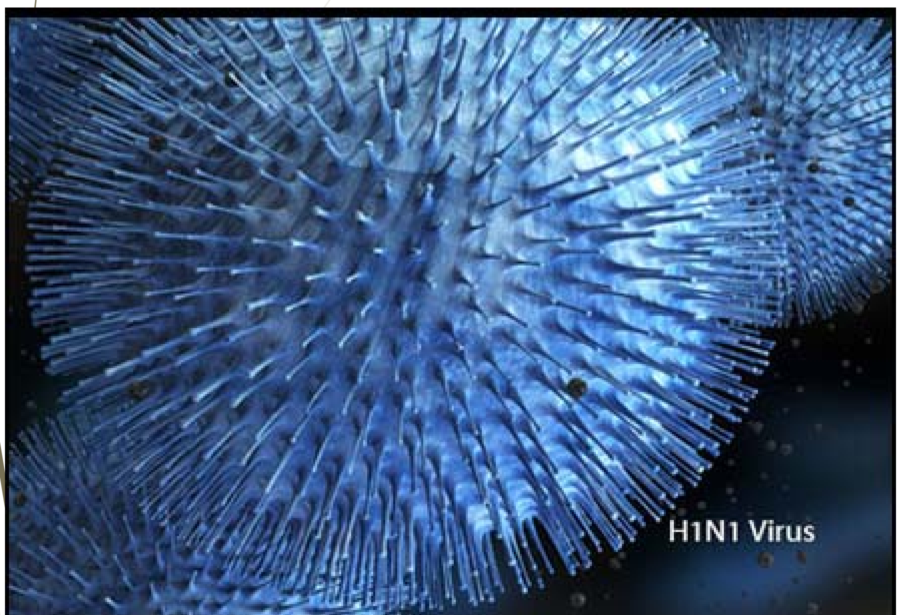
Nonlocal and delay reaction-diffusion equations in mathematical immunology

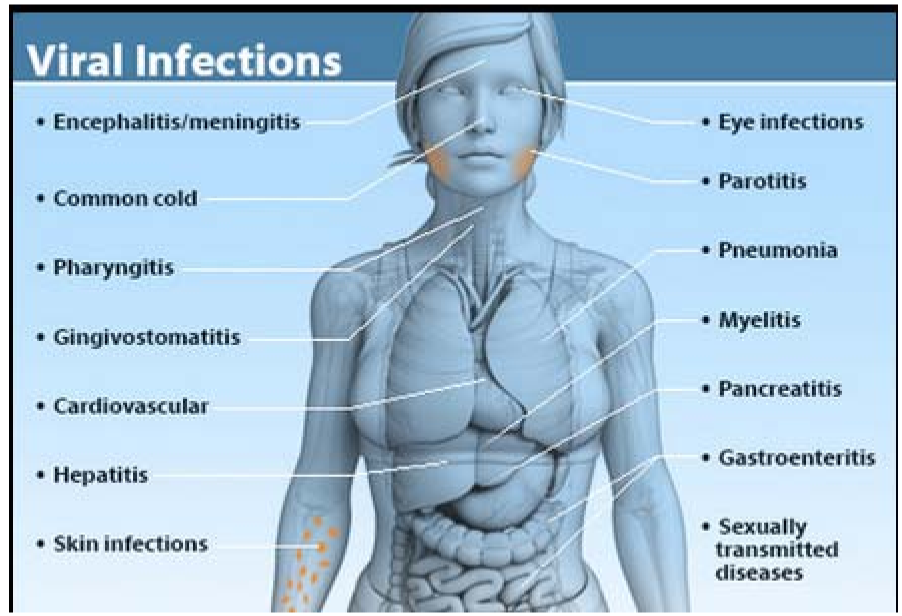
V. Volpert (CNRS, Lyon, France)

Dynamics Days 2020

Contents

Viral infections



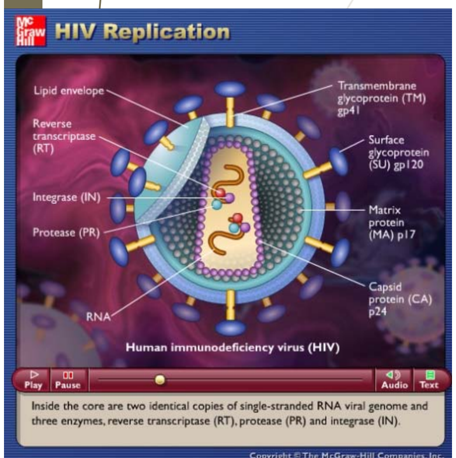


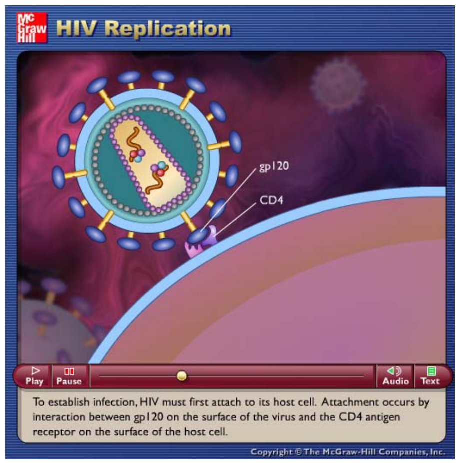
What Is a Virus?

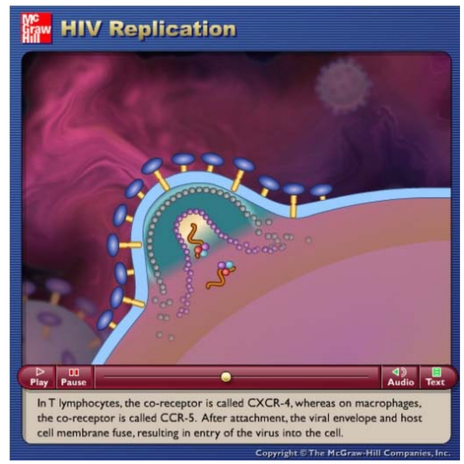
Viruses are small particles of genetic material (either DNA or RNA) that are surrounded by a protein coat. Some viruses also have a fatty "envelope" covering. They are incapable of reproducing on their own. Viruses depend on the organisms they infect (hosts) for their very survival. Viruses get a bad rap, but they also perform many important functions for humans, plants, animals, and the environment. For example, some viruses protect the host against other infections. Viruses also participate in the process of evolution by transferring genes among different species. In biomedical research, scientists use viruses to insert new genes into cells.

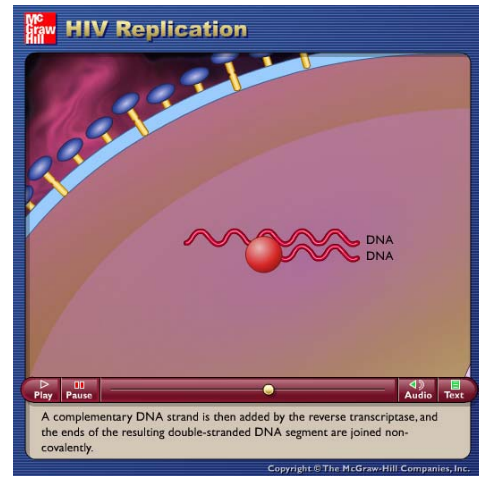
www.medicinenet.com/viral_infections_pictures_slideshow/article.htm

