Reaction-diffusion waves in biological applications

V. Volpert (CNRS, Univ. Lyon 1)

Reaction-diffusion equations

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

heat or mass production

mass diffusion or heat conduction

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- Heat explosion (Semenov, Frank-Kamenetskii, 1930s)

$$\frac{\partial u}{\partial t} = \Delta u + e^u$$

Figure 1: Explosion thermique

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Figure 1: Explosion thermique

- Pattern formation (Turing, 1952)

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

$$\frac{\partial v}{\partial t} = d_v \frac{\partial^2 v}{\partial x^2} + G(u,v)$$

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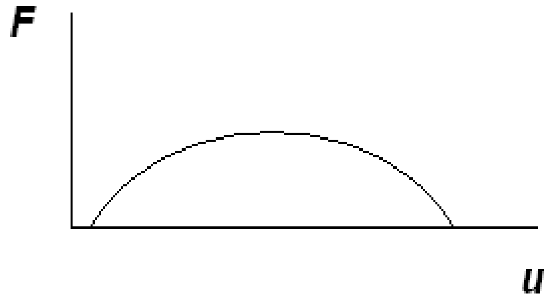
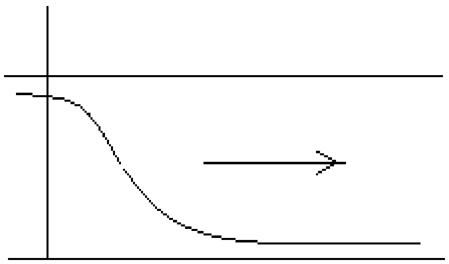
Reaction-diffusion waves

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





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

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

First works on chemical waves (1906)

Propagation of Chemical Reactions in Space

Robert Luther
Leipzig, Germany

Translated by:
Regina Arnold and Kenneth Showalter
Department of Chemistry, West Virginia University, Morgantown, WV 26506
John J. Tyson
Department of Biology, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061

The neutral alkyl sulfates are very stable in aqueous solution but slowly give off sulfuric acid upon acidification. If I introduce some acid on one end of the tube then, under the catalytic influence of H^+, hydrolysis ensues and new H^+ ions are formed. These ions diffuse to the right and cause the formation of more acid. In this way, the decomposition slowly moves through the tube.

The velocity of propagation is small, only a few centimeters per hour. Based on theory, this is to be expected. In principle, however, there is nothing to prevent any large velocity since the velocity of propagation (V) is given by

$$V = a\sqrt{K \cdot D \cdot C}$$

where a is a numeric factor, D a diffusion coefficient, C a …ration, and K a rate constant. When K increases …tly, so does the velocity of propagation.

Geheimrat Nernst—Berlin: Who has derived this formula?
Professor Luther—Leipzig: Myself.
Geheimrat Nernst—Berlin: But this is not published yet?
Professor Luther—Leipzig: No, but it is a simple consequence of the corresponding differential equation.

Comparison with propagation in nerve impulse

Comparison with combustion waves (cf. Mikhelson)

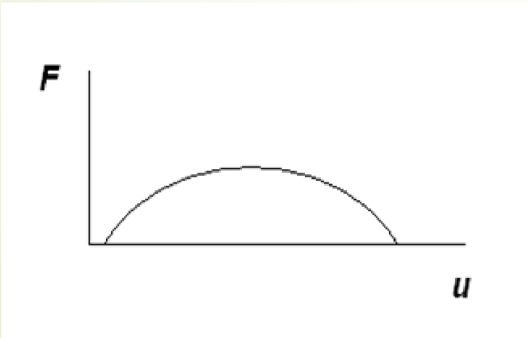
Reaction-diffusion waves: the beginning (the 1930s)

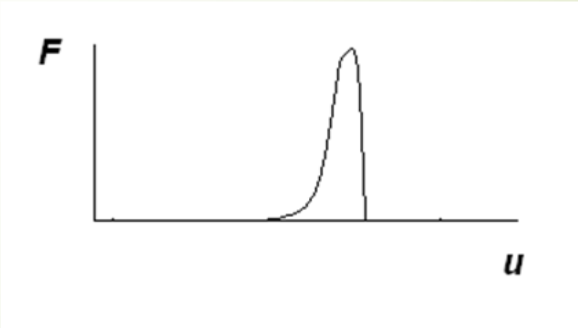
$$\frac{\partial u}{\partial t} = \frac{\partial^2 u}{\partial x^2} + F(u)$$

- Propagation of dominant gene (Fisher and KPP)

Cold flames or branching chain reactions (Semenov)

Combustion (Zeldovich and Frank-Kamenetskii)





Reaction-diffusion waves in biological applications

Ecology

Ecological invasions

Competition of species

Prey-predator

Speciation

Physiology

Normal

Pathological

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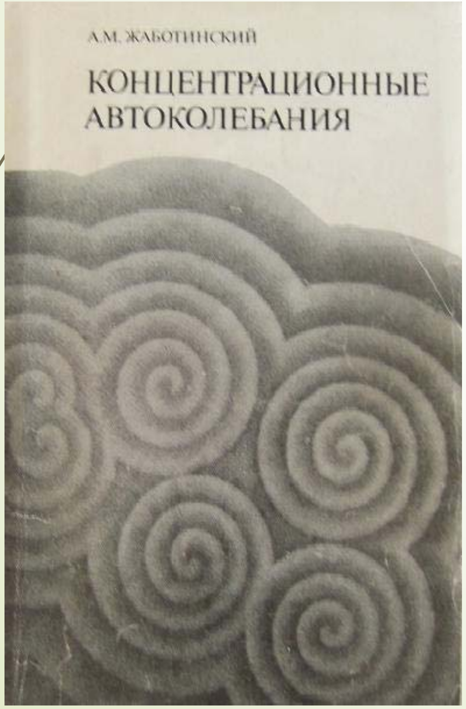
Reaction-diffusion waves in physiology

Excitable medium

(nerve impulse, heart)



Blood coagulation

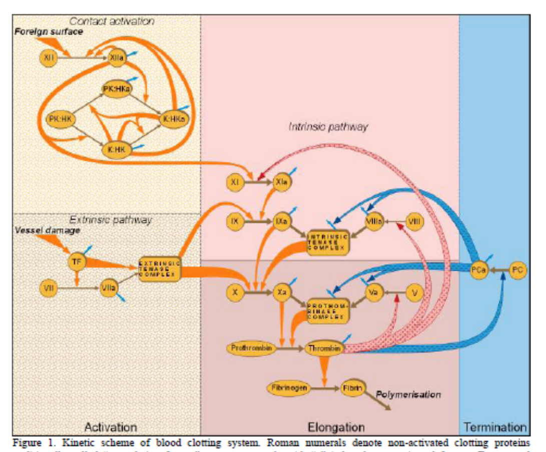
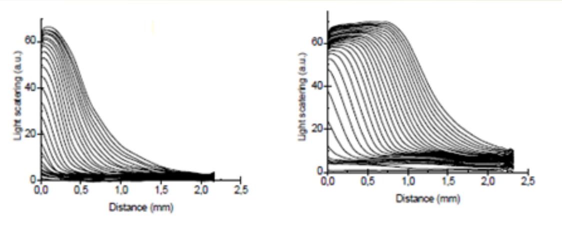


Figure 1. Kinetic scheme of blood clotting system. Roman numerals denote non-activated clotting proteins traditionally called "coagulation factors", roman numerals with "a" index denote activated factors. Tenase and



F. Ataullakhanov et al.

Reaction-diffusion waves in biological applications

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Reaction-diffusion waves: spreading diseases

