Spread of Viral Plaques

Don Jones , Gergely Rost, Horst Thieme , and Hal Smith

SCHOOL OF MATHEMATICAL & STATISTICAL SCIENCES
ARIZONA STATE UNIVERSITY

Emerging Challenges at the Interface of Mathematics, Environmental Science and Spatial Ecology

Outline

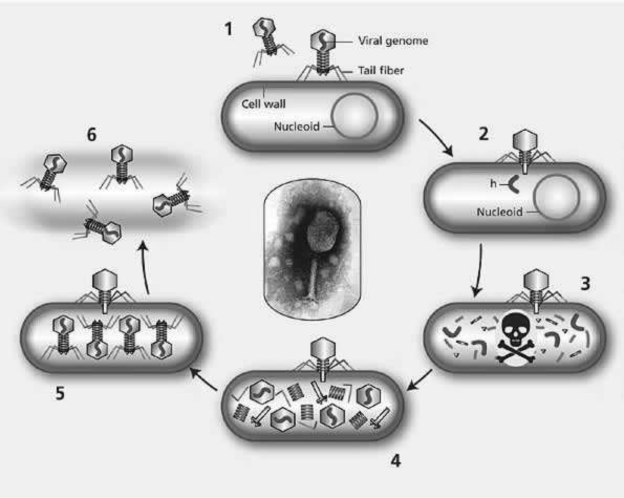
1. Bacteriophage and Plaques
2. Prior work on Plaque spread
   - Koch's formula
   - Model of Yin & McCaskill
3. Fixed-Duration Latent Period Model
4. Traveling Waves in One Space Dimension-a failed attempt
5. Asymptotic Spreading Speed Theory applied to a related scalar equation
6. Traveling Waves Solutions

Bacteriophage

Bacteriophage, phage for short, are virus that parasitize bacteria

1. most numerous life form on the planet
2. found in all reservoirs populated by bacterial hosts, such as soil, water, or the intestines of animals
3. possible therapy against multi drug resistant strains of many bacteria
4. played key role in showing DNA is carrier of hereditary information
5. model host-parasite system for evolution studies

Phage Life Cycle: adsorption to lysis

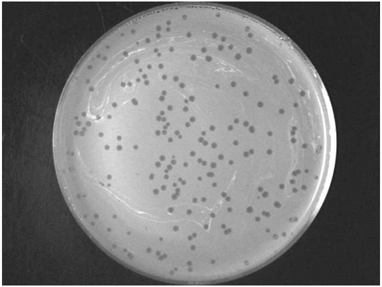


Latent Period: time from adsorption to burst $\approx 20 - 40$ min.

Burst size: 10-1000 virus.

Plaque Assay

“The plaque technique of virus assay has played an important role in the development of knowledge of the physiology and genetics of viruses. For bacteriophage the technique is quite simple and consists of adding a large number of susceptible bacteria and a few virus particles to a tube containing melted nutrient agar, which is then poured on a Petri plate that already contains a basal layer of nutrient agar. The virus adsorbs to the host bacteria, multiplies, and lyses the bacterial cell; the progeny viruses diffuse to neighboring bacterial cells and multiply further, yielding holes or plaques in the otherwise continuous sheet of bacterial growth." (A.L. Koch: JTB 1964)



Koch: JTB 1964

Using time scale arguments and well-known characteristics of the heat equation, Koch proposes that

$$\text{speed of plaque spread} \propto \left(\frac{\text{virus diffusion constant } (d)}{\text{latent period } (\tau)}\right)^{1/2}$$

For an *E. Coli* strain and T7 phage, $d = 4 \times 10^{-8} cm^2/sec$ and $\tau = 20$ min., so Koch's formula gives speed $=$ $0.2mm/hr$.

