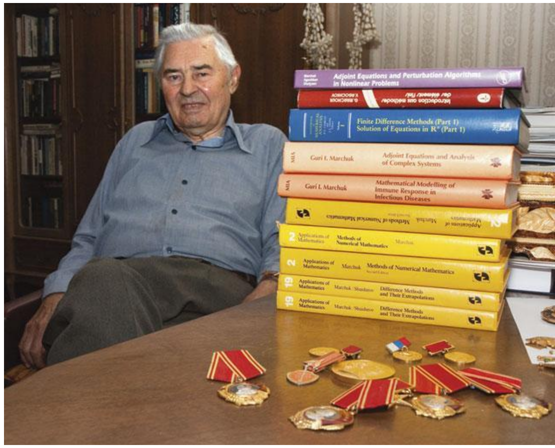
On the research by Guri Ivanovich Marchuk in mathematical immunology

1973 - 2013



Complex nature of the immune system

day/month

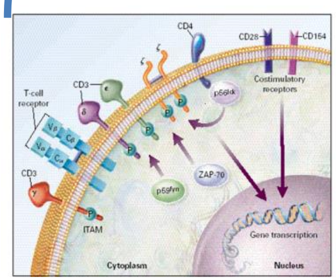
Systems level processes:
pathology, protection

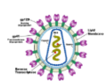
min/hour

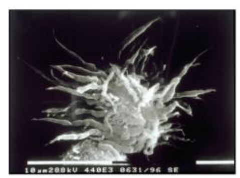
Cell populations:
proliferation,
differentiation,
apoptosis,
migration

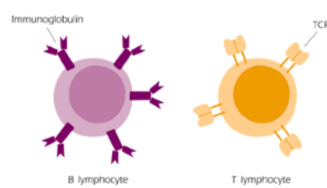
μsec/sec

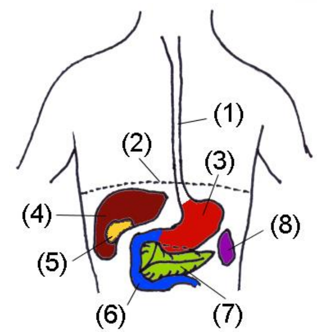
(molecular: receptor-ligand ,
signal transduction,
gene regulation)

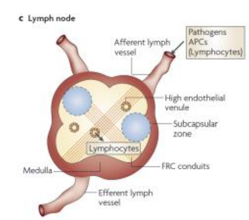


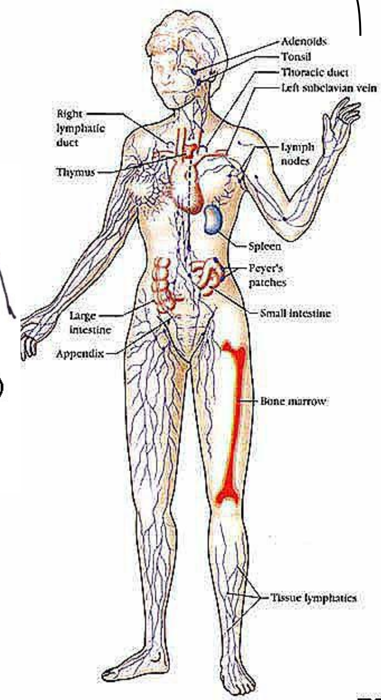












receptors,
proteins

viruses

cells

tissues

organs

Organism

1 nm = 10^{-9} m

1 μм = 10^{-6} m

1 mm = 10^{-3} m

1 m

Mathematical immunology

Mathematics:
Studies the Notions of
Quantity, Structure, Space and Change

Immunology: *The science of biological, chemical and physical aspects of the immune system functioning to maintain the antigenic homeostasis*

Underlying processes

Physical
- Transport
- Diffusion

Chemical
- Ligand-receptor
- Signal transduction
- Peptide synthesis

Biological
- Cell division (~6 hrs)
- Cell differentiation
- Cell apoptosis
- Gene regulation
- Generation of antigen receptor diversity

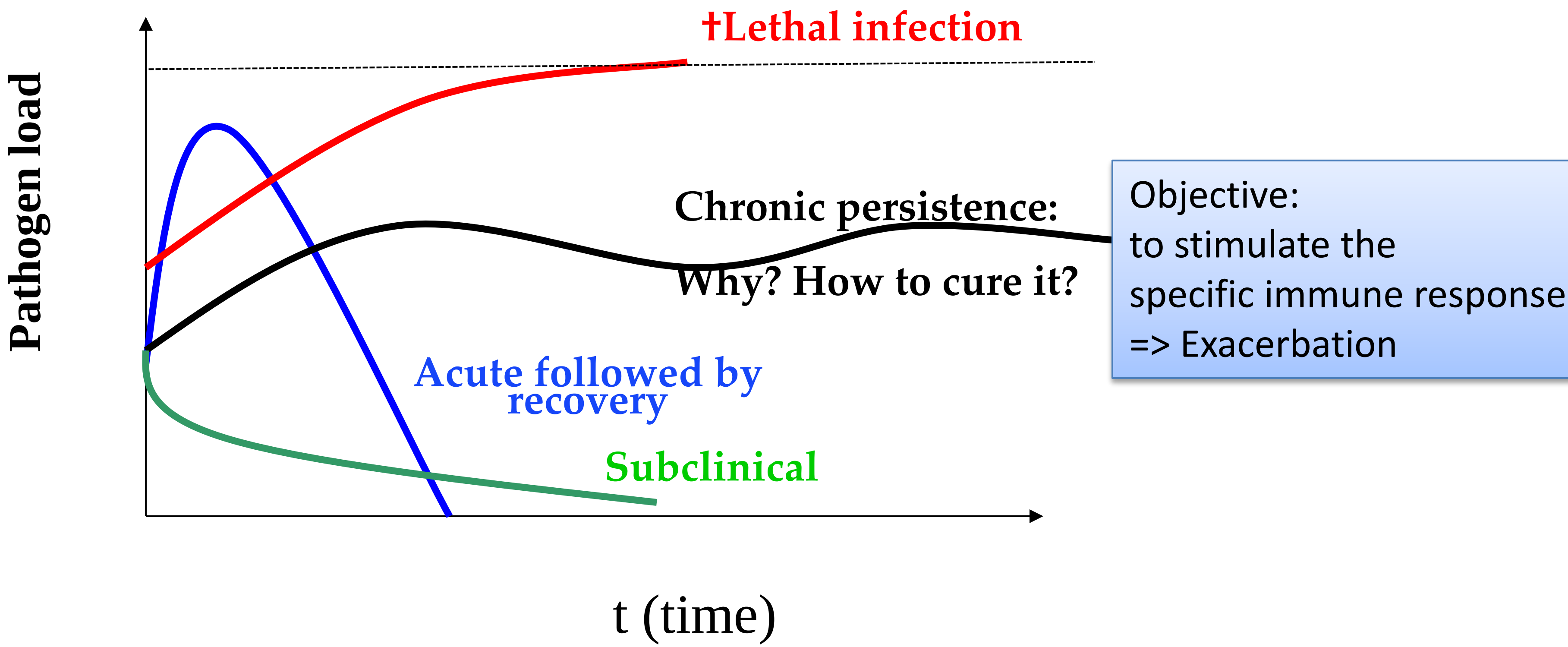
Mathematical immunology

can be defined as the branch of mathematics dealing with the application of mathematical methods and computer technologies to explore the structure, organization and regulation of the immune system in health and disease