Damaged part of the tissue grows in time

Tumor growth
Inflammation
Infection
Neurodegenerative disease

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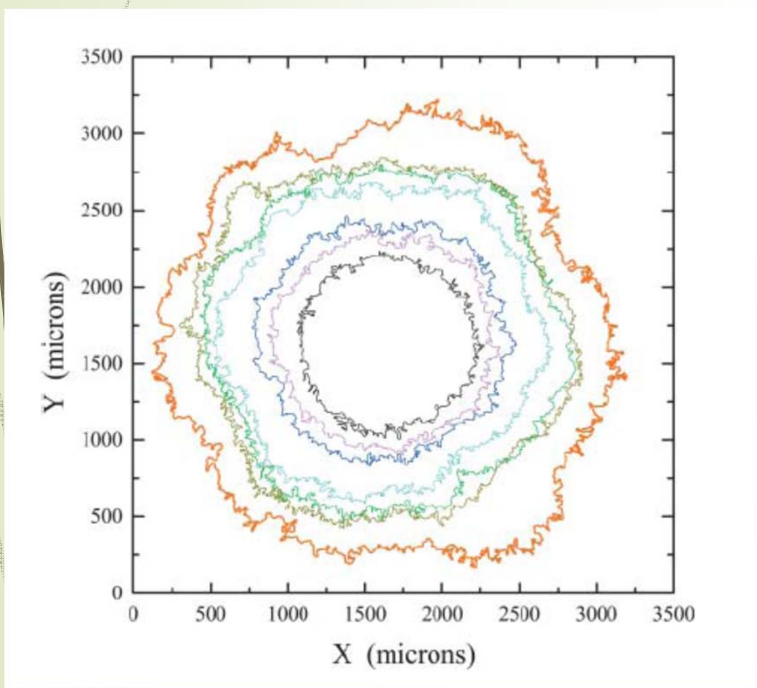
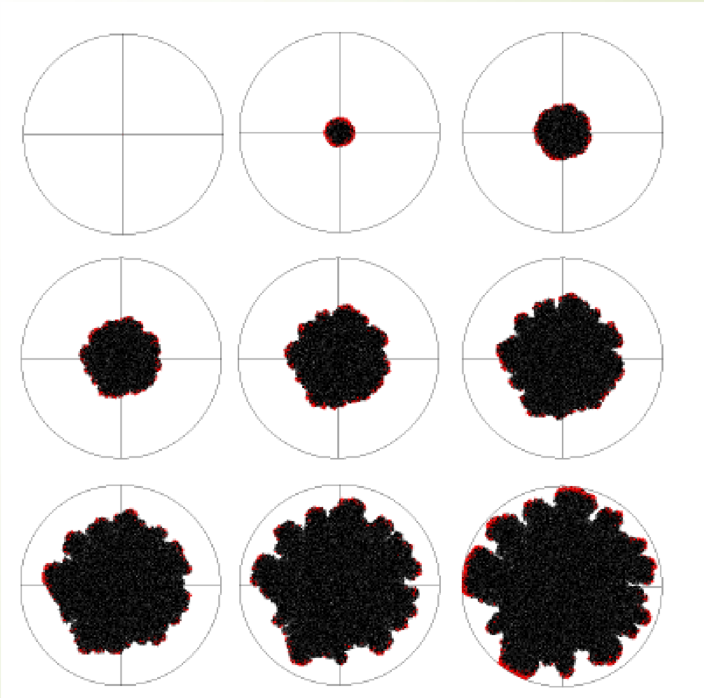
Tumor growth: excessive proliferation of malignant cells

$$\frac{\partial u}{\partial t} = d\,\frac{\partial^2 u}{\partial x^2} + au(1-u)$$

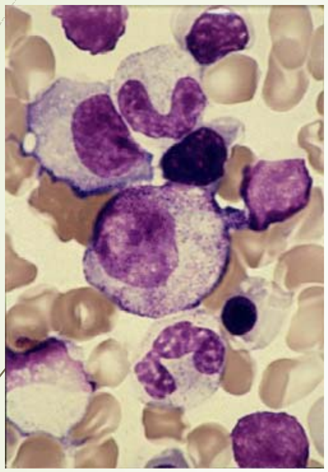


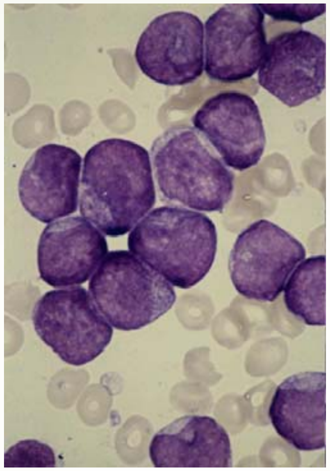
Experiments



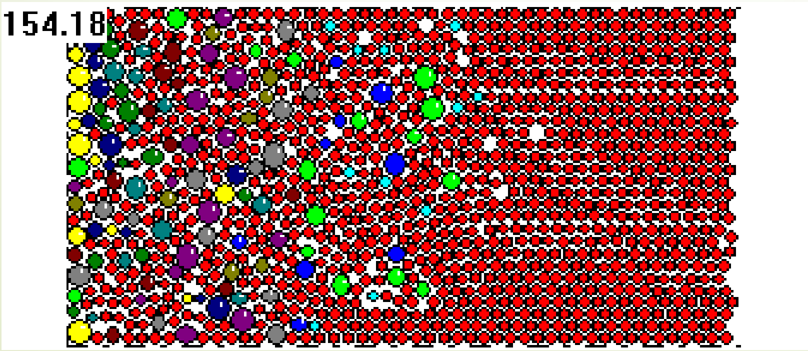
Simulations (hybrid model)