Yin & McCaskill (1992) BioPhysics J.

exponentially distributed latent period, adsorption/desorption:
V = virus, B = susceptible bacteria, I = infected bacteria.

$$V + B \underset{k_-}{\overset{k_+}{\rightleftarrows}} I \xrightarrow{k_2} \beta V, \quad \beta = \text{burst size}$$

Model equations:

$$\begin{aligned} V_t &= d(V_{rr} + \frac{1}{r} V_r) - k_+ VB + (k_2 \beta + k_-) I \\ B_t &= -k_+ BV + k_- I, \\ I_t &= k_+ BV - (k_- + k_2) I \end{aligned}$$

in the entire plane $\mathbb{R}^2$ with initial conditions:

$$V = \begin{pmatrix} V_0, & r \le r_0 \\ 0, & r > r_0 \end{pmatrix}, \; B = \begin{pmatrix} 0, & r \le r_0 \\ B_0, & r > r_0 \end{pmatrix}, \; I = 0$$

Yin et al.

Yin & McCaskill linearize the equations about the virus-free state:

$$(V, B, I) = (0, B_0, 0)$$

and seek the form of the “leading edge" of a 1D-traveling wave as

$$(V, B, I) = e^{-\lambda(x-ct)}(a_1, a_2, a_3), \quad a_1, a_3 > 0$$

Substituting this into the linearized equation, they obtain cubic equation for the “shape parameter" λ, with coefficients depending on c. The minimum value that c can take is identified as a solution of an associated cubic equation.

Yin and You (J.Theor.Biol.1999) use numerical simulations to support the claim that a wave develops and spreads.

Problems:
(1) their estimated wave speed greatly exceeds experimental values!
(2) 63% of infected cells lyse before the average for the exponential distribution.

Our Model: $V + B \xrightarrow{k} I \rightarrow \beta V,\ \tau = $ |latent period|

An infected cell remains so for τ time units, then lyses, releasing β phage.

First latent period: $0 \le t \le \tau$

$$\begin{aligned} V_t &= d\triangle V - kVB \\ B_t &= -kBV, \quad x \in D \\ I_t &= kBV \end{aligned}$$

with initial data: $V(0,x) = V_0(x), \quad B(0,x) = B_0(x), \quad I(0,x) = 0$.

For $t > \tau$:

$$\begin{aligned} V_t &= d\triangle V - kV(t,x)B(t,x) + \beta kB(t-\tau,x)V(t-\tau,x) \\ B_t &= -kB(t,x)V(t,x) \\ I_t &= kB(t,x)V(t,x) - kB(t-\tau,x)V(t-\tau,x) \end{aligned}$$

$I(t,x) = B(\max\{0, t-\tau\}, x) - B(t,x), \quad B(t,x) = B_0(x)\exp(-k\int_0^t V(s,x)ds)$

In the lab, D is disk in $\mathbb{R}^2$ (No-Flux B.C.), $V_0 = \sum_i \delta_{x_i}$, B_0 is a pos. const.

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Asymptotic Behavior in a Bounded Domain

Let D be a bounded domain in $\mathbb{R}^n$. If V satisfies Neumann B.C., then

$$v(t) = \int_D V(t,x)dx, \quad b(t) = \int_D B(t,x)dx$$

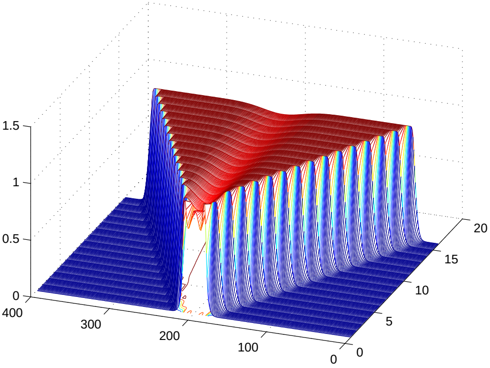
have limits as $t \to \infty$:

$$\begin{aligned} b(\infty) &= 0 \\ v(\infty) &= v(0) + (\beta - 1)b(0) \end{aligned}$$

provided $\beta > 1$ and $V_0(x)$ is not identically zero.