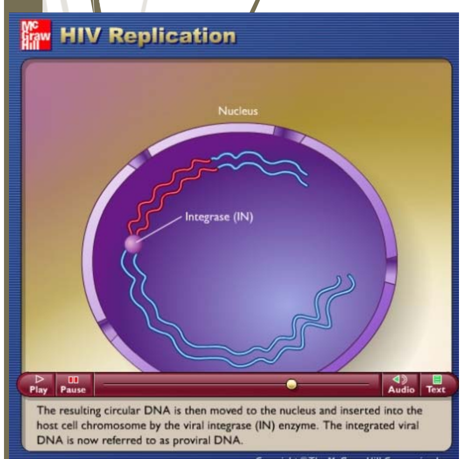
Virus replication

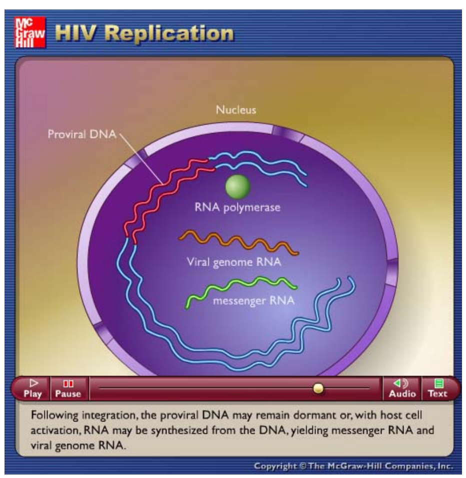


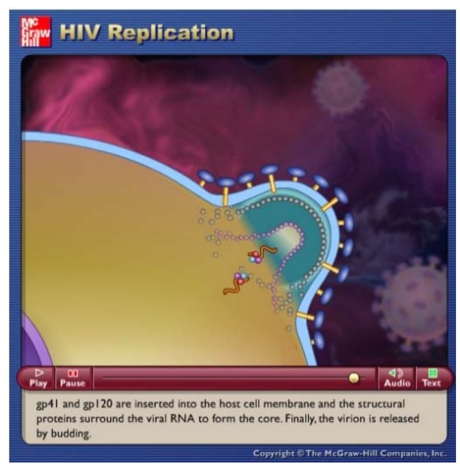




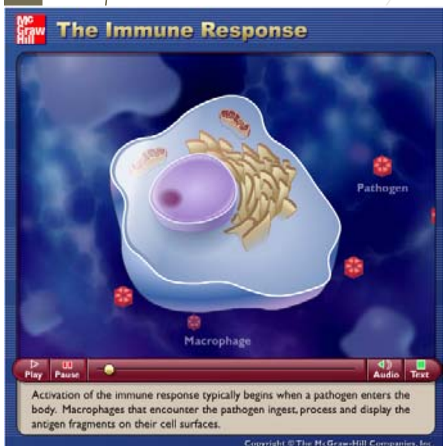


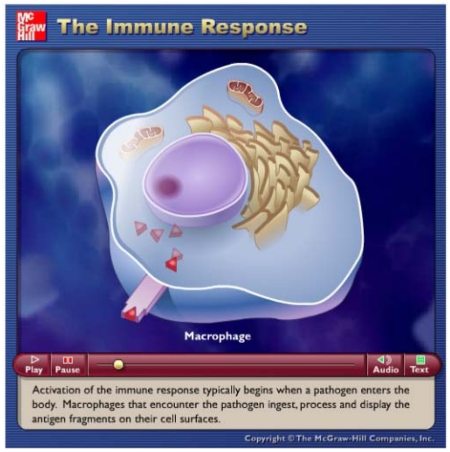


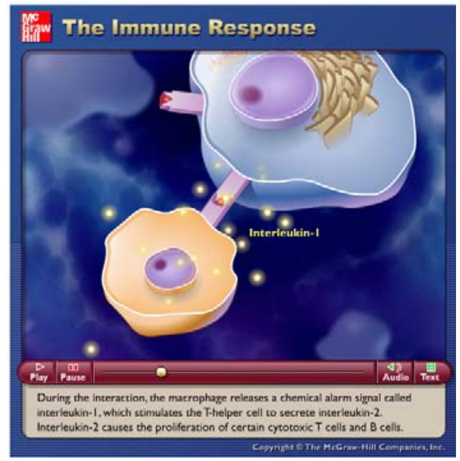


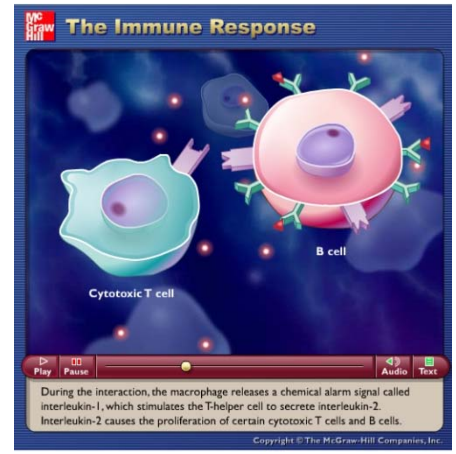


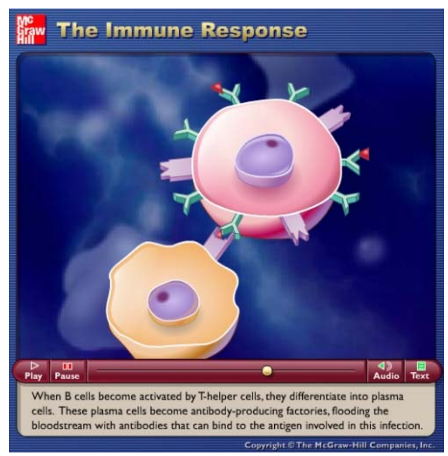
Innate and adaptive immune response

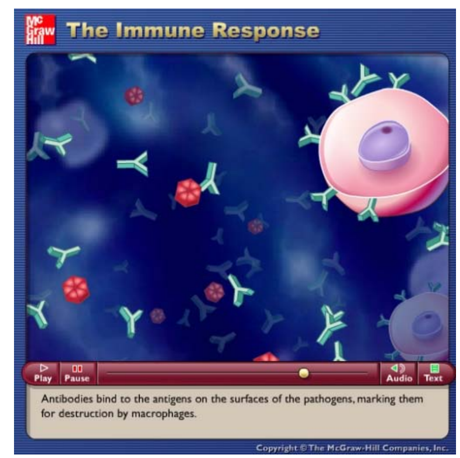






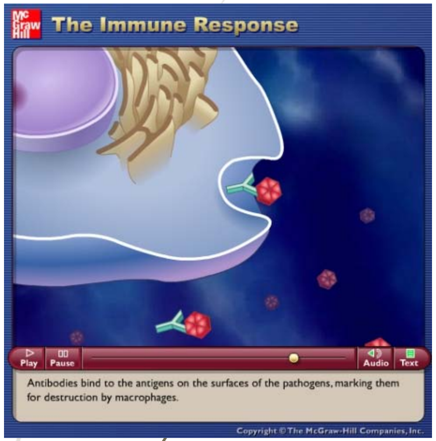


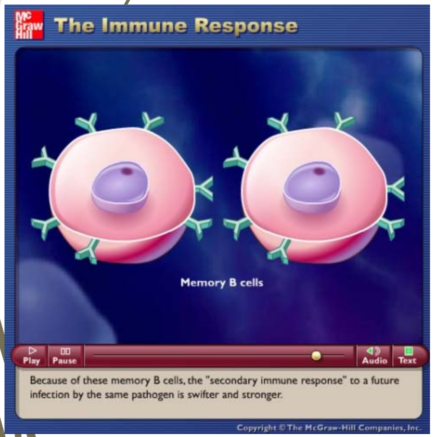


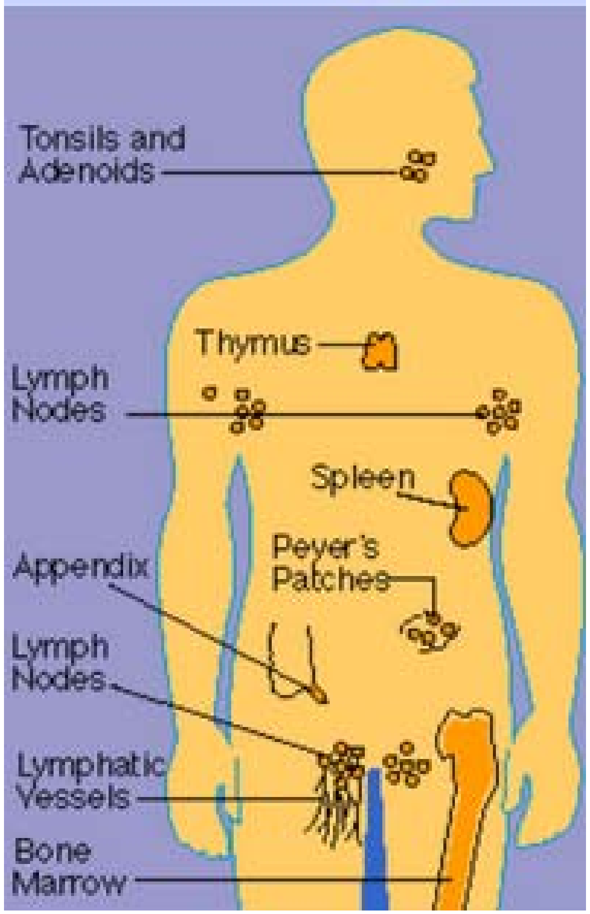


http://highered.mheducation.com/sites/0072495855/student_view0/chapter24/animation__the_immune_response.html