Leukemia: competition of normal and malignant cells



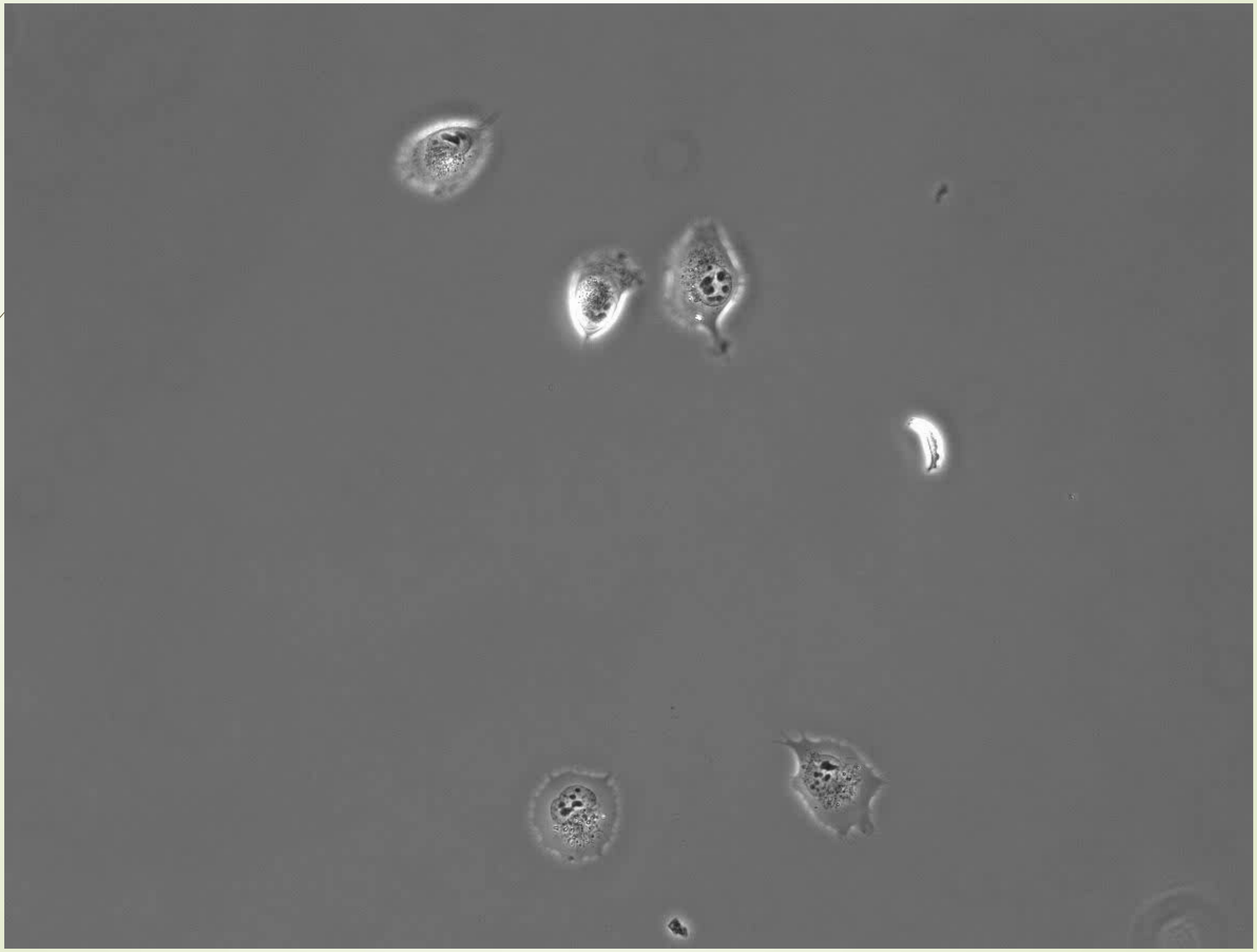


Normal bone marrow Leukemic bone marrow

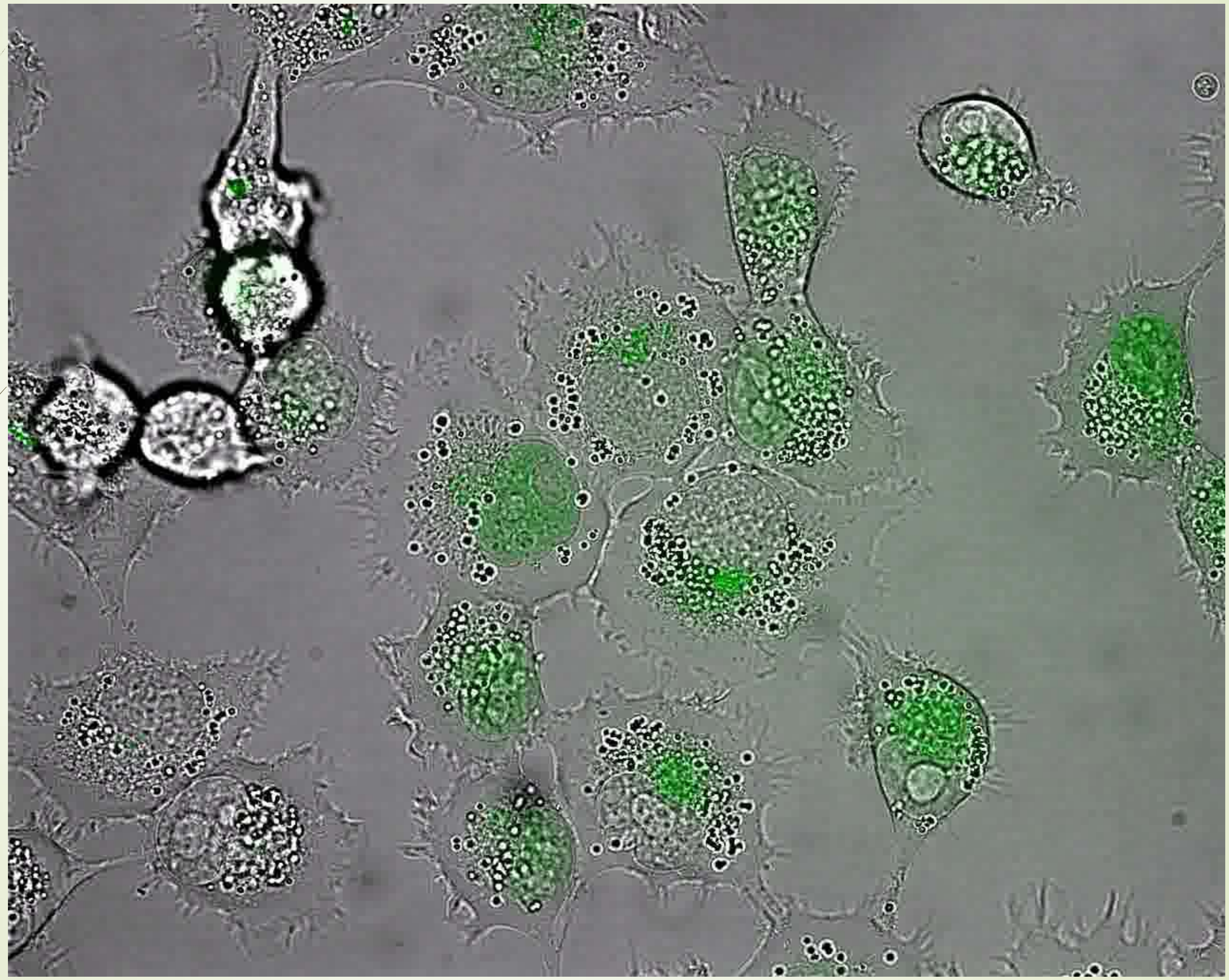


- ~1/1000 live with leukemia or in remission
- Five year relative survival rate: 14% in 1960, 54% in 2005
- Possible causes: radiation, chemicals, but mostly unknown
- Median patient age at diagnosis 66 years; 27% of all cancer cases for children

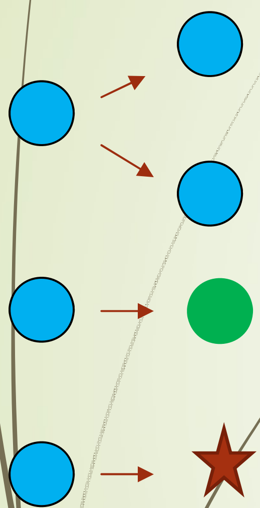
Concise cell biology for mathematicians: cell motion and division



Apoptosis



The model of cell competition



$$\begin{cases} \dfrac{\partial P}{\partial t} = D_P \dfrac{\partial^2 P}{\partial x^2} + H + (s-d)P(P_0 - P - Q) - aP, \\ \dfrac{\partial Q}{\partial t} = D_Q \dfrac{\partial^2 Q}{\partial x^2} + (s_m - d_m)Q(P_0 - P - Q) - a_m Q, \end{cases}$$

Normal

mutated

s, d, a – rates of self-renewal, differentiation, apoptosis

Mutation strength

$$M = \frac{s_m - d_m}{s - m} \; \frac{a}{a_m}$$

M small: disease free equilibrium is glob asym stable
M large: Leukemia development (reac-diff wave)

Reaction-diffusion waves: spreading diseases

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Atherosclerosis: chronic inflammation in blood vessel walls

Vessel walls become thick

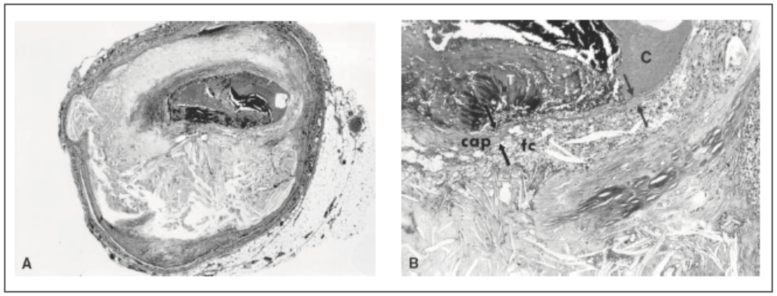
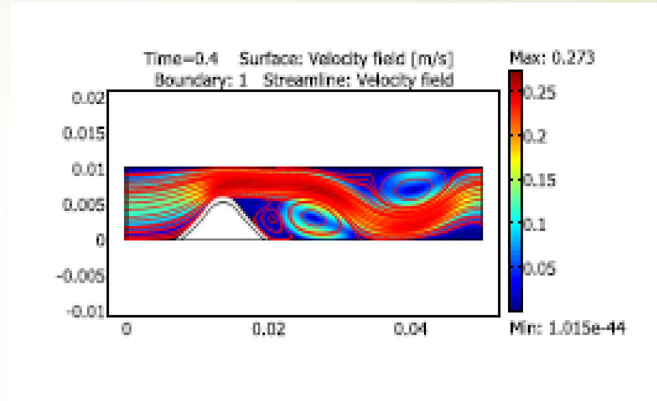
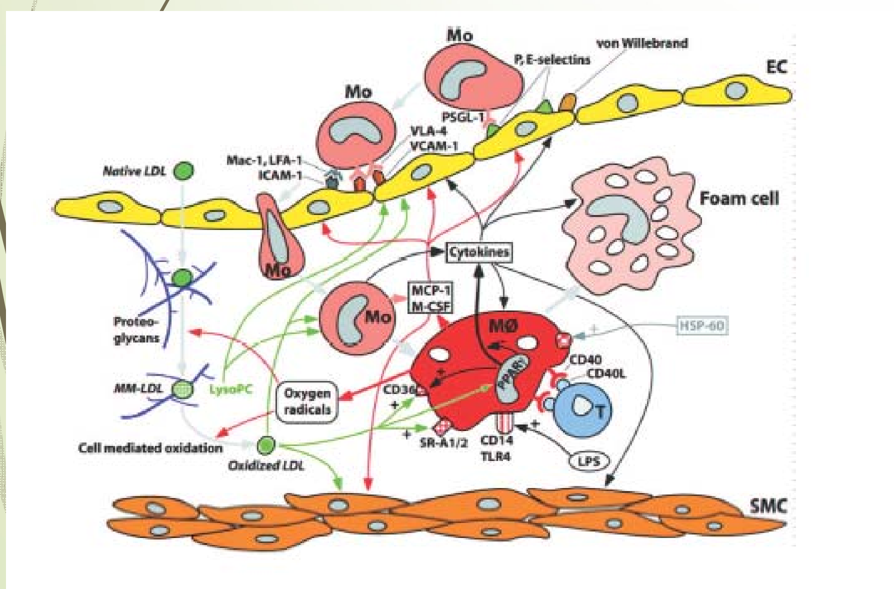