Основная функция – защита от инфекций

Four dynamic patterns of infectious diseases:

(i) subclinical,
(ii) acute with recovery,
(iii) chronic,
(iv) lethal infection



„Parameters“ that determine the outcome of virus infection:

Underlying processes

Physical

•Transport

•Diffusion

Chemical

• Ligand-receptor

• Signal transduction

• Peptide synthesis

Biological

•Cell division (~6 hrs)

•Cell differentiation

•Cell apoptosis

•Gene regulation

•Generation of antigen receptor diversity

The clinician‘s perspective:

Health condition of the infected individual (Tx patient, newborn etc., age)

Immunopathology

Cytopathicity of virus

Persistence

Tropism

Latency

Dose of infection

The „numbers game“ (mathematical) perspective:

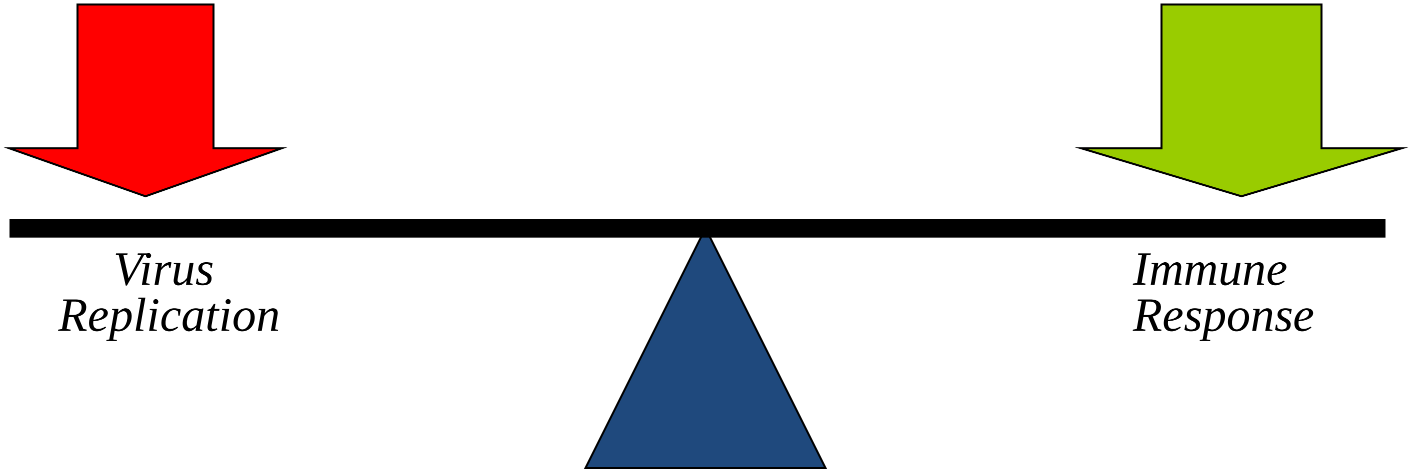
•*replication rate*

•*immunological parameters of the host*

•*kinetics of the virus-host interaction*

Dynamic interplay between virus & host factors in the outcome of infection

View of the viruses & the host as competitors for 'resources' of survival

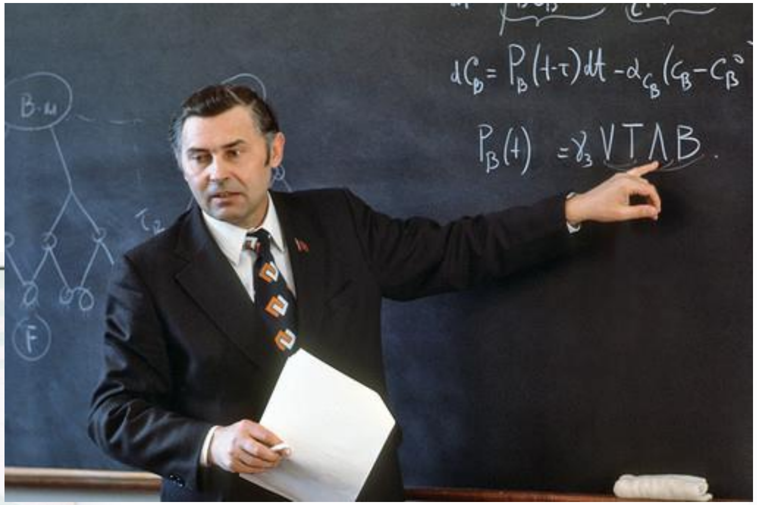


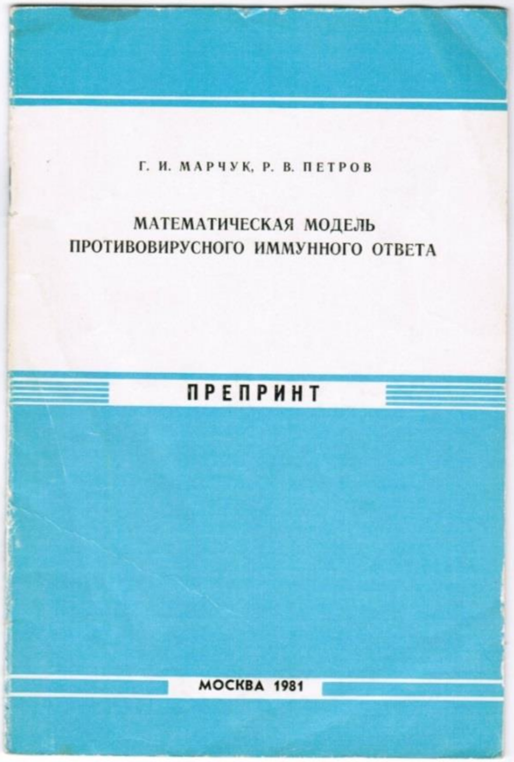
Replication rate in virus persistence: pro & contra

- Earlier experimental studies with LCMV infection in mice suggested that the faster speed of virus replication is an advantage for a virus in overcoming the immune system control and establishing the persistent infection – the tolerance by exhaustion (Moskophidis et al., *Nature* (1993) 362: 758-761)
- Theoretical prediction:

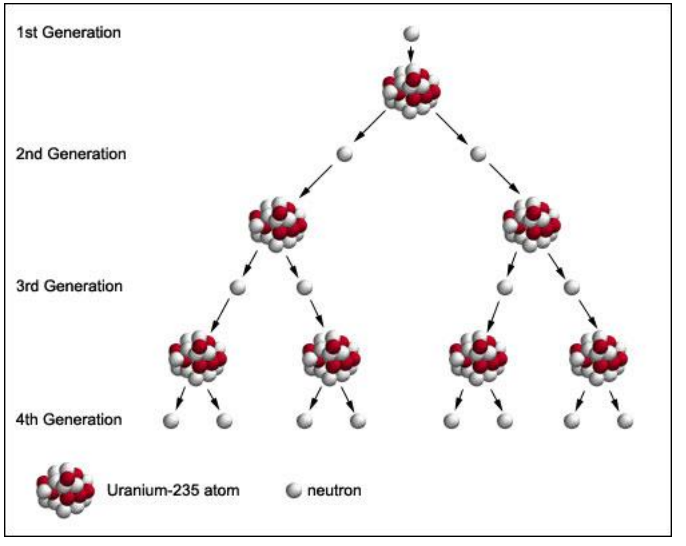
❑ Slow virus replication favors the long-term persistence (Marchuk and Belykh, 1980)

Fundamental models





Mathematical immunology and the nuclear chain reaction



George Irving Bell

4.08.1926-28.05.2000

- Harvard University (Physics) - 1947
- Division "T" Los Alamos Scientific Laboratory - 1947
- **"Nuclear reactor theory"** - 1970
- Quantitative models in immunology - 1970
- Theoretical Biology & Biophysics. Los Alamos NL - 1974
- Humane genome Project – 1988

Гурий Иванович Марчук

8.06.1925-24.03.2013

- Math-Mech. Of the LSU – 1949
- Division "B" of the Physics and Energetics Institute - 1953
- **"Numerical Methods for Nuclear Reactors"** – M. 1959
- Mathematical modelling in immunology - 1975
- CS of the SB of the USSR AS (1964), INM USSR AS, RAS (1980)

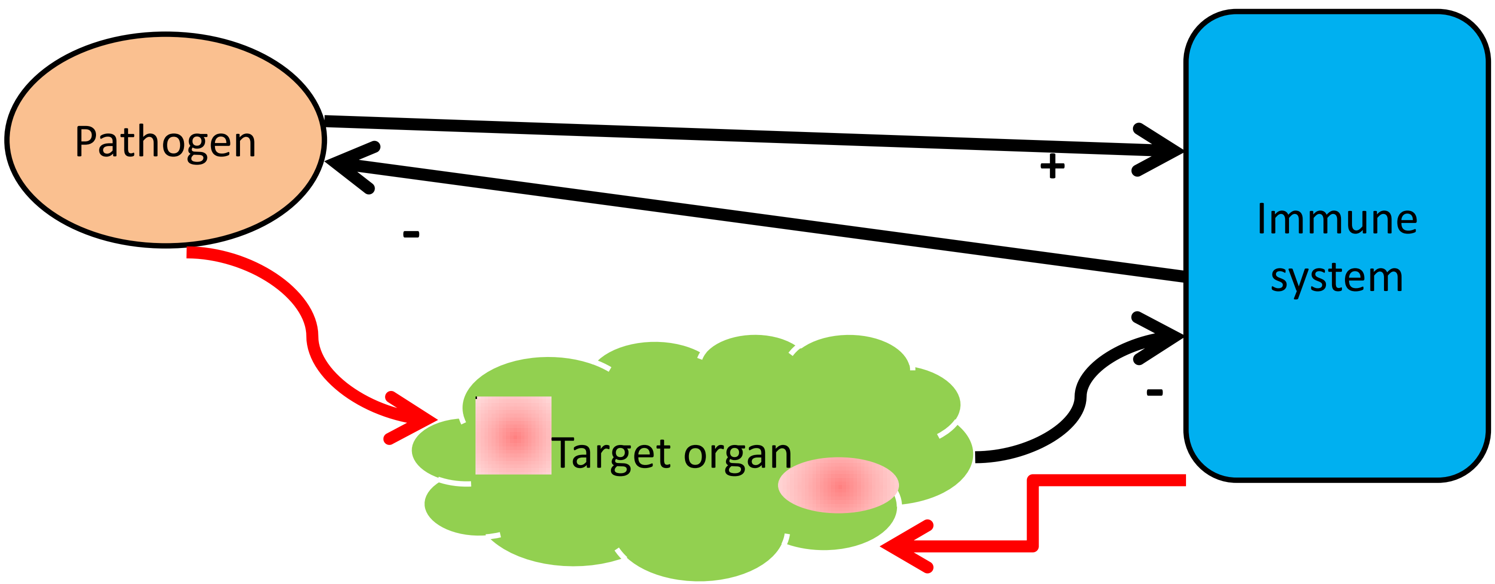
Математические модели иммунного ответа на размножающийся антиген

G.I. Bell: A mathematical description for replicating antigen (1973)

- *Lotka-Volterra*-type of equations
- ***Predator-Prey view***

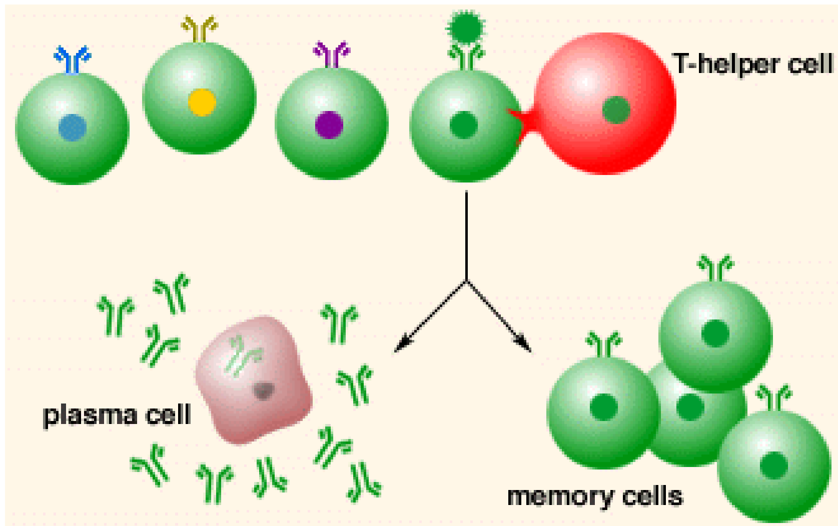
Г.И. Марчук: Mathematical model of infectious disease (1974)

- *Original system of delay differential equations*
- *Target organ damage*
- *Competition between the virus population and the host for the survival resources*

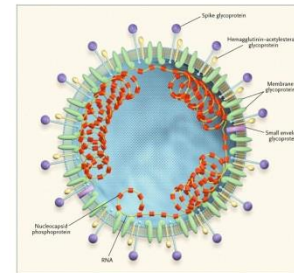


Clonal Selection Theory: F. Burnet, N. Jerne, D. Talmage

Lymphocytes bearing Ag-specific receptors (Ig)