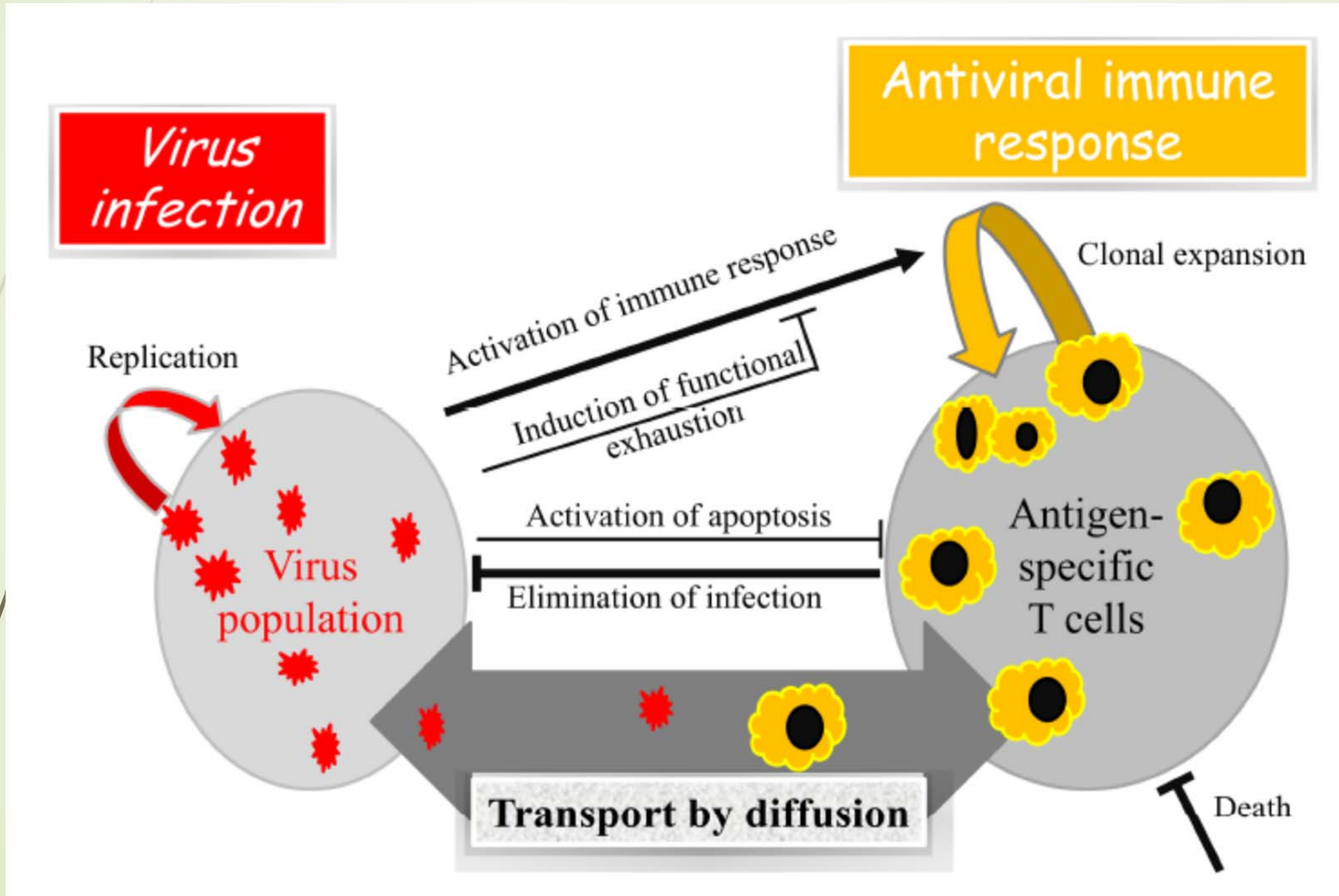
Immune response







Immune response



Nonlocal and delay equations

u(x,t) – virus density

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + ru(1 - qJ(u)) - uf(S(u_\tau)) - \sigma(x)u$$

Diffusion or mutations

Replication

Immune response

Death

$$J(u) = \int_{-\infty}^{\infty} \phi(x-y)u(y,t)dy$$

$$S(u_\tau)(y,t) = \int_{-\infty}^{\infty} \psi(y-z)u(z,t-\tau)dz$$

Time delay in adaptive immune response

Models: ODE-DDE system

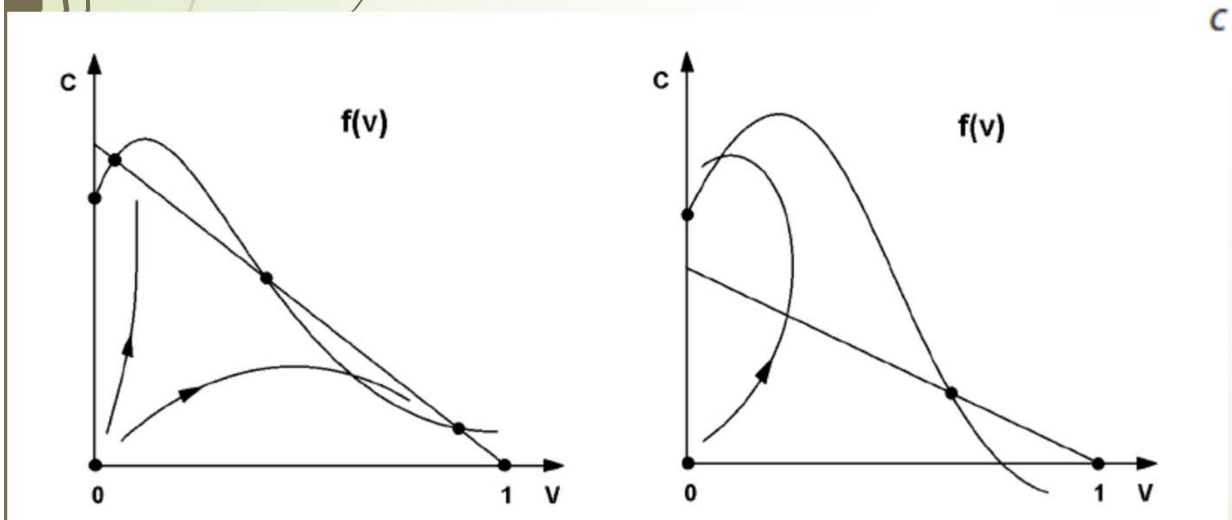
$$\frac{dv}{dt} = kv(1-v) - vc,$$

Virus

$$\frac{dc}{dt} = \phi(v_\tau)c(1-c) - \psi(v_\mu)c.$$

Immune cells

$$c = f(v), \text{ where } f(v) = 1 - \frac{\psi(v)}{\phi(v)}.$$



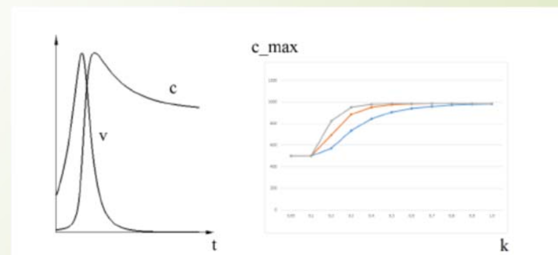


Figure 4: Time dynamics of virus and immune cell populations described by the ODE model (left). The maximum value of the T cell clonal expansion of $c(t)$ as a function of k without time delay $\tau = 0$ (lower curve), with $\tau = 1$ (middle curve), with $\tau = 2$ (upper curve) (right).