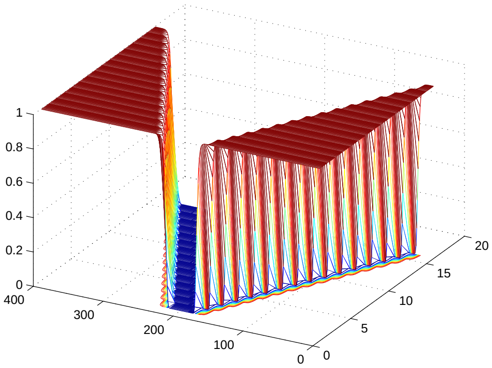
All the bacteria are converted into virus.

Simulations: $\beta = 100$, $kB_0\tau = 1$



Spreading Phage Plaque. $V(t,x)/B_0(\beta - 1)$ is plotted.

Simulations



Bacteria are infected and lysed. $B(t,x)/B_0$ is plotted.

Traveling Waves

Seek a traveling wave solution in one space dimension ($x \in \mathbb{R}^1$):

$$V(t,x) = V(s),\ B(t,x) = B(s),\ s = x + ct$$

where $c > 0$ denotes the wave speed. This leads to a system of delay equations:

$$\begin{aligned} cV'(s) &= dV''(s) - kB(s)V(s) + \beta kB(s - c\tau)V(s - c\tau) \\ cB'(s) &= -kB(s)V(s) \end{aligned}$$

we seek a wave satisfying

$$(V(-\infty), B(-\infty)) = (0, B_0), \quad (V(+\infty), B(+\infty)) = (V_0, 0),\ B_0, V_0 > 0.$$

The second equation may be used to rewrite the first as:

$$cV'(s) = dV''(s) + cB'(s) - c\beta B'(s - c\tau)$$

Integrating over the real line gives

$$V_0 = (\beta - 1)B_0$$

$\beta > 1$ is a necessary condition for the existence of a wave.

Heteroclinic Orbit for DDE

After scaling space, time, and dependent variables, the system of delay equations is obtained for the wave profile:

$$\begin{aligned}(1/c^2)v'(s) &= v(s) + \frac{1}{\beta - 1}(1 - b(s)) - \frac{\beta}{\beta - 1}(1 - b(s-1)) \\ b'(s) &= -k(\beta - 1)b(s)v(s)\end{aligned}$$

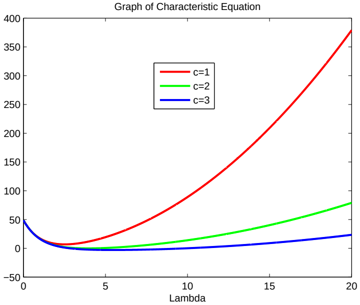
It has equilibria:

$$E_- \equiv (v, b) = (0, 1) \quad \text{and} \quad (v, b) = (1, 0) \equiv E_+$$

We seek a heteroclinic orbit issuing from E_- and joining to E_+.

Traveling Wave Conjecture

Necessary condition for non-oscillatory heteroclinic orbit:
(a) E_+ has a negative characteristic exponent. ✓
(b) E_- has a positive characteristic exponent.
Characteristic equation at E_-: $0 = \frac{\lambda^2}{c^2} - \lambda + k(\beta e^{-\lambda} - 1)$
has a pair of positive roots for all large values of c, say, $c > c^*$.



Conjecture: There is a heteroclinic orbit whenever $c > c^*$.

Spreading Speed Theory of Thieme & Zhao (2003)

Let $u(t,x) = \begin{pmatrix} \int_0^t V(s,x)ds, & t > 0,\ x \in \mathbb{R}^n \\ 0, & t \leq 0,\ x \in \mathbb{R}^n \end{pmatrix}$, $B(t,x) = B(0,x)e^{-ku(t,x)}$.

$u(t,x)$ satisfies:

$$u_t(t,x) = d\Delta u(t,x) + V_0(x) - B_0(x)kf(u(t,x)) + \beta B_0(x)kf(u(t-\tau,x)),$$

where $f(u) = (1 - e^{-ku})/k$.