Figure 1: Plaque disruption and thrombosis. **A.** A stenotic coronary plaque containing a huge atheromatous core that is separated from the vascular lumen by a very thin cap of fibrous tissue, ie, a "vulnerable plaque". The fibrous cap is disrupted with superimposed non-occlusive luminal thrombosis. **B.** Higher magnification of the plaque-thrombus interface. The fibrous cap is very thin (between arrows) and heavily infiltrated by foam cells (fc), probably of macrophage origin. C: contrast medium injected post mortem; T: thrombus

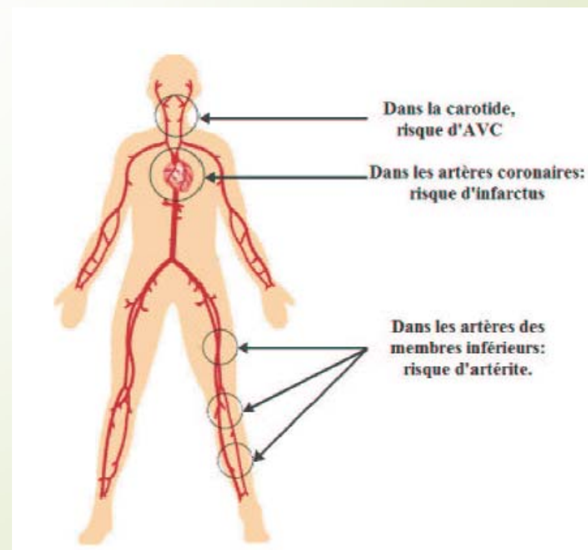
Blood flow changes; plaque rupture; oxygen supply



Inflammation development

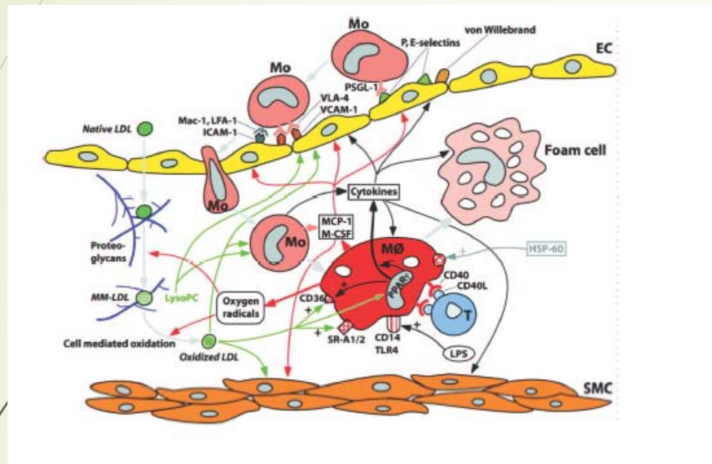


Sites of atherosclerosis



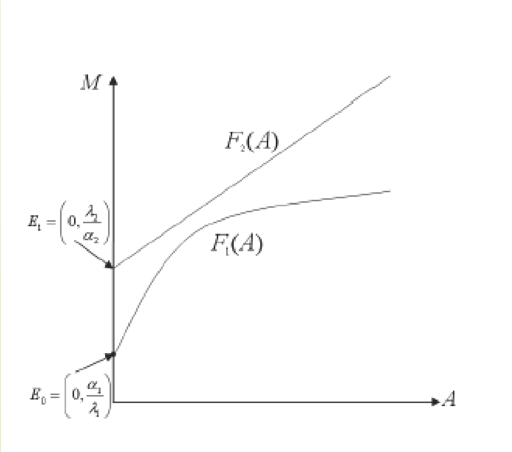
Atherosclerosis and cholesterol

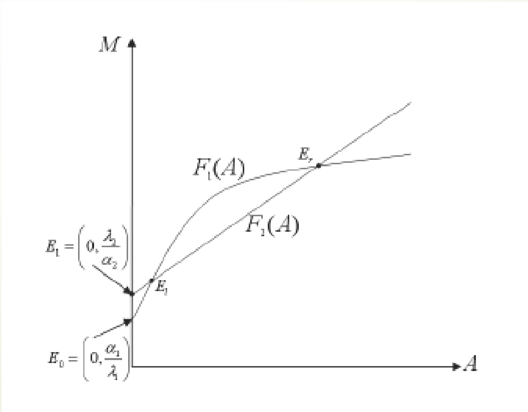
(Genieys, El Khatib, VV, MMNP, 2007)

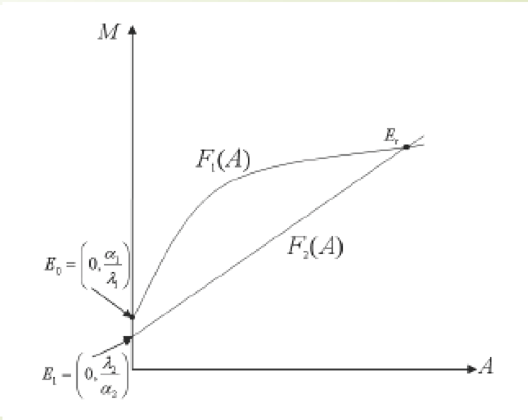


$$\begin{cases} \dfrac{dM}{dt} = f_1(A) - \lambda_1 M \\ \dfrac{dA}{dt} = f_2(A)M - \lambda_2 A \end{cases}$$

$$f_1(A) = \frac{\alpha_1 + \beta_1 A}{1 + A/\tau_1} \qquad f_2(A) = \frac{\alpha_2 A}{1 + A/\tau_2}$$



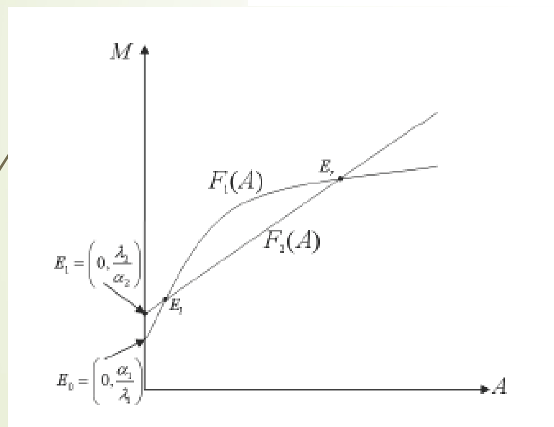


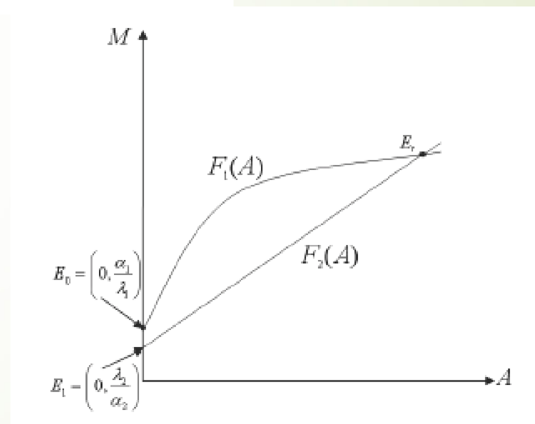


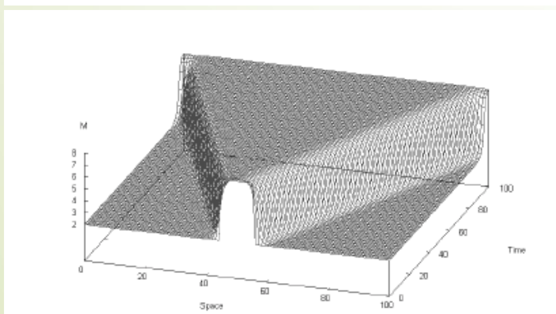
Cholesterol level: **low** **intermediate** **high**

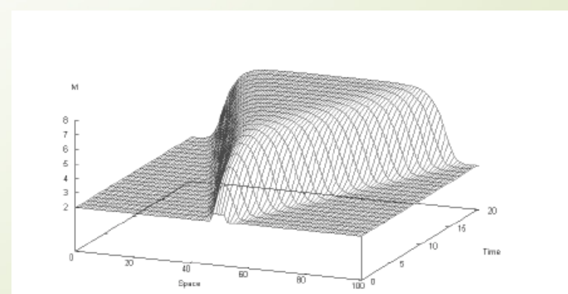
Atherosclerosis: reaction-diffusion waves

$$\begin{cases} \dfrac{\partial M}{\partial t} = d_1 \dfrac{\partial^2 M}{\partial x^2} + f_1(A) - \lambda_1 M \\ \dfrac{\partial A}{\partial t} = d_2 \dfrac{\partial^2 A}{\partial x^2} + f_2(A)M - \lambda_2 A \end{cases}$$