Different regimes: acute infection (cured), chronic infection, immunodeficiency

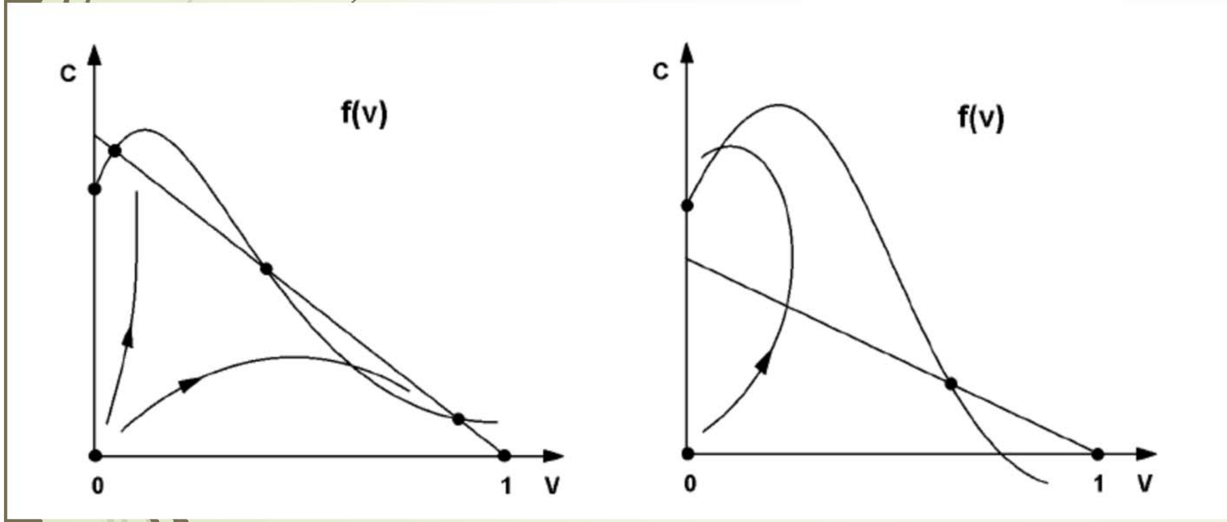
Models: ODE system and single equation

$$\frac{dv}{dt} = kv(1-v) - vc,$$

$$\frac{dc}{dt} = \phi(v_\tau)c(1-c) - \psi(v_\mu)c.$$

Virus

Immune cells

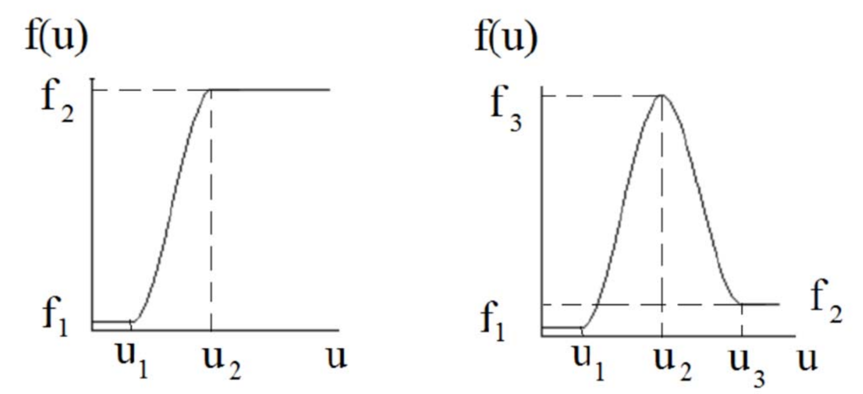


$c = f(v)$, where $f(v) = 1 - \frac{\psi(v)}{\phi(v)}$.

$$\frac{du}{dt} = ku(1 - u - f(u_\tau))$$

Single delay equation: linear stability

$$\frac{du}{dt} = ku(1 - u - f(u_\tau))$$



$$v(x,t) = v_0 + \epsilon e^{\lambda t + iax}$$

$$\lambda = -Da^2 - v_0\left(1 + f'(v_0)e^{-\lambda\tau}\right)$$

Stability boundary

$$i\phi = -Da^2 - v_0\left(1 + f'(v_0)e^{-i\phi\tau}\right).$$

$$Da^2 + v_0 + v_0 f'(v_0)\cos(\phi\tau) = 0,$$

$$v_0 f'(v_0)\sin(\phi\tau) = \phi.$$

Set $z = \phi\tau$. Then from (2.2), (2.3) we obtain

$$\cos z = -\frac{Da^2 + v_0}{v_0 f'(v_0)}, \quad \tau = \frac{z}{(v_0 f'(v_0)\sin z)}.$$

Proposition 1. *If $f'(v_0) > 1 + Da^2/v_0$, then for all $\tau > z/(v_0 f'(v_0)\sin z)$ the solution v_0 of equation (1.1) is unstable. Here z is determined from the first equation in (2.4).*

Single delay equation: global stability

$$\begin{cases} \frac{du}{dt} = u(1 - u - f(u_\tau)), & t > 0, \\ u(t) = \phi(t), & -\tau \le t \le 0. \end{cases}$$

(H1) $(1 - s)f(s)$ is non-increasing over $[0, 1]$.
(H2) $(1 - s) + f(s)$ is non-increasing over $[0, 1]$.
(H3) $(1 - s) + f(s) + (1 - s)f(s)$ is non-increasing over $[0, 1]$.

(K1) $1 - M < f(s)$ *for all* $0 < s \le 1$.
(K2) $f(0) > 1-M$ *and* $f(s) > 1-A$ *for all* $M \le s \le 1$ *with* A *is defined as* $f(A) = 1-M$ *and* $M < A < 1$.

We will suppose now that $f(u)$ has a single maximum, $f(M) = \max_{0 \le u \le 1} f(u)$ and f is increasing over $(0, M)$ and decreasing over $(M, 1)$.

Theorem 4. *Assume that either condition (K1) or (K2) hold, and let* $f(M) < 1$. *Then the equilibrium* u_0 *is globally attractive if there exists at least one test function* $T(s)$ *strictly monotone on the interval* $[0, M]$.

Theorem 5. *Assume that either condition (K1) or (K2) hold. Let* $f(M) \ge 1$ *and* $f(0) > 1 - \theta$ *where* $0 < \theta \le M$ *is determined from the equation* $f(\theta) = 1$. *Then the equilibrium* u_0 *is globally attractive if there exists at least one test function* $T(s)$ *strictly monotone on the interval* $[0, M]$.

Single delay equation: period doubling

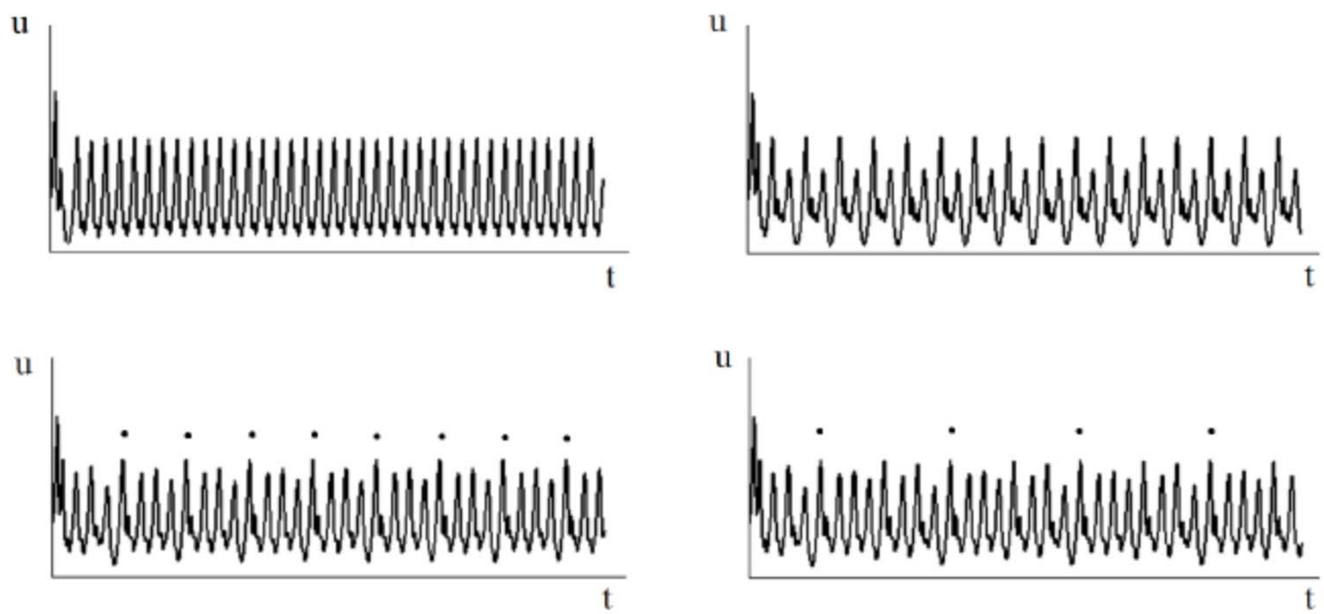


Figure 2: Period doubling bifurcations for the non-monotone function $f(u)$. Upper row: simple oscillations ($f_3 = 2.5$) and period 2 oscillations ($f_3 = 2$). Lower row: period 4 oscillations ($f_3 = 1.899$) and period 8 oscillations ($f_3 = 1.898$). The dots show the beginning of the periods. The values of parameters: $f_1 = 0$, $f_2 = 0.1$, f_3 varies, $u_1 = 0.1$, $u_2 = 0.3$, $u_3 = 0.5$, $\tau = 2$.