Virus expressing Ag

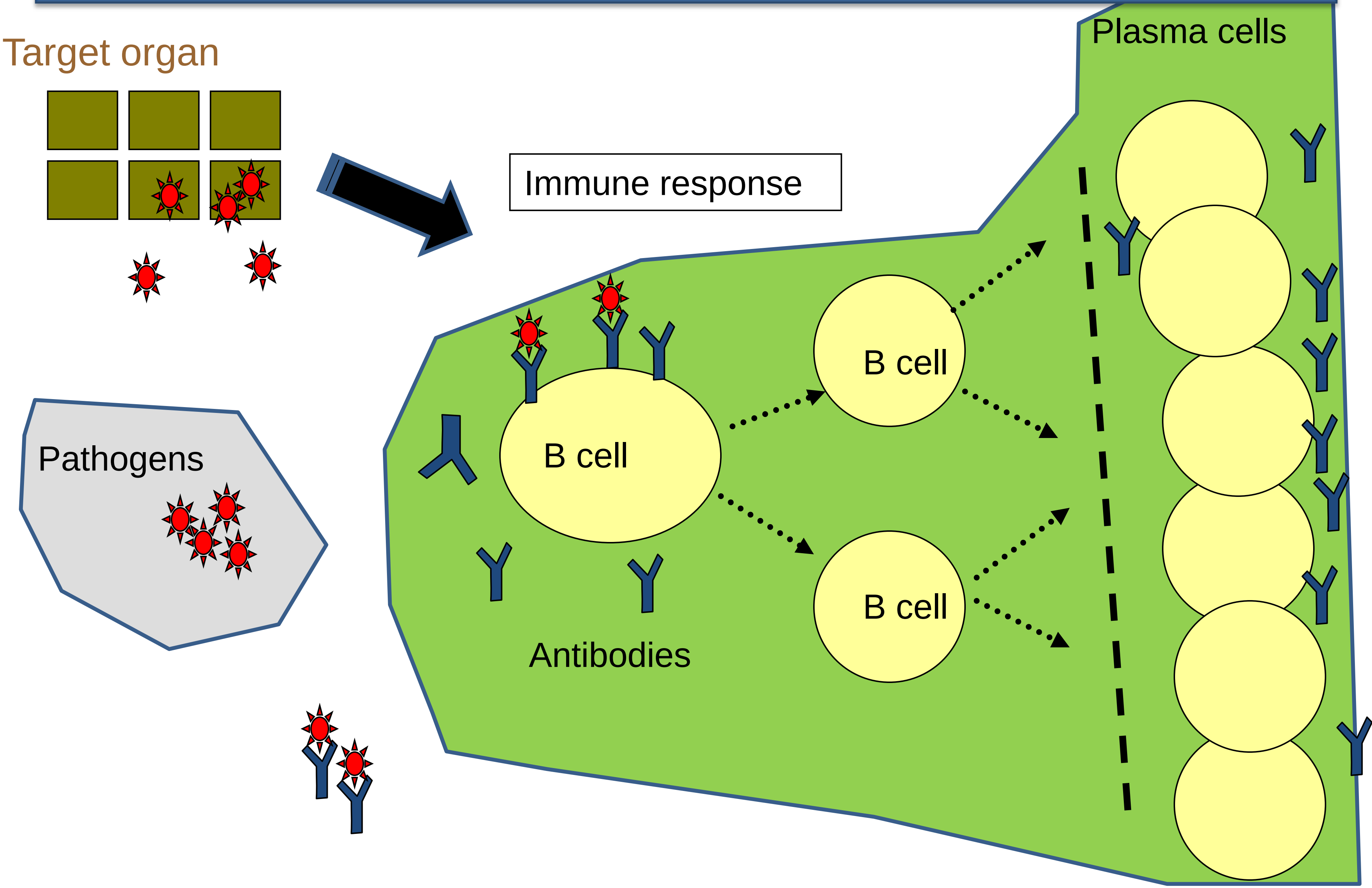


www.biology.arizona.edu

Key postulates:

1. Each responsive cell makes & expresses on its surface only a single type of antibody (Ig) molecule
2. The selective event is the stimulation by antigen of those cells which make complementary antibodies
3. This results is proliferation of cells and secretion of the Abs

Immunological Scheme of the basic model of infectious disease



Basic model of infectious disease (1975)

State space variable

1. Pathogen population
2. Antibodies
3. Plasma cells
4. Tissue damage

System of Delay-Differential Equations

$$\frac{d}{dt}V(t) = \left(\beta - \gamma \cdot F(t)\right) \cdot V(t)$$

$$\frac{d}{dt}F(t) = \rho \cdot C(t) - \eta \cdot \gamma \cdot F(t) \cdot V(t) - \mu_f \cdot F(t)$$

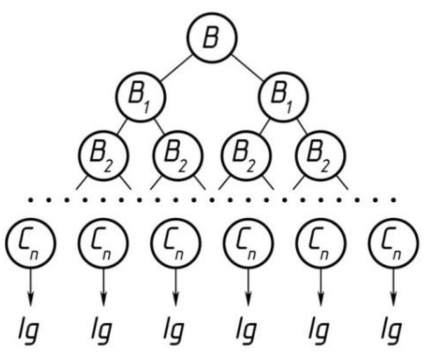
$$\frac{d}{dt}C(t) = \xi(m) \cdot \alpha \cdot V(t-\tau) \cdot F(t-\tau) - \mu_f \cdot \left(C - C^*\right)$$

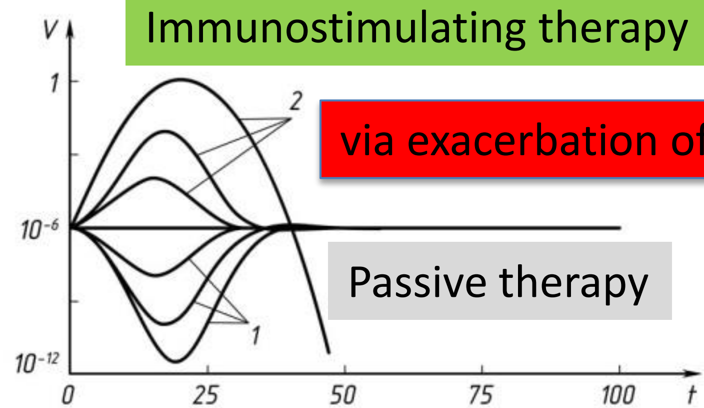
$$\frac{d}{dt}m(t) = \sigma \cdot V(t) - \mu_m \cdot m(t)$$

Initial data

$$V(t_0) = V_0, \quad F(t_0) = F_0, \quad C(t_0) = C_0, \quad m(t_0) = m_0,$$

$$V(t) = 0, \quad F(t) = F_0 \quad \text{for } t \in \left[t_0 - \tau, t_0\right)$$





Immunostimulating therapy

via exacerbation of the chronic infection

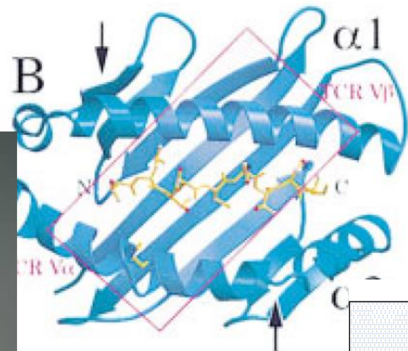
Passive therapy

Major breakthrough made by G.I Marchuk by 1980

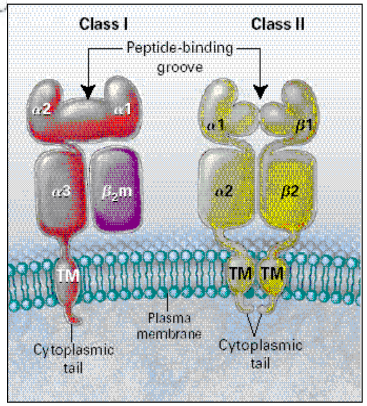
(A.L. Asachenkov, L.N. Belykh, I.B. Pogozhev, A.A. Romanyukha, N.V. Pertcev, S.M. Zuev,)