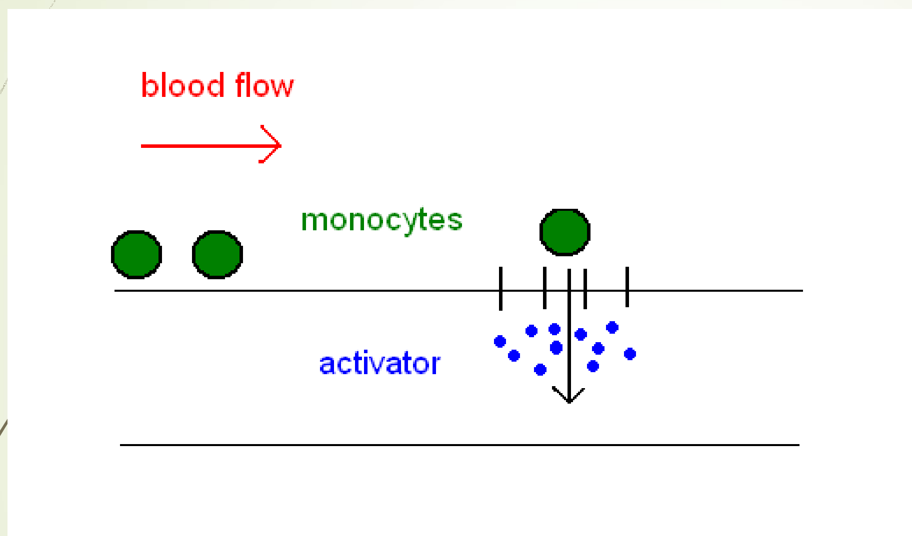








2D model: nonlinear boundary conditions



N. Apreutesei, VV

$$\frac{\partial M}{\partial t} = d_M \Delta M - \beta M,$$

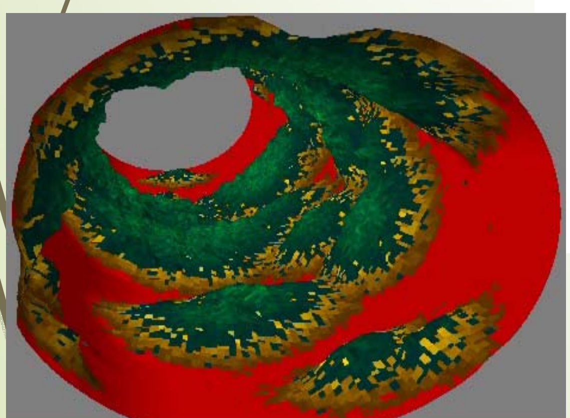
$$\frac{\partial A}{\partial t} = d_A \Delta A + f(A)M - \gamma A + b$$

in the two-dimensional strip $\Omega \subset \mathbb{R}^2$,

$$\Omega = \{(x, y), -\infty < x < \infty,\ 0 \le y \le h\}$$

with the boundary conditions

$$y = 0: \ \frac{\partial M}{\partial y} = 0, \ \frac{\partial A}{\partial y} = 0, \ \ y = h: \ \frac{\partial M}{\partial y} = g(A), \ \frac{\partial A}{\partial y} = 0$$



Cellular automata (Poston, MMNP, 2007)

First conclusion

- Tumor growth, atherosclerosis, other spreading diseases represent reaction-diffusion waves

Reaction-diffusion waves in biological applications

Ecology	Physiology
Ecological invasions	Normal
Competition of species	Pathological
Prey-predator	
Speciation	

Reaction-diffusion waves in biological applications

Ecology

Ecological invasions

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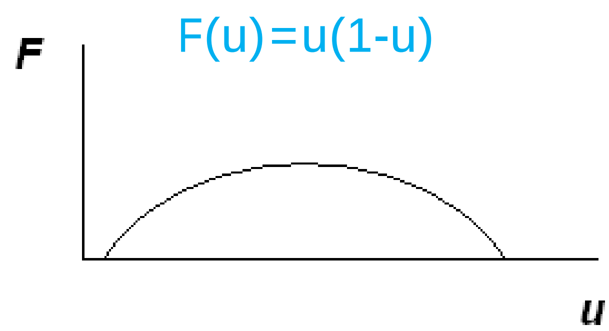
Physiology

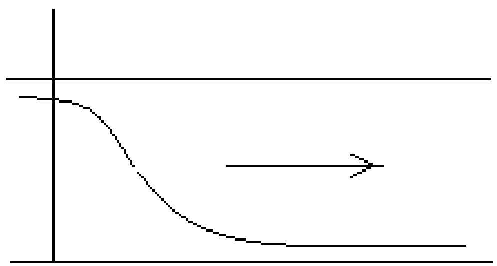
Normal

Pathological

Fisher – KPP equation: propagation of dominant gene

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





Existence for all speeds > or = minimal velocity

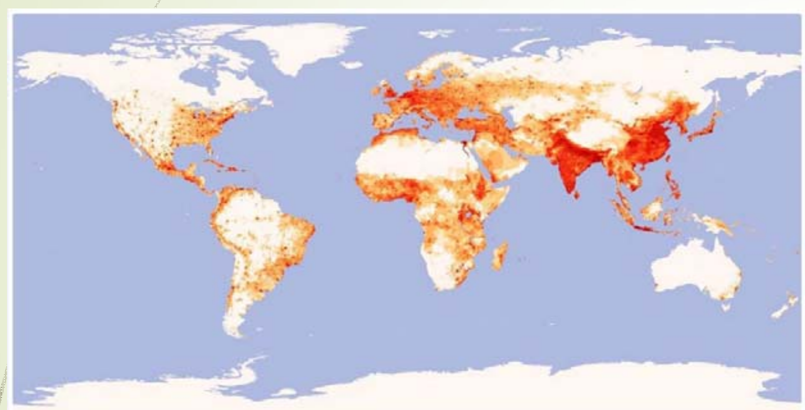
Global convergence to waves

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

$w'' + c\,w' + F(w) = 0$

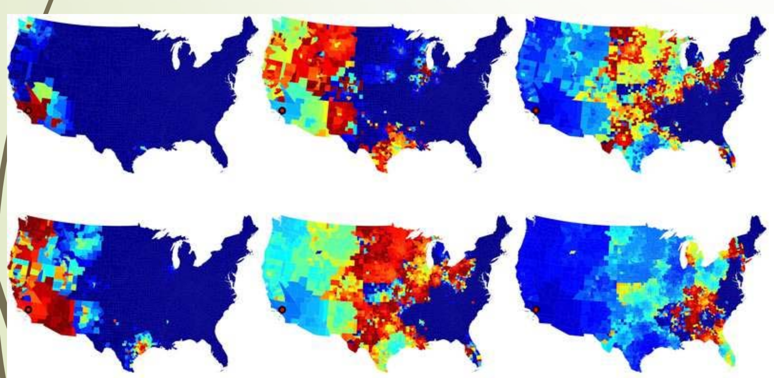
Biological invasions

(what is the difference between homo sapiens and influenza?)