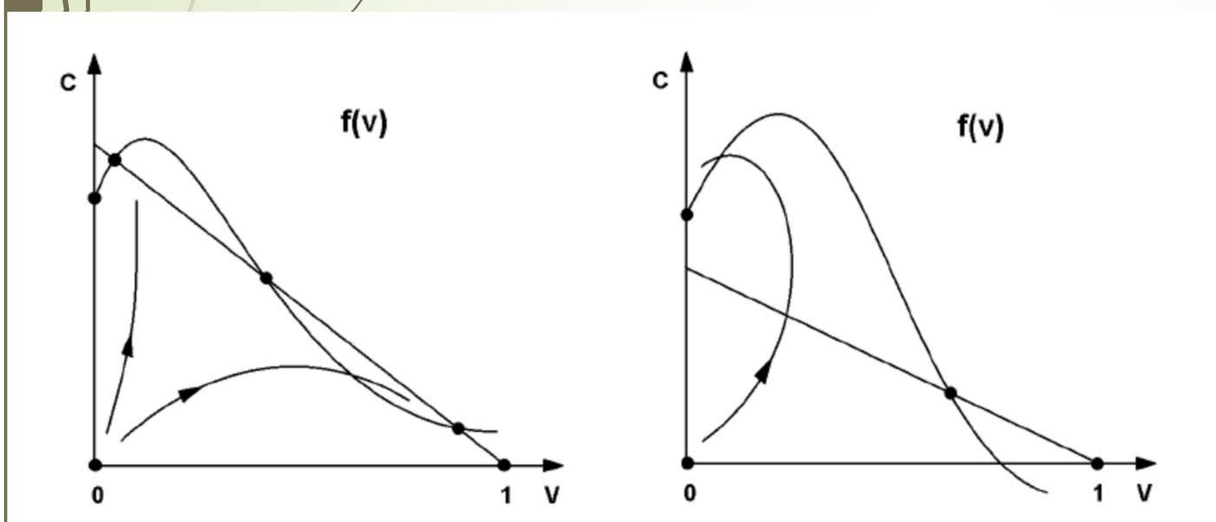
DDE system

$$\frac{dv}{dt} = kv(1-v) - vc,$$

Virus

$$\frac{dc}{dt} = \phi(v_\tau)c(1-c) - \psi(v_\mu)c.$$

Immune cells



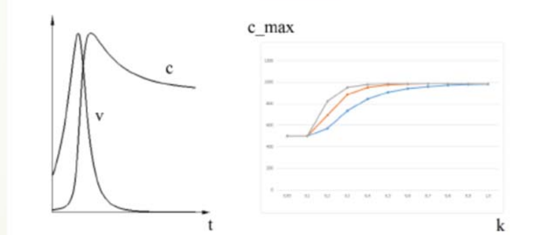


Figure 4: Time dynamics of virus and immune cell populations described by the ODE model (left). The maximum value of the T cell clonal expansion of $c(t)$ as a function of k without time delay $\tau = 0$ (lower curve), with $\tau = 1$ (middle curve), with $\tau = 2$ (upper curve) (right).

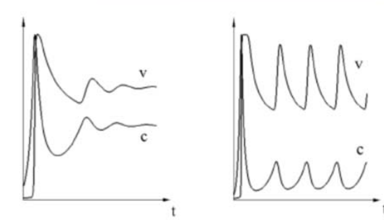


Figure 5: Damped oscillation type of virus infection dynamics in the ODE model and the existence of periodic oscillations in the models with time delay (DDEs) ($\tau = 2$) for the sigmoid type function $\phi(v)$ shown in Figure 3 (right).

Different regimes: acute infection (cured), chronic infection, immunodeficiency

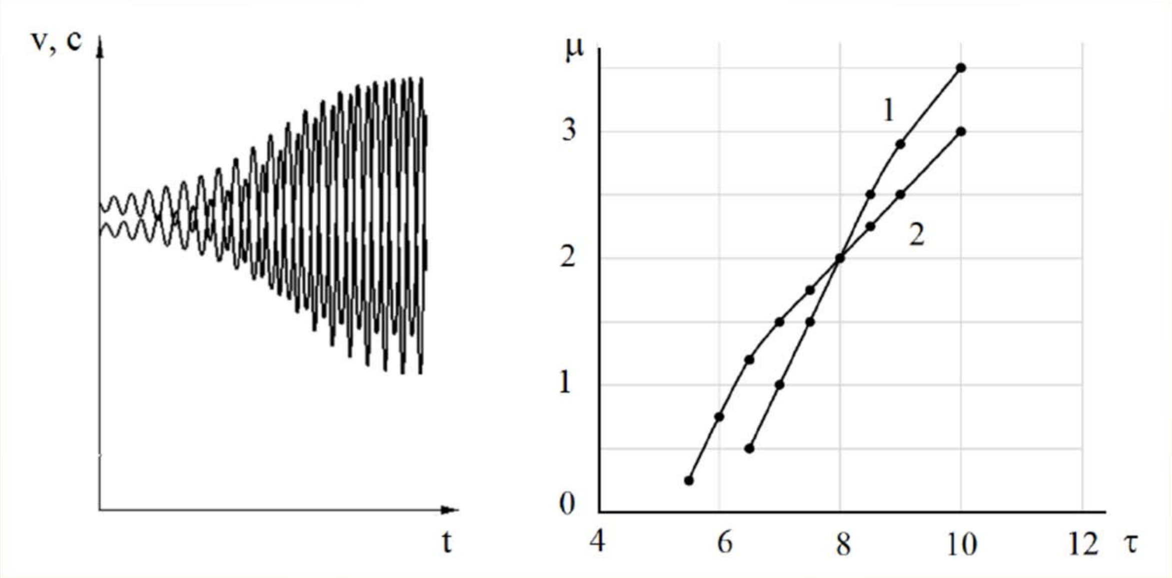
DDE system: two time delays

$$\frac{dv}{dt} = kv(1-v) - vc,$$

Virus

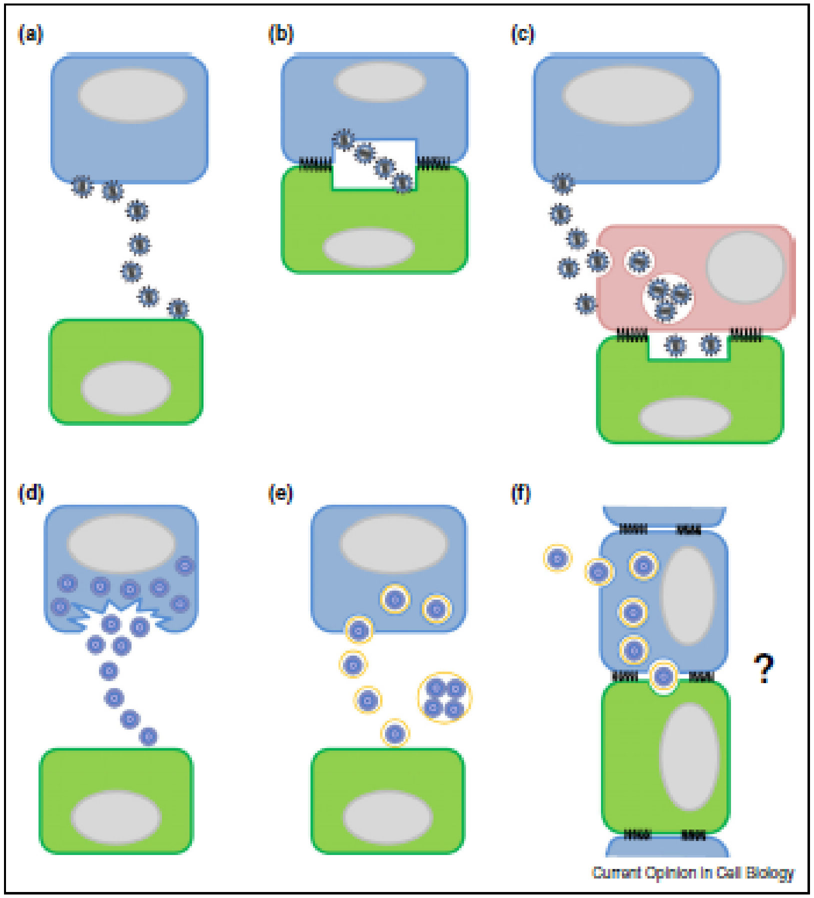
$$\frac{dc}{dt} = \phi(v_\tau)c(1-c) - \psi(v_\mu)c.$$

Immune cells



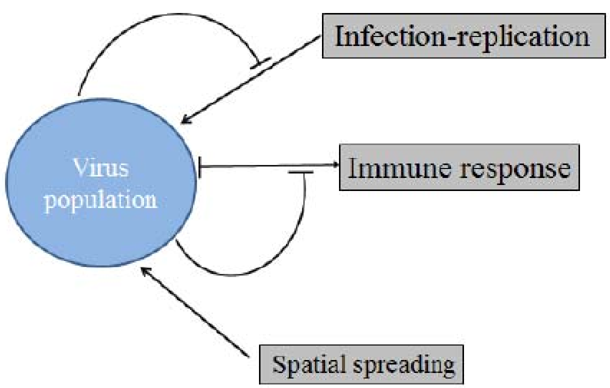
Available online at www.sciencedirect.com
ScienceDirect
Current Opinion in Cell Biology
Viruses exploit the tissue physiology of the host to spread *in vivo*
Xaver Sewald[1], Nasim Motamedi[1] and Walther Mothes[2]