- Kinetic basis of the chronisation of infectious diseases
- Quantification of the immunological barrier (V_{IB})
- Influence of organism's temperature reaction on the course of disease
- Novel views on treatment (1) of the hypertoxic form of disease and (2) the chronic infections via exacerbation

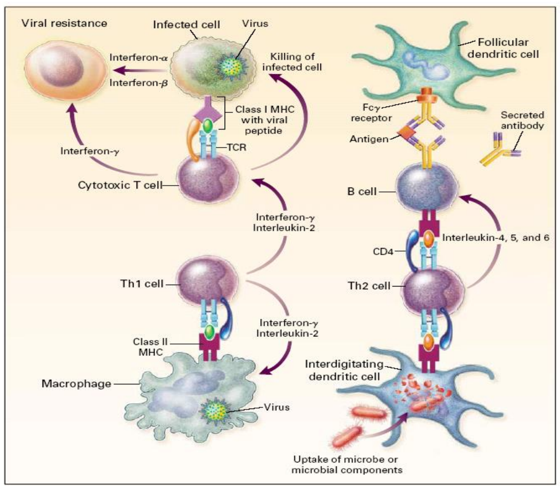
Dual Recognition Principle via MHC restriction: P. Doherty and R.M.Zinkernagel



MHC class I – Ag complex



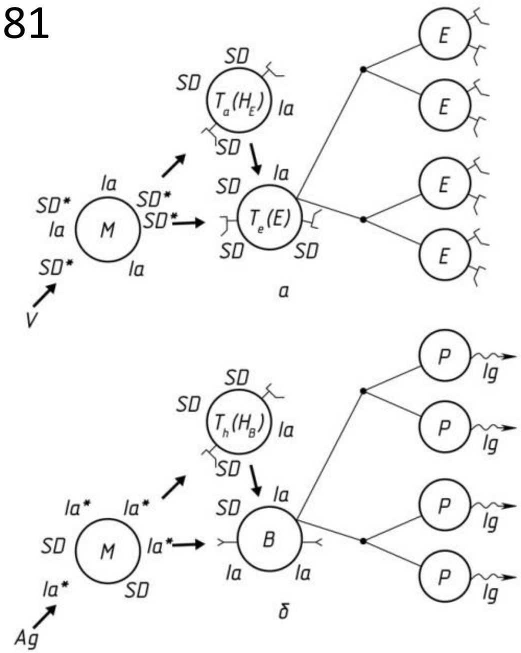
Components of the antiviral immune response



The New England Journal of Medicine

Академик
Рем Викторович Петров

Mathematical Model Scheme
1981



Marchuk-Petrov model of the antiviral immune response (1981)

•Virus population

$$\frac{dV_f}{dt} = \nu C_V + n b_{CE} C_V E - \gamma_{VF} V_f F - \gamma_{VM} V_f - \gamma_{VC} V_f (C^* - C_V - m),$$

•Antigen-presenting cells

$$\frac{dM_V}{dt} = \gamma_{MV} M^* V_f - \alpha_M M_V,$$

•Th1 cells

$$\frac{dH_E}{dt} = b_H^E[\xi(m)\rho_H^E M_V(t-\tau_H^E)H_E(t-\tau_H^E) - M_V H_E] - b_p^{H_E} M_V H_E E + \alpha_H^E(H_E^* - H_E),$$

•Th2 cells

$$\frac{dH_B}{dt} = b_H^B[\xi(m)\rho_H^B M_V(t-\tau_H^B)H_B(t-\tau_H^B) - M_V H_B] - b_p^{H_B} M_V H_B B + \alpha_H^B(H_B^* - H_B),$$

•T-cell effectors

$$\frac{dE}{dt} = b_p^E[\xi(m)\rho_E M_V(t-\tau_E)H_E(t-\tau_E)E(t-\tau_E) - M_V H_E E] - b_{EC} C_V E + \alpha_E(E^* - E),$$

•B-cells

$$\frac{dB}{dt} = b_p^B[\xi(m)\rho_B M_V(t-\tau_B)H_B(t-\tau_B)B(t-\tau_B) - M_V H_B B] + \alpha_B(B^* - B),$$

$$\frac{dP}{dt} = b_p^P \xi(m)\rho_P M_V(t-\tau_P)H_B(t-\tau_P)B(t-\tau_P) + \alpha_P(P^* - P),$$

•Antibodies

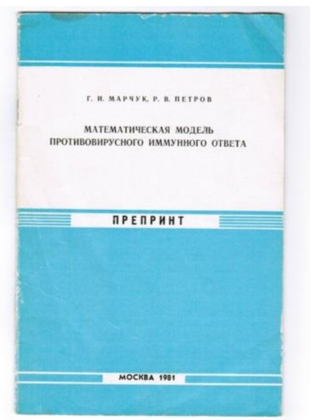
$$\frac{dF}{dt} = \rho_F P - \gamma_{FV} F V_f - \alpha_F F,$$

•Infected cells of the target organ

$$\frac{dC_V}{dt} = \sigma V_f(C^* - C_V - m) - b_{CE} C_V E - b_m C_V,$$

•Destroyed tissue

$$\frac{dm}{dt} = b_{CE} C_V E + b_m C_V - \alpha_m m, \quad \xi(m) = 1 - m/C^*.$$



Family of Nested Mathematical Models

$$
\begin{cases}
\frac{d}{dt}V(t) = (\beta - \gamma \cdot F(t)) \cdot V(t) \\
\frac{d}{dt}F(t) = \rho \cdot C(t) - \eta \cdot \gamma \cdot F(t) \cdot V(t) - \mu_f \cdot F(t) \\
\frac{d}{dt}C(t) = \xi(m) \cdot \alpha \cdot V(t-\tau) \cdot F(t-\tau) - \mu_f \cdot (C - C^*) \\
\frac{d}{dt}m(t) = \sigma \cdot V(t) - \mu_m \cdot m(t)
\end{cases}
$$

$$V(t_0) = V_0, \quad F(t_0) = F_0, \quad C(t_0) = C_0, \quad m(t_0) = m_0,$$
$$V(t) = 0, \quad F(t) = F_0 \quad \text{при } t \in [t_0 - \tau, t_0)$$