Homo sapiens

(KPP model)



Influenza virus
(SIR model)

Competition of species and prey-predator models (A. Lotka and V. Volterra)

$$\frac{du}{dt} = auv - bu$$

$$\frac{dv}{dt} = cv - duv$$

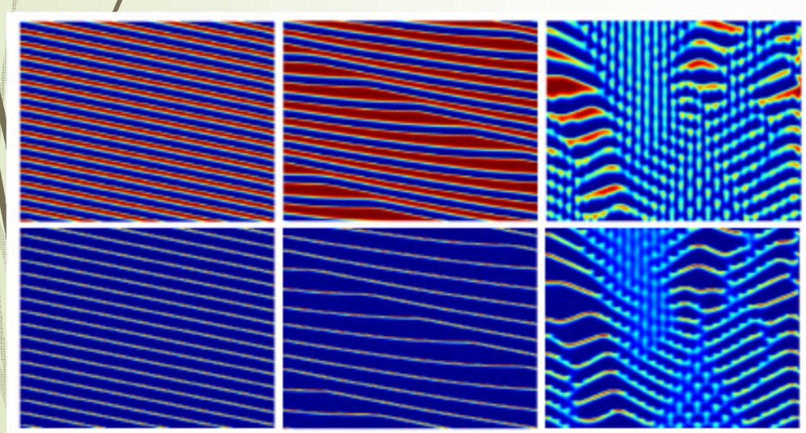
$$\frac{du}{dt} = k_1 u(1 - au - bv),$$

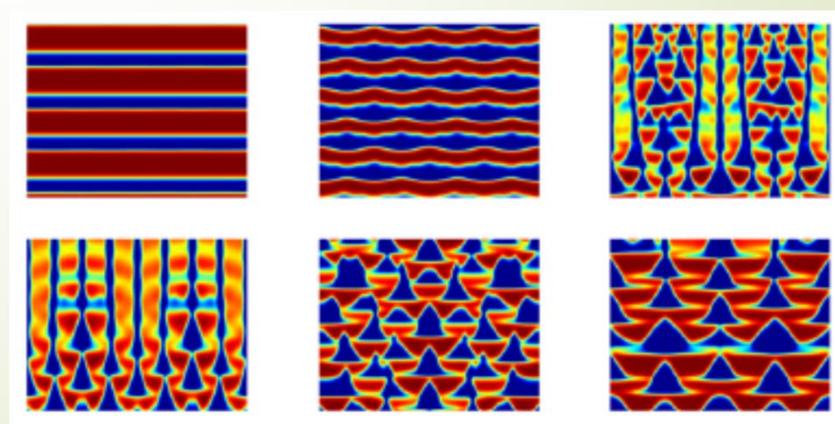
$$\frac{dv}{dt} = k_2 v(1 - cu - dv)$$

Prey-predator model

Competition of species

+ diffusion





M. Banerjee, VV, Chaos, 2016

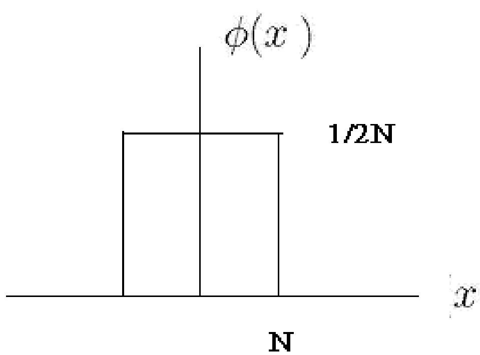
Nonlocal consumption of resources and speciation

Nonlocal reaction-diffusion equations

$$\frac{\partial u}{\partial t} = d\,\frac{\partial^2 u}{\partial x^2} + \overbrace{ku\left(1 - \underbrace{\int_{-\infty}^{\infty} \phi(x-y)u(y,t)dy}_{\text{resources}}\right)}^{\text{reproduction}}$$

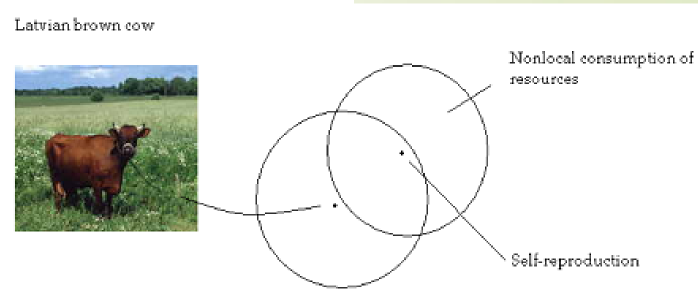
density of the population

nonlocal consumption



reproduction = u(1-u) if $\phi = \delta$

(N –> 0)



Stability analysis – Pattern formation

Britton, Gourley, …

$$\frac{\partial u}{\partial t} = d\,\frac{\partial^2 u}{\partial x^2} + ku\left(1 - \int_{-\infty}^{\infty} \phi(x-y)u(y,t)dy\right)$$

Homogeneous in space stationary solutions: $u = 0$, $u = 1$

Spectrum of the linearized operator

$$du'' - \sigma \int_{-\infty}^{\infty} \phi(x-y)u(y)dy = \lambda u$$

Fourier transform

$$-\lambda = d\xi^2 + \frac{\sigma}{\xi N}\ \sin(\xi N$$

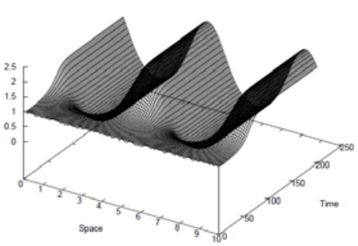
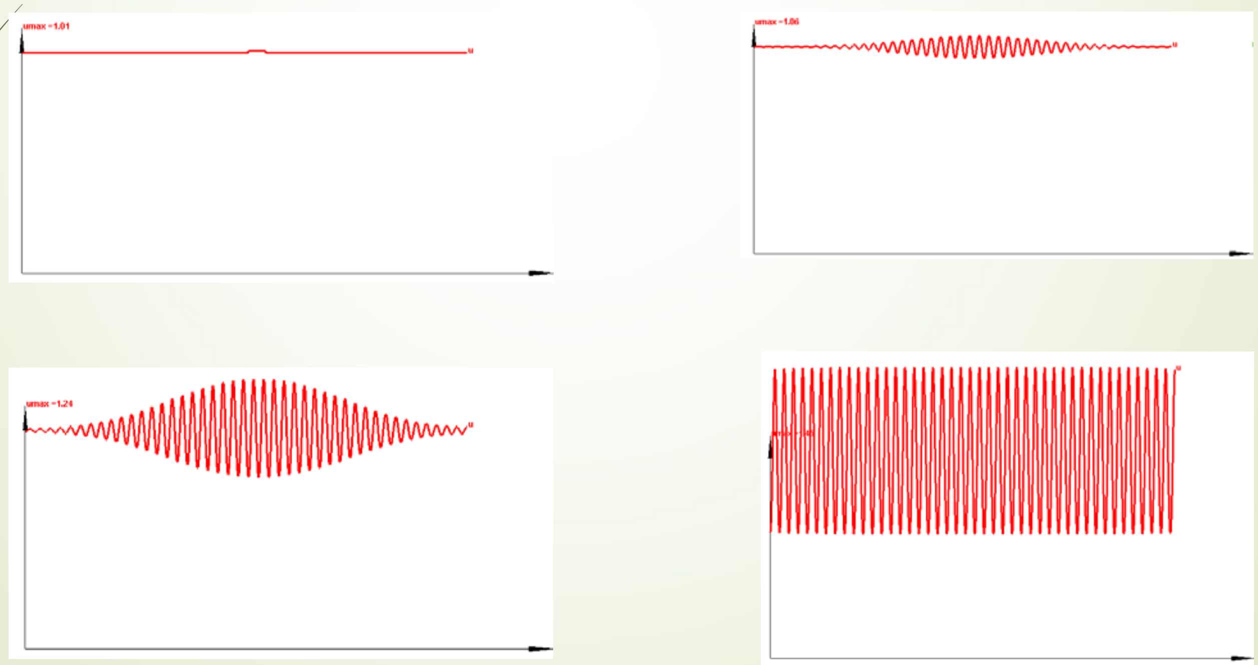


Figure 13: L'instabilité de la solution $u = 1$ et l'emergence de la solution périodique.