Mechanisms of virus spreading



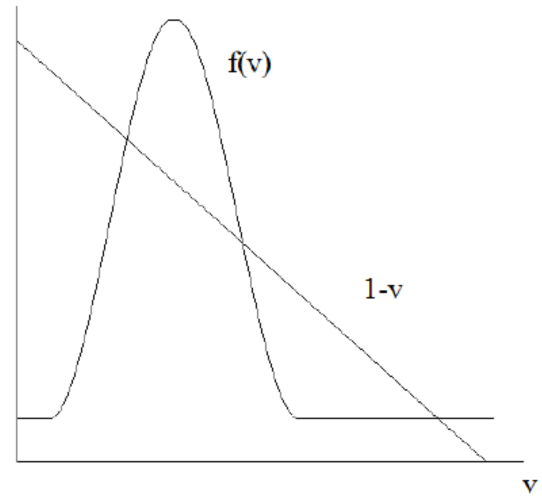
In vitro pathways of virus cell transmission. (a–c) Enveloped viruses have evolved with the host cell to efficiently spread from an infected cell (depicted in blue) to a non-infected cell (depicted in green). Cell-free transmission of enveloped viruses by diffusion through the extracellular environment after budding from an infected cell (a). Productively infected cell transfer virus particles across a virological synapse for cis-infection (b). For trans-infection, cell-free virus particles are captured by a cell that itself does not get infected (depicted in pink) and then presented to a target cell at a cell–cell contact designated infectious synapse (c). (d–e) Non-enveloped viruses can be released from an infected cell after cell-lysis (d) or non-lytically by acquisition of temporary host membrane to infect susceptible target cells via cell-free transmission (e). Panel (f) depicts a hypothesis for cell-to-cell transmission of non-enveloped viruses with acquired host membrane after polarized release at cell contact sites. Grey ovals represent cell nuclei.

Delay RD equation



Immune response:

Time delay
Growth for small load
Decay for large load



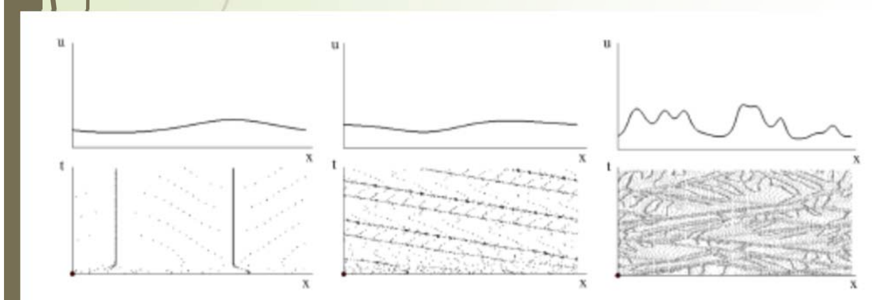
Local virus concentration in the tissue (lymph node, spleen)

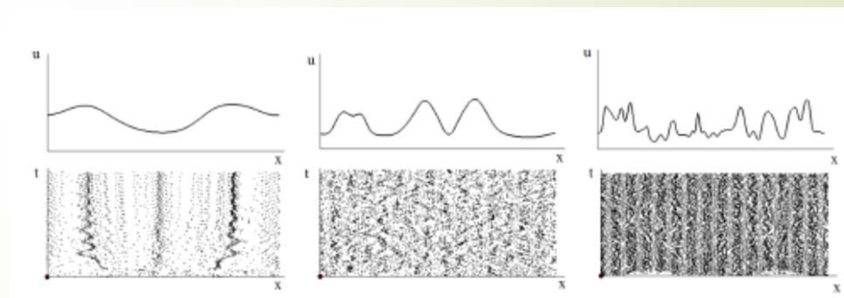
$$\frac{\partial v}{\partial t} = D\frac{\partial^2 v}{\partial x^2} + kv(1-v) - f(v_\tau)v.$$

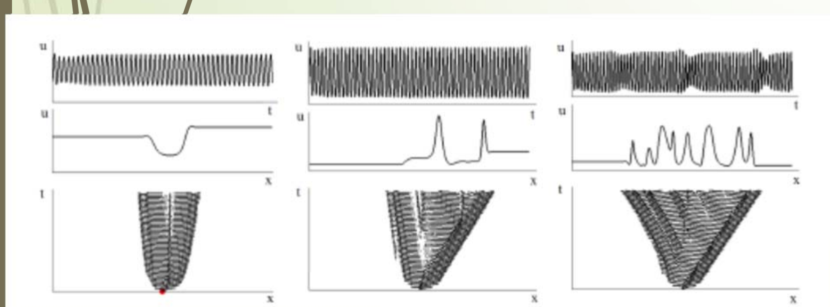
$$v = v(x,t),\ v_\tau = v(x, t-\tau)$$

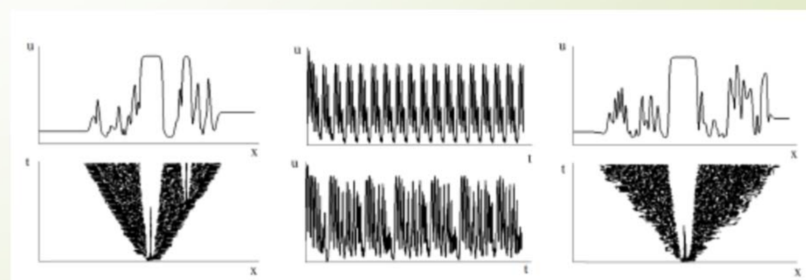
Delay RDE: spatio-temporal patterns and quasi-waves

$$\frac{\partial u}{\partial t} = D\Delta u + ku(1 - u - f(u_\tau)),$$





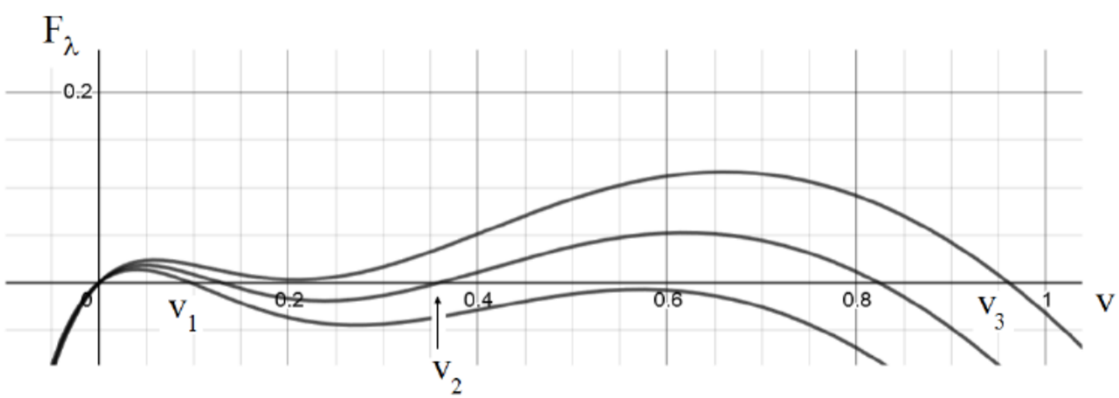




Single RDE without delay: waves and systems of waves

Virus spread without time delay

$$\frac{\partial v}{\partial t} = D\,\frac{\partial^2 v}{\partial x^2} + kv(1-v) - f(v)v.$$



$$F(v) = v\,(1 - v - f(v))\,.$$

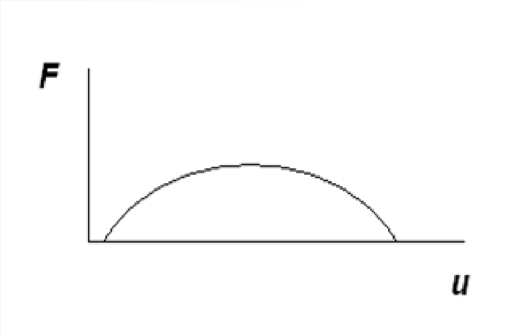
Reaction-diffusion waves: the beginning (the 1930s)

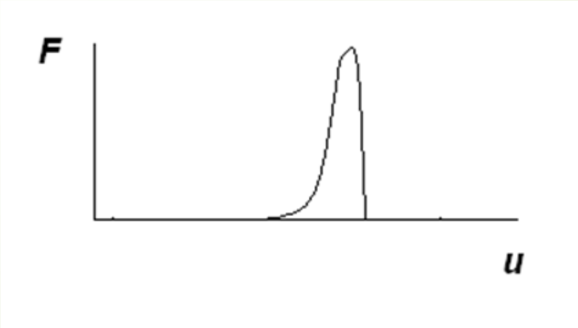
$$\frac{\partial u}{\partial t} = \frac{\partial^2 u}{\partial x^2} + F(u)$$