$$
\begin{aligned}
\frac{dV_f}{dt} &= \nu C_V + n b_{CE} C_V E - \gamma_{VF} V_f F \\
&\quad - \gamma_{VM} V_f - \gamma_{VC} V_f (C^* - C_V - m) \\
\frac{dM_V}{dt} &= \gamma_{MV} M^* V_f - \alpha_M M_V \\
\frac{dH_E}{dt} &= b_H^E [\xi(m) \rho_H^E M_V (t - \tau_H^E) H_E (t - \tau_H^E) - M_V H_E] \\
&\quad - b_p^{H_E} M_V H_E E + \alpha_H^E (H_E^* - H_E) \\
\frac{dH_B}{dt} &= b_H^B [\xi(m) \rho_H^B M_V (t - \tau_H^B) H_B (t - \tau_H^B) - M_V H_B] \\
&\quad - b_p^{H_B} M_V H_B B + \alpha_H^B (H_B^* - H_B) \\
\frac{dE}{dt} &= b_p^E [\xi(m) \rho_E M_V (t - \tau_E) H_E (t - \tau_E) E (t - \tau_E) \\
&\quad - M_V H_E E] - b_{EC} C_V E + \alpha_E (E^* - E) \\
\frac{dB}{dt} &= b_p^B [\xi(m) \rho_B M_V (t - \tau_B) H_B (t - \tau_B) B (t - \tau_B) \\
&\quad - M_V H_B B] + \alpha_B (B^* - B) \\
\frac{dP}{dt} &= b_p^P \xi(m) \rho_P M_V (t - \tau_P) H_B (t - \tau_P) B (t - \tau_P) \\
&\quad + \alpha_P (P^* - P) \\
\frac{dF}{dt} &= \rho_F P - \gamma_{FV} F V_f - \alpha_F F \\
\frac{dC_V}{dt} &= \sigma V_f (C^* - C_V - m) - b_{CE} C_V E - b_m C_V \\
\frac{dm}{dt} &= b_{CE} C_V E + b_m C_V - \alpha_m m, \\
&\qquad \xi(m) = 1 - m/C^*.
\end{aligned}
$$

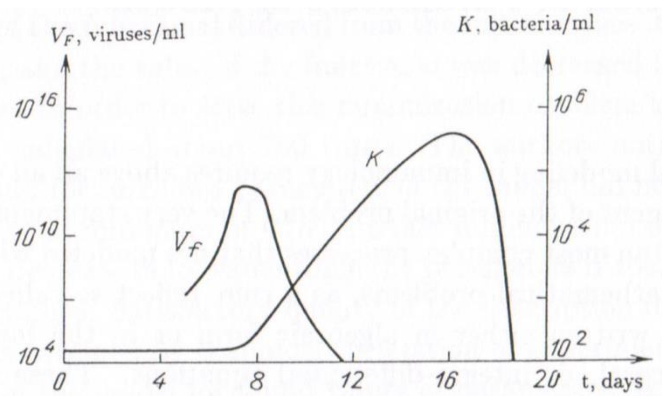
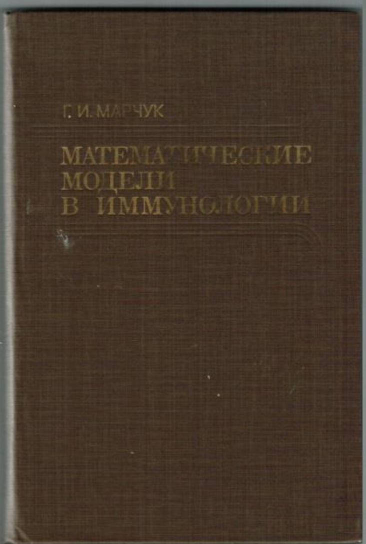


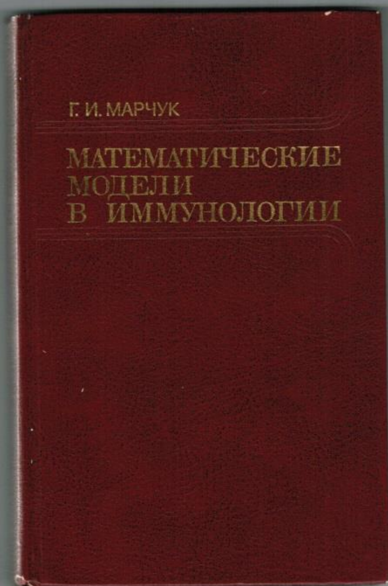
Fig. 33. Simulation of mixed infection: the development of acute viral infectior against the background of chronic bacterial infection.

$$
\begin{aligned}
\frac{dV_f}{dt} &= \nu C_V + n b_{CE} C_V E_V - \gamma_{VM} M V_f - \gamma_{VF} F_V V_f \\
&\quad - \gamma_{VC} (C^* - C_V - m) V_f, \\
\frac{dM_V}{dt} &= \gamma_{VM} M V_f - \alpha_M M_V, \\
\frac{dH_{E_V}}{dt} &= b_H^{(E_V)} \left[\xi(m) \rho_H^{(E_V)} M_V (t - \tau_H^{(E_V)}) H_{E_V} (t - \tau_H^{(E_V)}) - M_V H_{E_V}\right] \\
&\quad - b_p^{(H_{E_V})} M_V H_{E_V} E_V + \alpha_H^{(E)} \left(H_{E_V}^* - H_{E_V}\right), \\
\frac{dH_{B_V}}{dt} &= b_H^{(B_V)} \left[\xi(m) \rho_H^{(B_V)} M_V (t - \tau_H^{(B_V)}) H_{B_V} (\tau - \tau_H^{(B_V)}) - M_V H_{B_V}\right] \\
&\quad - b_p^{(H_{B_V})} M_V H_{B_V} B + \alpha_H^{(B)} \left(H_{B_V}^* - H_{B_V}\right), \\
\frac{dE_V}{dt} &= \xi(m) q_{E_V}(t) - b_p^{(E_V)} M_V H_{E_V} E_V - b_{EC} C_V E_V \\
&\quad + \alpha_E (E_V^* - E_V), \\
\frac{dB_V}{dt} &= b_p^{(B_V)} [\xi(m) \rho_{B_V} M_V (t - \tau_{B_V}) H_{B_V} (t - \tau_{B_V}) B_V (t - \tau_{B_V}) \\
&\quad - M_V H_{B_V} B_V] + \alpha_B (B_V^* - B_V), \\
\frac{dP_V}{dt} &= \xi(m) q_{P_V}(t) + \alpha_P (P_V^* - P_V), \qquad (4.5.6) \\
\frac{dF_V}{dt} &= \rho_F P_V - \gamma_{FV} V_f F_V - \alpha_F F_V, \\
\frac{dC_V}{dt} &= \sigma V_f (C^* - C_V - m_V) - b_{CE} C_V E_V - b_m C_V, \\
\frac{dm_V}{dt} &= b_{CE} C_V E_V + b_m C_V - \alpha_{m_V} m_V, \\
\frac{dK}{dt} &= \beta K - \gamma_{KM} M K - \gamma_{KF} F_K K, \\
\frac{dM_K}{dt} &= \gamma_{MK} K M - \alpha_M M_K, \qquad (4.5.6) \\
\frac{dH_{B_K}}{dt} &= b_H^{(B_K)} \left[\xi(m) \rho_H^{(B_K)} M_K (t - \tau_H^{(B_K)}) H_{B_K} (\tau - \tau_H^{(B_K)}) - M_K H_{B_K}\right] \\
&\quad - b_p^{(H_{B_K})} M_K H_{B_K} B_K + \alpha_H \left(H_{B_K}^* - H_{B_K}\right), \\
\frac{dB_K}{dt} &= b_p^{(B_K)} [\xi(m) \rho_{B_K} M_K (t - \tau_{B_K}) H_{B_K} (t - \tau_{B_K}) B_K (t - \tau_{B_K}) \\
&\quad - M_K H_{B_K} B_K] + \alpha_B (B_K^* - B_K), \\
\frac{dP_K}{dt} &= \xi(m) q_{P_K}(t) + \alpha_P (P_K^* - P_K), \\
\frac{dF_K}{dt} &= \rho_F P_K - \eta_F \gamma_{FK} K F_K - \alpha_F F_K, \\
\frac{dm_K}{dt} &= \sigma_K K - \alpha_{m_K} m_K.
\end{aligned}
$$