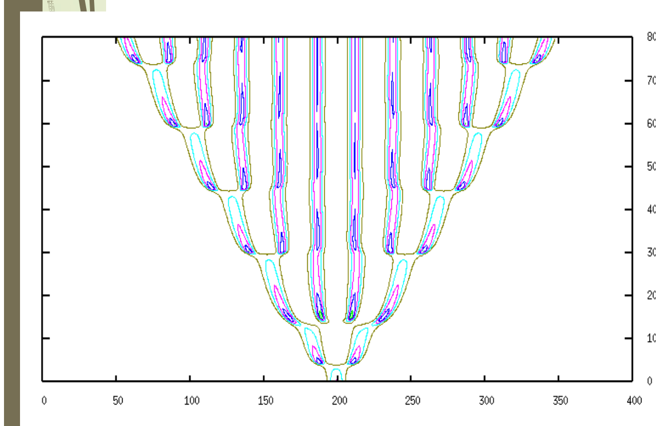
Instability of the constant solution

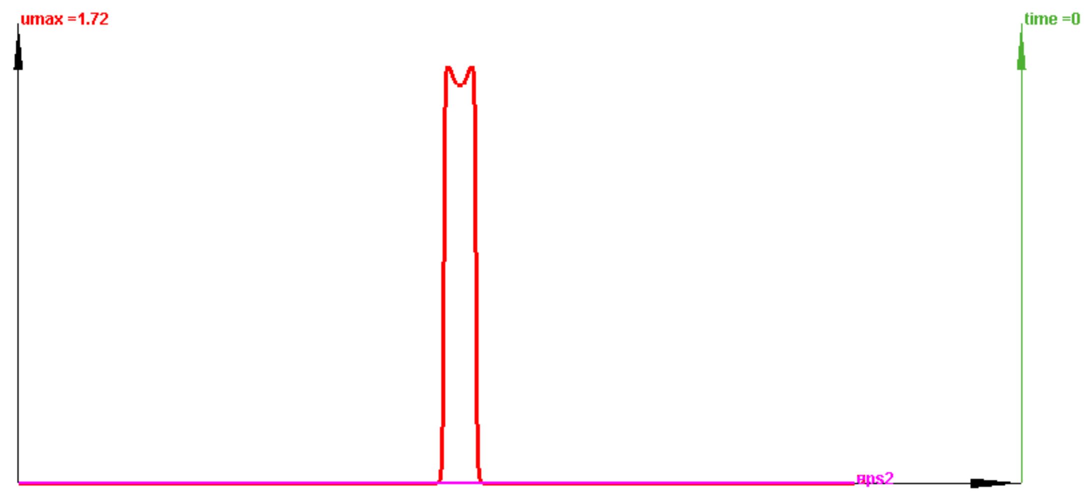
$$\frac{\partial u}{\partial t} = d\,\frac{\partial^2 u}{\partial x^2} + ku\left(1 - \int_{-\infty}^{\infty} \phi(x-y)u(y,t)dy\right)$$



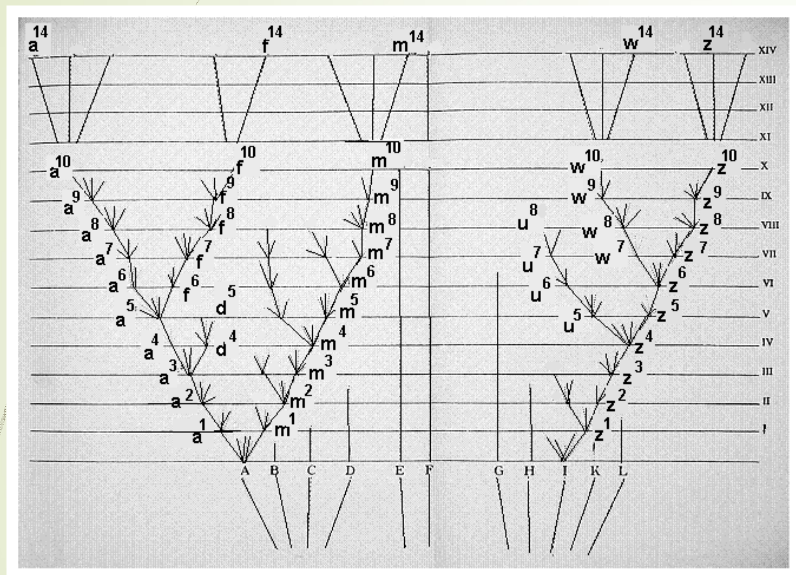
Periodic wave propagation

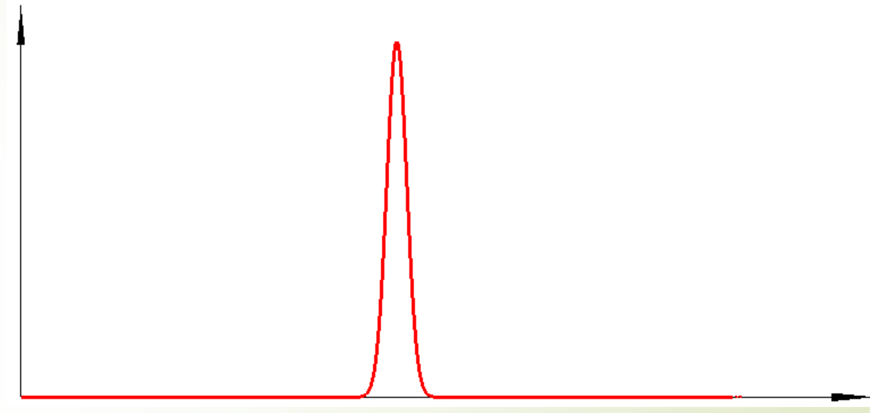
$$\frac{\partial u}{\partial t} = d\,\frac{\partial^2 u}{\partial x^2} + ku\left(1 - \int_{-\infty}^{\infty} \phi(x-y)u(y,t)dy\right)$$





Darwin's diagram and its mathematical interpretation



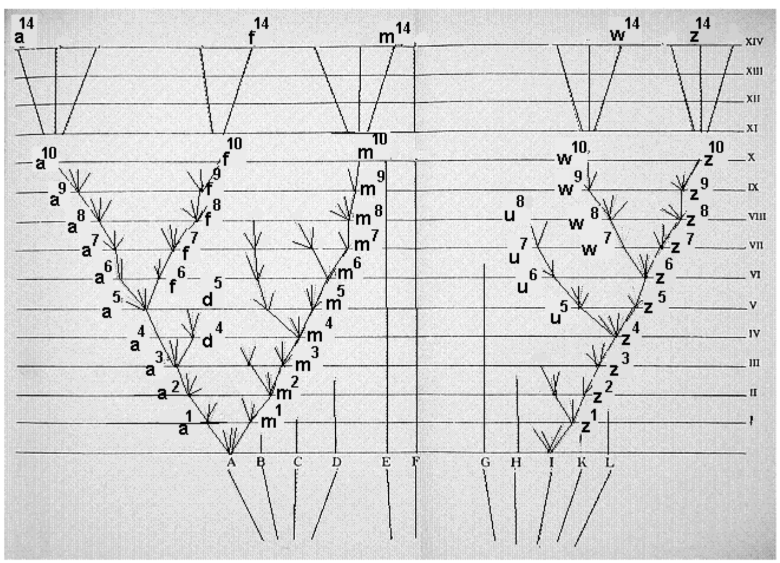


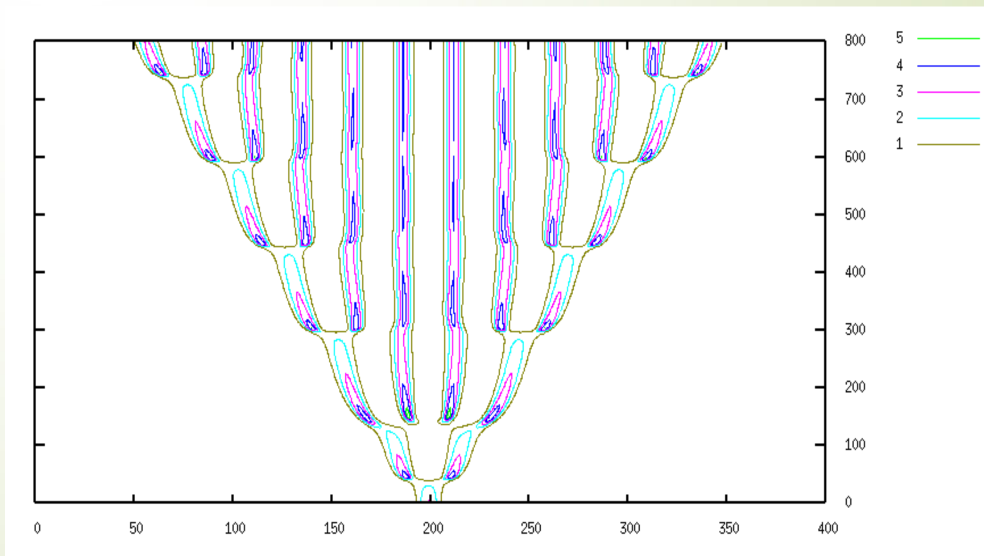
Let A to L represent the species of a genus large in its own country; these species are supposed to resemble each other in unequal degrees, as is so generally the case in nature, and is represented in the diagram by the letters standing at unequal distance ... The little fan of diverging dotted lines of unequal length proceeding from (A), may represent its varying offspring.