- Propagation of dominant gene (Fisher and KPP)

Cold flames or branching chain reactions (Semenov)

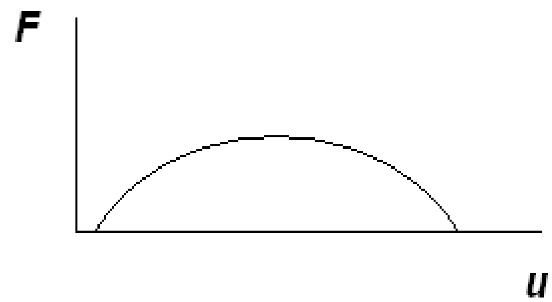
Combustion (Zeldovich and Frank-Kamenetskii)

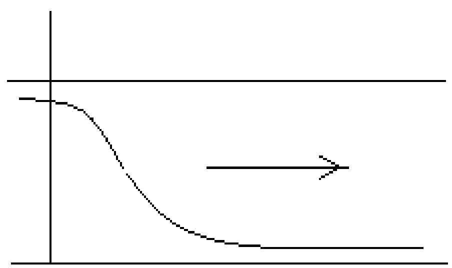




Reaction-diffusion waves

$$\frac{\partial u}{\partial t} = d\,\frac{\partial^2 u}{\partial x^2} + F(u)$$



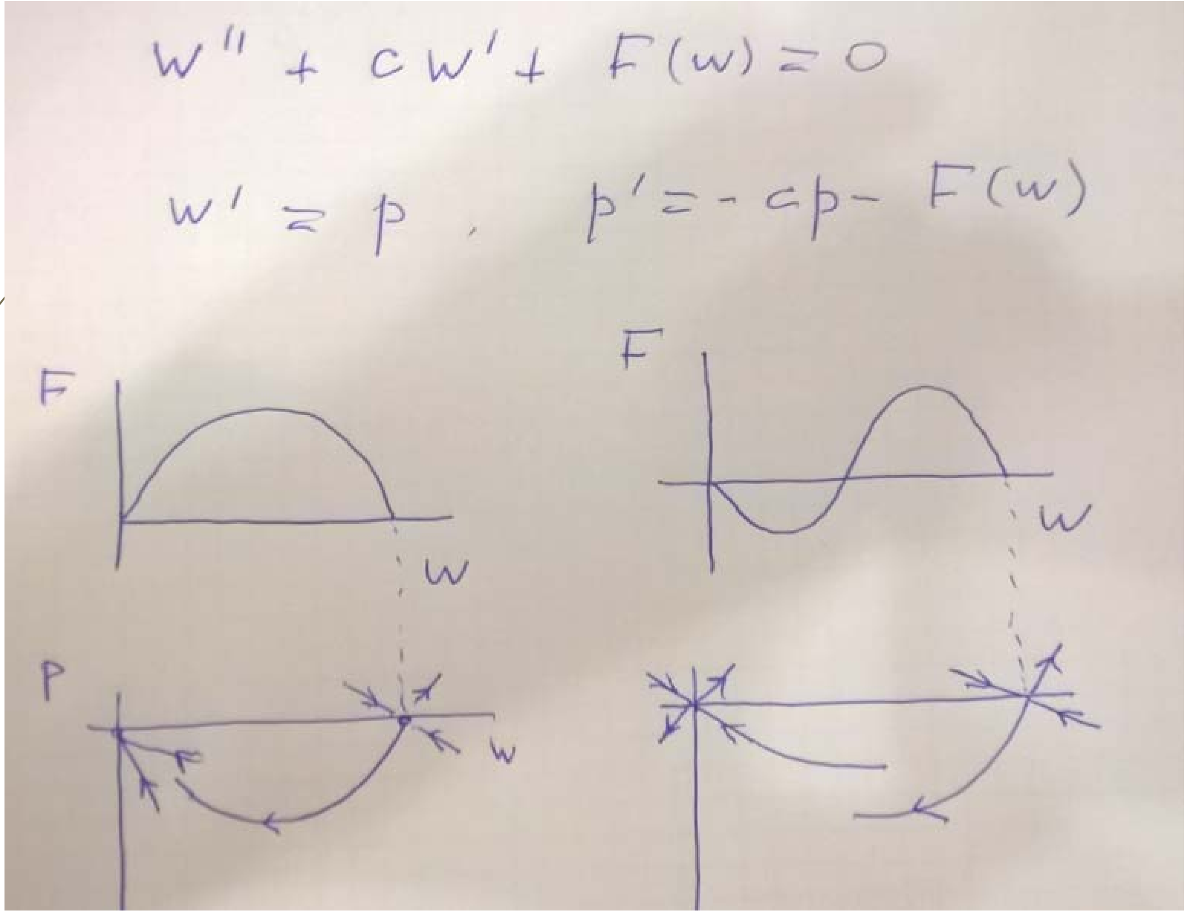


u(x,t) = w(x-ct)

w'' + c w' + F(w) = 0

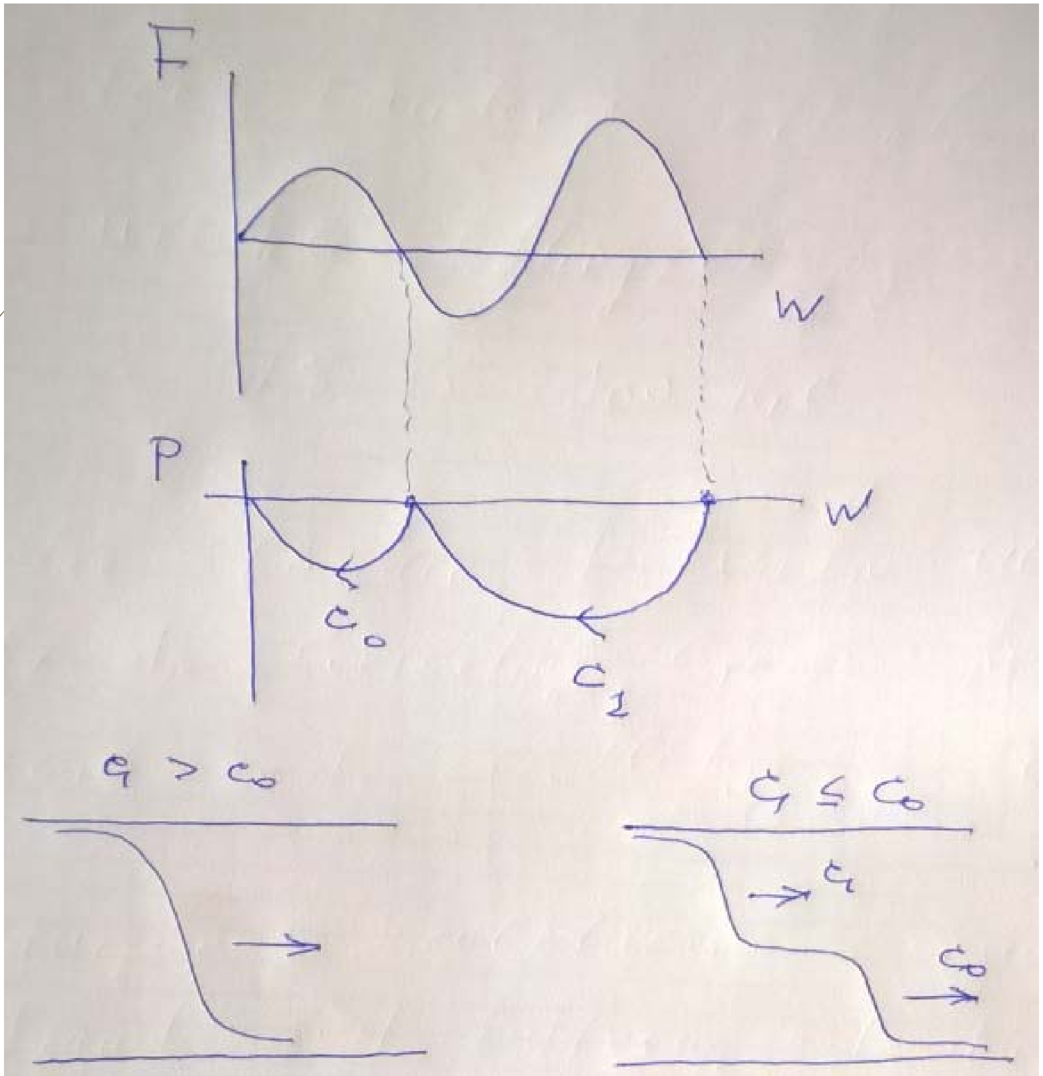
Reaction-diffusion waves

Monostable case: wave speeds greater than or equal to the minimal speed



Bistable case: single wave speed

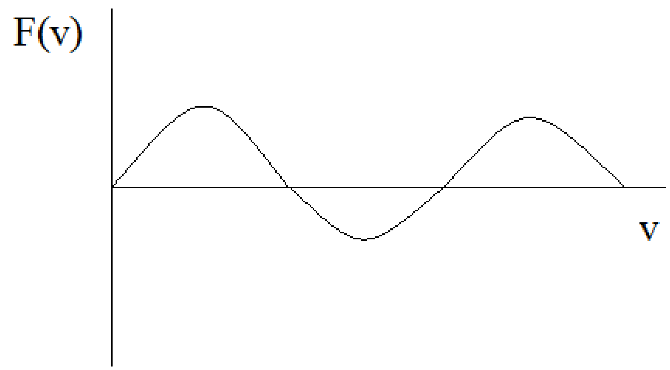
Systems of waves: existence and convergence