Hereafter, $B(0,x) \equiv B_0 > 0$. Rewrite eqn. as

$$u_t(t,x) = d\Delta u(t,x) + V_0(x) - B_0 ku(t,x) + B_0 kg(u(t,x)) + \beta B_0 kf(u(t-\tau,x))$$

Both $f(u) \geq 0$ and $g(u) = u - f(u) \geq 0$ are increasing functions!

By comparison theorem, $u(t,x) \geq v(t,x)$ where:

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As $f(u) \leq f'(0)u$, spreading speed theory of Thieme & Zhao applies!.

The Characteristic Equation

Setting $V_0 = 0$ and Linearizing

$$v_t(t,x) = d\Delta v(t,x) - B_0 k v(t,x) + \beta B_0 k f(v(t-\tau,x))$$

about $v = 0$, using $f(v) = v + O(v^2)$:

$$v_t(t,x) = d\Delta v(t,x) - B_0 k v(t,x) + \beta B_0 k v(t-\tau,x)$$

Trying for a traveling wave solution with exponential profile:

$$v(t,x) = e^{\lambda(ct + x\cdot z)}, \quad z \in \mathbb{R}^n, |z| = 1,$$

leads to the an equation for the “shape parameter" λ and wave speed c:

$$F(\lambda,c) \equiv d\lambda^2 - \lambda c - kB_0 + \beta k B_0 e^{-\lambda c\tau} = 0$$

This equation is identical, up to scaling, as the previous one!

Lower Bound on Speed of Spread

Let (λ^*, c^*) be the unique solution of

$$F(\lambda, c) = F_\lambda(\lambda, c) = 0$$

Now apply result of Thieme (1979):

Theorem: Let $\beta > 1$ and let v^* be the unique positive solution of

$$v^* = \beta f(v^*) = \beta(1 - e^{-kv^*})/k$$

Then, for every $c \in (0, c^*)$,

$$\liminf_{t\to\infty} \inf_{|x|\leq ct} v(t,x) \geq v^*$$

provided V_0 is measurable, nonnegative, and not zero a.e.

Because $u(t,x) \geq v(t,x)$, and one can argue that for every $c \in (0, c^*)$,

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Spreading speed

Having shown that for every $c \in (0, c^*)$,

$$\inf_{|x| \leq ct} u(t,x) \to \infty, \qquad t \to \infty,$$

we now seek to show that for every $c > c^*$

$$\sup_{|x| \geq ct} u(t,x) \to 0, \qquad t \to \infty,$$

If this holds for all suitably restricted solutions of our equation, then “c^* is THE spreading speed" for the equation.

Estimates of $u(t,x)$ from above

Comparison arguments and concavity of $f(u)$ show that if V_0 has compact support, then $\exists\eta > 0$ such that $\forall z \in \mathbb{R}^n, |z| = 1$:

$$u(t,x) \leq \eta e^{\lambda(ct+x\cdot z)}, \quad x \in \mathbb{R}^n,\ t \geq 0$$

In particular, taking $z = -x/|x|$,

$$u(t,x) \leq \eta e^{\lambda(ct-|x|)}$$

provided either:

1. $\beta e^{-2\lambda^* c^* \tau} \geq 1$, $c > c^*$, $\lambda < \lambda^*$, and $c\lambda = c^*\lambda^*$. Therefore

$$\lim_{t\to\infty} \sup_{|x|\geq ct} u(t,x) \to 0, \quad c > c^*$$

2. $c > c^o$, $\lambda < \lambda^*$, and $c\lambda = c^o\lambda^*$ where (λ^*, c^o) is the unique double root of $F(\lambda, c) + kB_0 = 0$. Therefore

$$\lim_{t\to\infty} \sup_{|x|\geq ct} u(t,x) \to 0, \quad c > c^o$$

Note: $c^0 > c^*$.

Spread Results for $B - V$ System

Using that $I(t,x) = B(t-\tau,x) - B(t,x),\ t > \tau$ and $B(t,x) = B_0 e^{-ku(t,x)}, t > 0$ and the previous results, we have the following result.