Emergence of species

S, Genieys, VV,P. Auger, MMNP, 2006

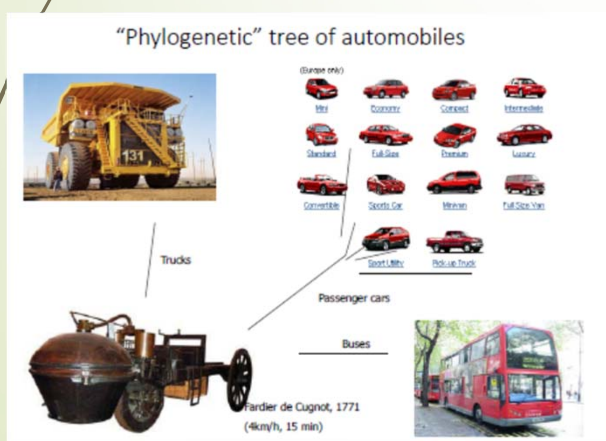
$$\frac{\partial u}{\partial t} = \frac{\partial^2 u}{\partial x^2} + ku^2 \left(1 - \int_{-\infty}^{\infty} \varphi(x-y)\, u(y,t)\, dy \right) - bu$$

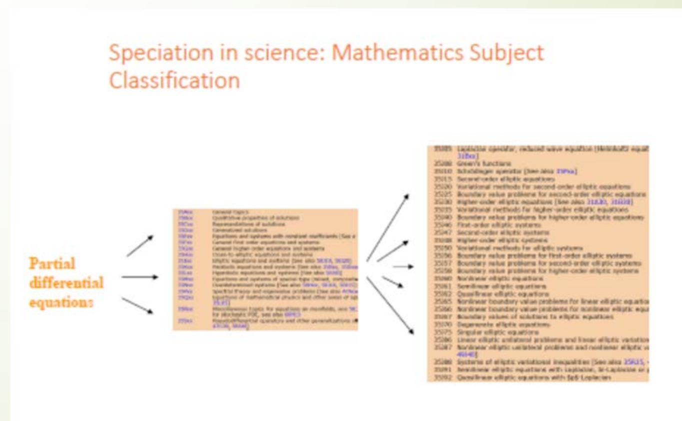




Conditions of (simpatric) speciation

- Nonlocal consumption of resources (intra-specific competition)
- Self-reproduction
- Diffusion (mutations)



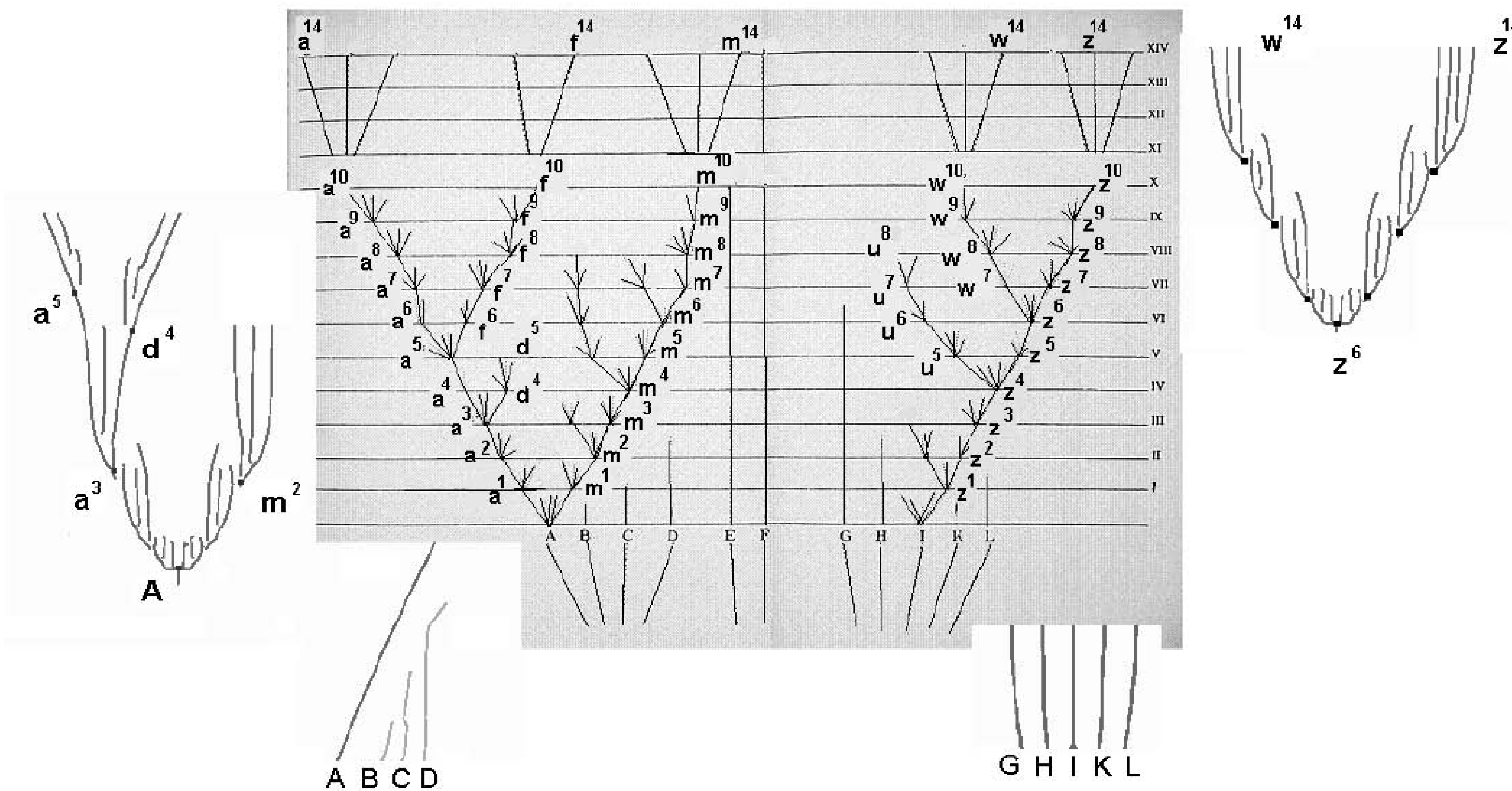


Second conclusion

- Emergence of species – ecological invasion in the morphological space – periodic reaction-diffusion wave

Darwin's diagram: survival, disappearance and competition of species

N. Bessonov, N. Reinberg, VV, MMNP, 2015



Definition of species: Darwin vs Mayr

M. Banerjee, V. Vougalter, VV. AMM,2016

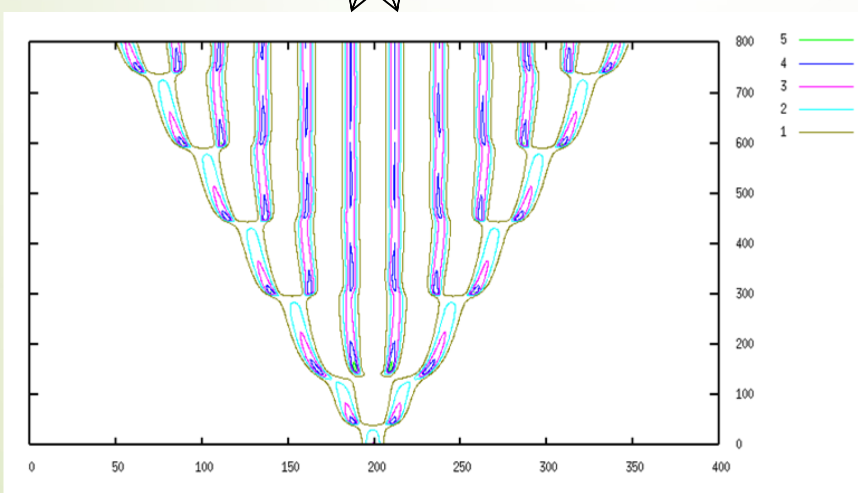
Darwin: morphologically similar individuals
Mayr: reproduction

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + a(S(u))^2(1 - J(u)) - bu,$$

$$S(u) = \frac{1}{2h_1}\int_{-\infty}^{\infty} \psi(x-y)u(y,t)dy, \quad \psi(z) = \begin{cases} 1, & |z| \le h_1 \\ 0, & |z| > h_1 \end{cases},$$

$$J(u) = r(h_2)\int_{-\infty}^{\infty} \phi(x-y)u(y,t)dy, \quad \phi(z) = \begin{cases} 1, & |z| \le h_2 \\ 0, & |z| > h_2 \end{cases}.$$

Phenotypes of parents can be different



Species do not emerge if reproduction of different is allowed

Mayr’s condition is necessary for Darwin’s speciation

Conclusions

- Biological systems often possess multiple equilibria
- Transition between them are described by reaction-diffusion waves (biological invasions, spreading diseases)
- Mathematical analysis allows us (sometimes) to determine their existence, stability and speed of propagation