Virus spread without time delay

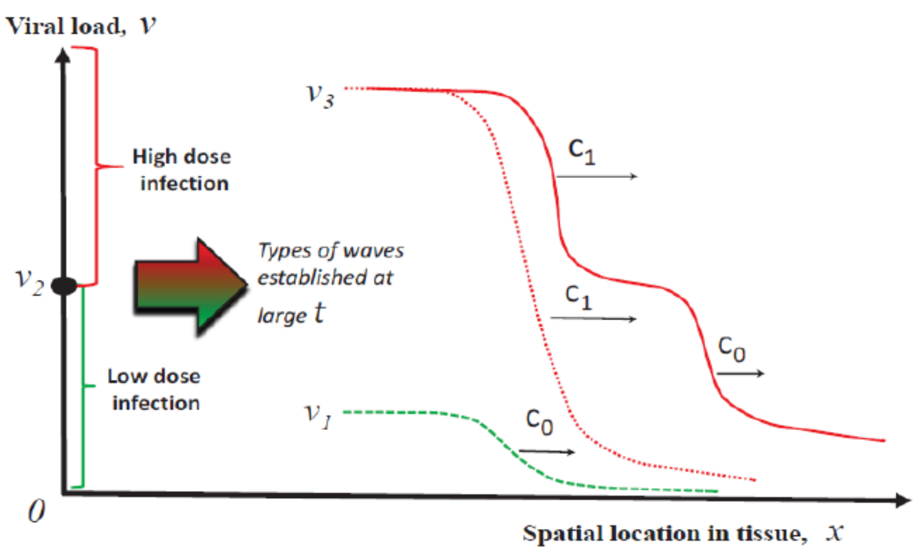
$$\frac{\partial v}{\partial t} = D\,\frac{\partial^2 v}{\partial x^2} + kv(1-v) - f(v)v.$$

$$F(v) = v\left(1 - v - f(v)\right).$$



Three regimes of infection spreading:

Low dose
High dose
Low-High dose



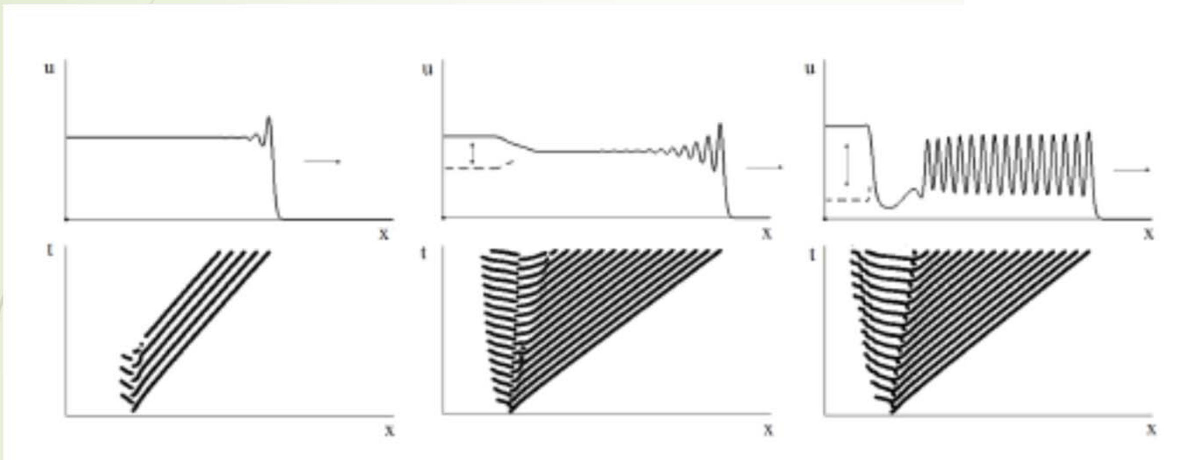
Delay RDE: waves

PLOS | ONE

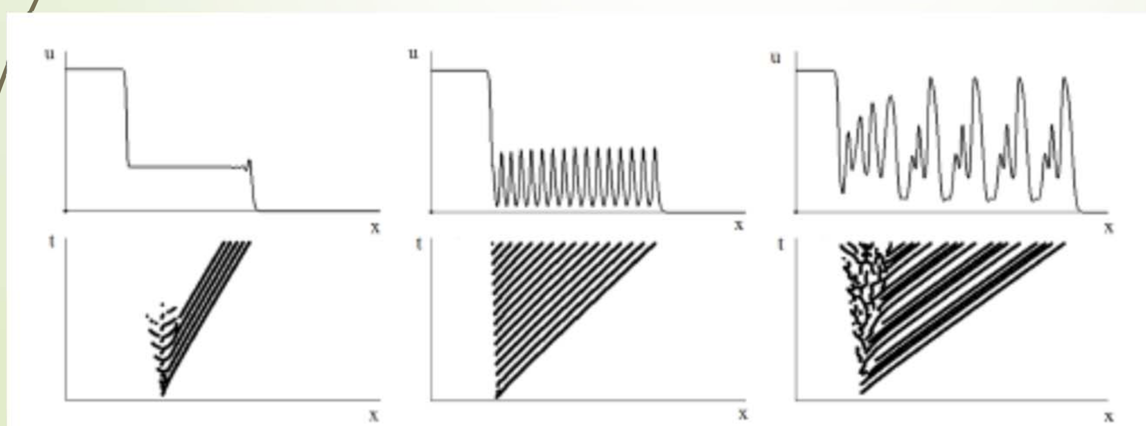
RESEARCH ARTICLE

Spatiotemporal Dynamics of Virus Infection Spreading in Tissues

Gennady Bocharov[1,9,10]*, Andreas Meyerhans[1,2,3], Nickolai Bessonov[4], Sergei Trofimchuk[5], Vitaly Volpert[1,6,7,8]



Monostable



Monostable-bistable

Wave existence in delay RDE

Single equation

$$\frac{\partial u}{\partial t} = D\Delta u + ku(1 - u - f(u_\tau)),$$

SIAM J. MATH. ANAL.
Vol. 50, No. 1, pp. 1175–1199

© 2018 Society for Industrial and Applied Mathematics

TRAVELING WAVES FOR A BISTABLE REACTION-DIFFUSION EQUATION WITH DELAY*

SERGEI TROFIMCHUK† AND VITALY VOLPERT‡

System of equations

$$\frac{\partial v}{\partial t} = D_1 \frac{\partial^2 v}{\partial x^2} + kv(1-v) - cv,$$
$$\frac{\partial c}{\partial t} = D_2 \frac{\partial^2 c}{\partial x^2} + \phi(v_\tau)c(1-c) - \psi(v_\tau)c,$$

Journal of Dynamics and Differential Equations
https://doi.org/10.1007/s10884-019-09751-4

Check for updates

Existence of Waves for a Bistable Reaction–Diffusion System with Delay

V. Volpert[1,2,3,4]

Existence of waves: mathematical theory

1. Linear elliptic problems in unbounded domains, Fredholm property, index, solvability conditions
2. Topological degree, Leray-Schauder method
3. A priori estimates of solutions in weighted spaces
4. Existence of waves for monotone and locally monotone systems, bistable delay and nonlocal equations, existence of pulses, …

Covid

- Pathophysiology:

lung alveoli – spontaneous coagulation;

lung bronchi – cilia cells – mucus production and motion;

ACE2 receptors – endothelial and epithelial cells – other organs

- Immunology: deficient lymphocytes – cytokine storm – excessive immune response

Stay healthy !