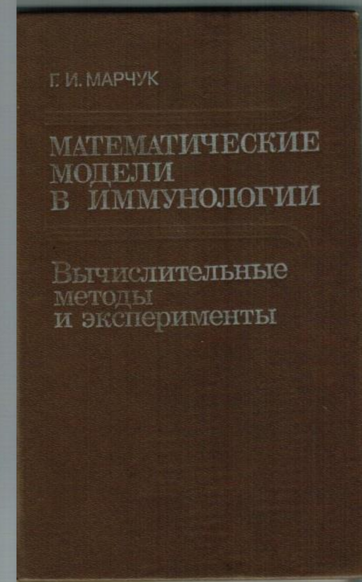
Scientific monographs by G. I Marchuk



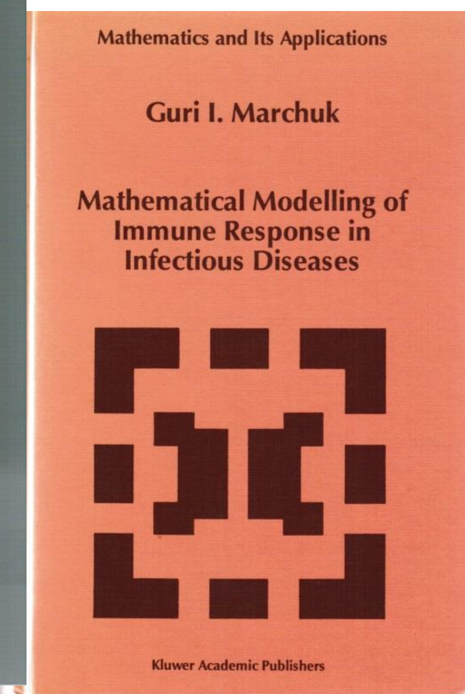
1980 г.



1985 г.



1991 г.



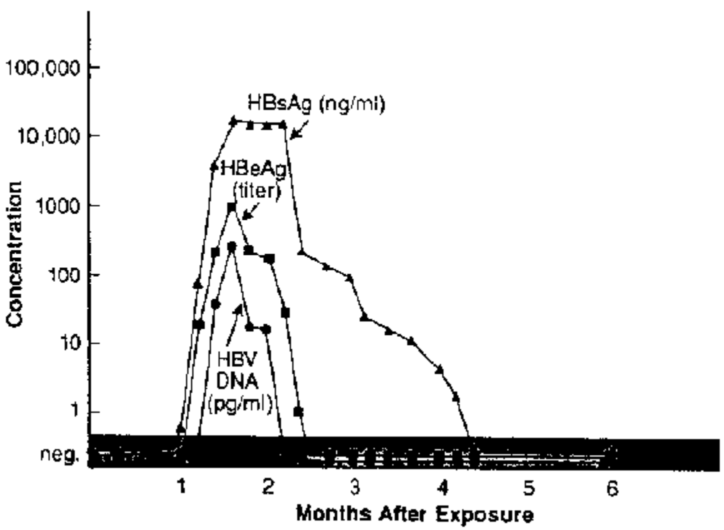
1997 г.

Application example: Hepatitis B Virus Infection

HBV infection dynamics in volunteer subjects
(from Fong et al., *J. Medical Virology*, (1994) 155-158)

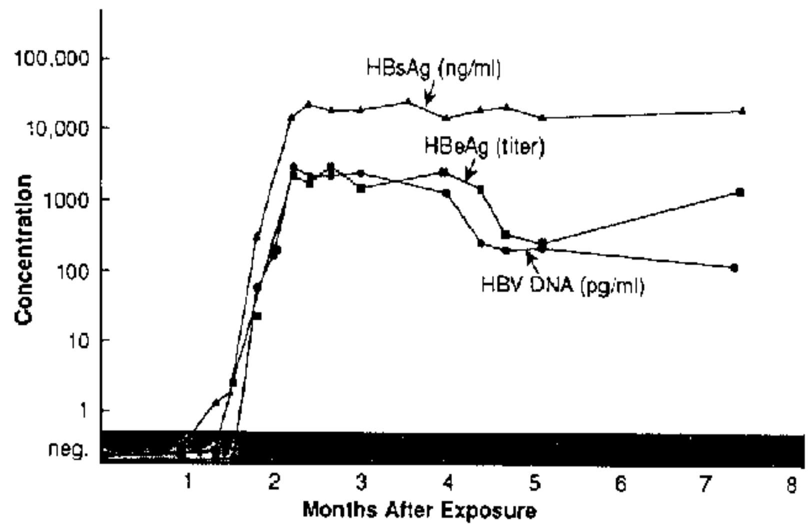
6 patients out of 12

Acute Hepatitis B



3 patients out of 12

Chronic Hepatitis B



What are the factors that determine whether an individual with acute hepatitis B will resolve the illness or will develop chronic infection?

Sensitivity analysis using Adjoint Equations

Сопряженные уравнения в иммунологии

Рассмотрим простейшую модель

$$
\begin{array}{ll}
v^* & \dfrac{dv}{dt} - \beta v + \gamma F v = 0 \\
C^* & \dfrac{dC}{dt} - \xi(m)\,\alpha\, v(t-\tau)\, F(t-\tau) = 0, \\
F^* & \dfrac{dF}{dt} - \rho C + \gamma v F = 0, \\
m^* & \dfrac{dm}{dt} - \sigma v + \mu m = 0,
\end{array}
$$

$v = v_0,\ C = C_0,\ F = F_0,\ m = m_0$ при $t=0$

Рассмотрим функционал

$$J = \int_0^T v^2\, dt = \min$$

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Journal of Computational and Applied Mathematics 184 (2005) 177–204

JOURNAL OF COMPUTATIONAL AND APPLIED MATHEMATICS

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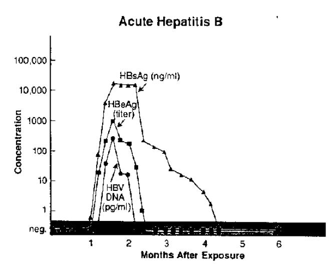
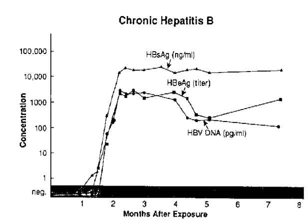
Adjoint equations and analysis of complex systems: Application to virus infection modelling