Theorem: Let (V, B) be a solution with initial data $V(0,x) = V_0(x) \geq 0$, and $B(0,\cdot) \equiv B_0 > 0$ where $V_0(x)$ is not zero a.e. Then, for every $c \in (0, c^*)$,

$$\lim_{t\to\infty, |x|\leq ct} B(t,x) = 0, \quad \lim_{t\to\infty, |x|\leq ct} I(t,x) = 0.$$

In addition, assume that V_0 has compact support and one of the following hold:

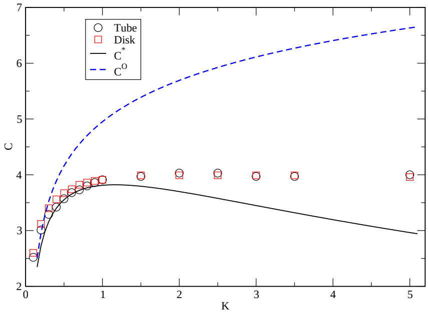
(1) $c > c^*$, and $\beta e^{-2\lambda^* c^* \tau} \geq 1$, or

(2) $c > c^0$

Then,

$$\lim_{t\to\infty, |x|\geq ct} B(t,x) = B_0, \quad \lim_{t\to\infty, |x|\geq ct} I(t,x) = 0.$$

Theoretical vs Simulated Spread Speed



scaled c^* vs $K = kB_0\tau$ in black

$$c^* = \sqrt{\frac{d \ln(\beta)}{\tau}}, \quad kB_0\tau = 1$$

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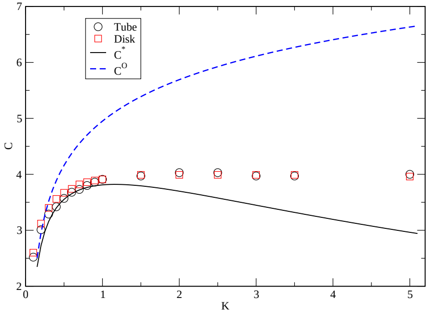

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Existence of Traveling Wave Solutions: $x \in \mathbb{R}$

Theorem: Assume one of the following hold:

(1) $c > c^*$ and $\beta e^{-2\lambda^* c^* \tau} \geq 1$, or

(2) $c > c^o$.

Then there exists a traveling wave solution $V(x+ct) > 0$ and $B(x+ct) > 0$ of

$$\begin{aligned} V_t &= dV_{xx} - kVB + \beta kB(t-\tau, x)V(t-\tau, x) \\ B_t &= -kBV \end{aligned}$$

satisfying:

$$B(-\infty) = B_0, \quad B(+\infty) = 0, \; V(-\infty) = 0, \quad V(+\infty) = B_0(\beta - 1).$$

Proof Ideas

Adapt approach of Diekmann 1977, as in Thieme & Zhao:
Start by finding wave solution $u = U(ct + x)$ for:

$$u_t = du_{xx} - B_0 ku + B_0 kg(u(t,x)) + \beta B_0 kf(u(t-\tau,x))$$

with $U(s)$ monotone increasing, $U(-\infty) = 0$ and $U(+\infty) = +\infty$.
U must be a fixed point of ($\mu = kB_0,\ \nu = \beta\mu$)

$$\begin{aligned} U(\xi) &= \int_0^\infty \int_{\mathbb{R}} e^{-\mu s}\Gamma(s,y)\mu g(U(\xi - cs - y))dyds \\ &\quad + \int_0^\infty \int_{\mathbb{R}} e^{-\mu s}\Gamma(s,y)\nu f(U(\xi - c(s+\tau) - y))dyds = F(U)(\xi). \end{aligned}$$

$F : M(\mathbb{R},\mathbb{R}_+) \to M(\mathbb{R},\mathbb{R}_+)$ is monotone. Now find an upper solution $W \geq F(W)$ and a lower solution $F(w) \geq w$ with $0 < w < W$. Then

$$W \geq F(W) \geq F^2(W) \geq \cdots \geq F^k(W) \to U \geq w$$

The End

Thanks For Your Attention