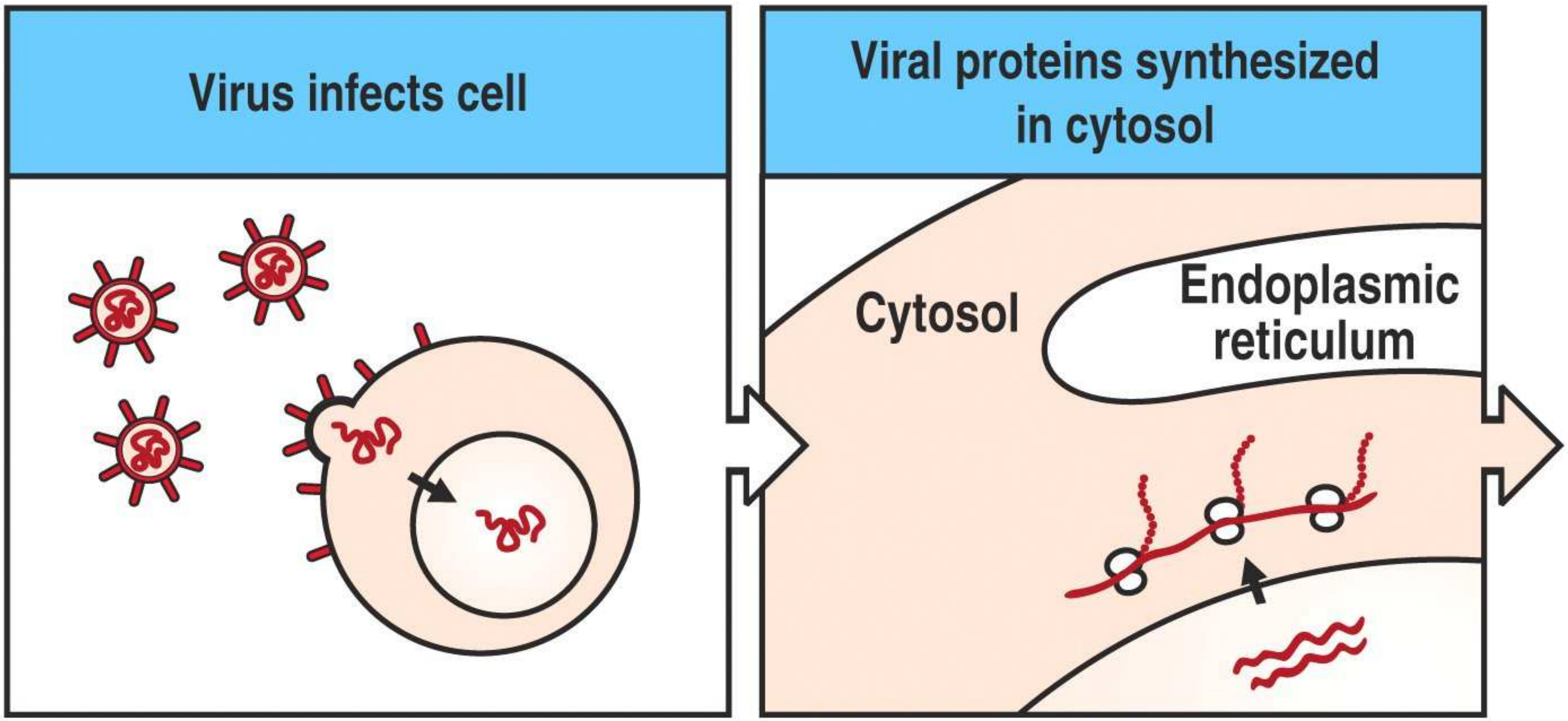

Figure 1-28 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)