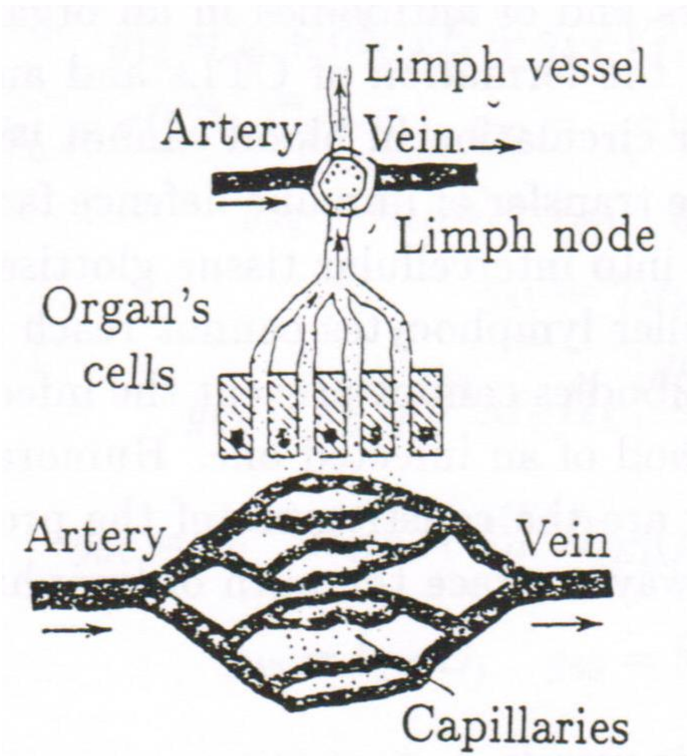
G.I. Marchuk*, V. Shutyaev, G. Bocharov





the results of the above analysis we propose that (*prop*1) the efficacy of antigen presentation might be the main cause of the chronic HBV infection in patient 2; (*prop*2) the parameters of virus infection seem to be rather close for the acutely and chronically infected patients.

Modelling of Immunophysiological Processes



Academician
V.A. Chereshnev

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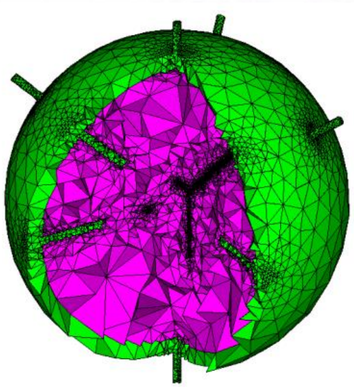
Original Russian Text © G.A. Bocharov, A.A. Danilov, Yu.V. Vassilevski, G.I. Marchuk, V.A. Chereshnev, B. Ludewig, 2011, published in Doklady Akademii Nauk, 2011, Vol. 439, No. 3, pp. 413–415.

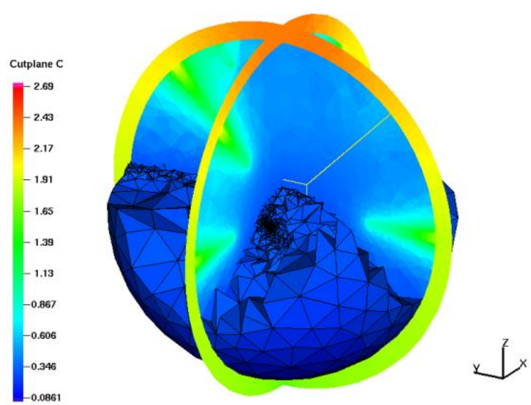
PHYSIOLOGY

Simulation of the Interferon-Mediated Protective Field in Lymphoid Organs with Their Spatial and Functional Organization Taken into Consideration

G. A. Bocharov[a], A. A. Danilov[a], Yu. V. Vassilevski[a],
Academician G. I. Marchuk[a], Academician V. A. Chereshnev[b], and B. Ludewig[c]

Received January 14, 2011





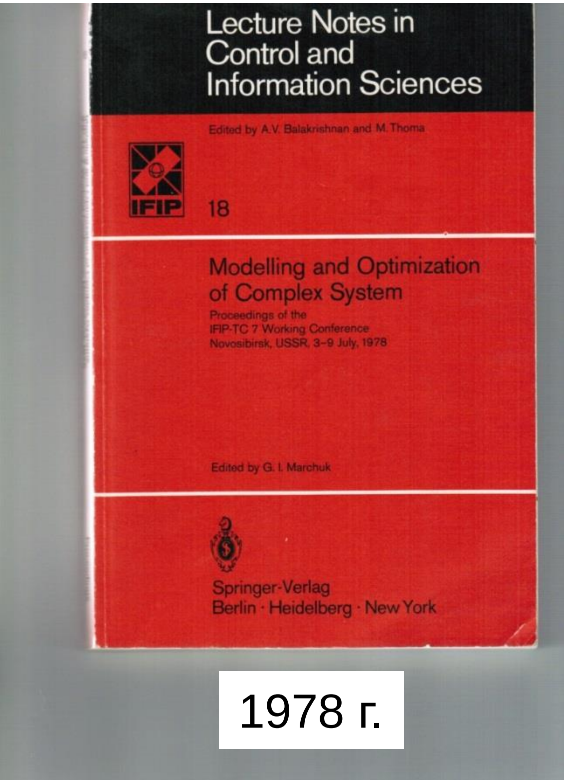
. *Model. Nat. Phenom.*
6, No. 7, 2011, pp. 13-26
10.1051/mmnp/20116702

Reaction-Diffusion Modelling of Interferon Distribution in Secondary Lymphoid Organs

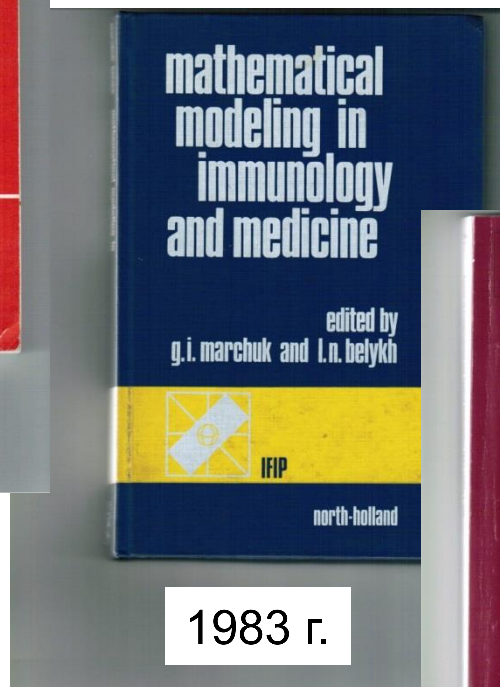
G. Bocharov[1*†], A. Danilov[1*†], Yu. Vassilevski[1],
G.I. Marchuk[1], V.A. Chereshnev[2] and B. Ludewig[3]

Special Issues related to Mathematical Immunology

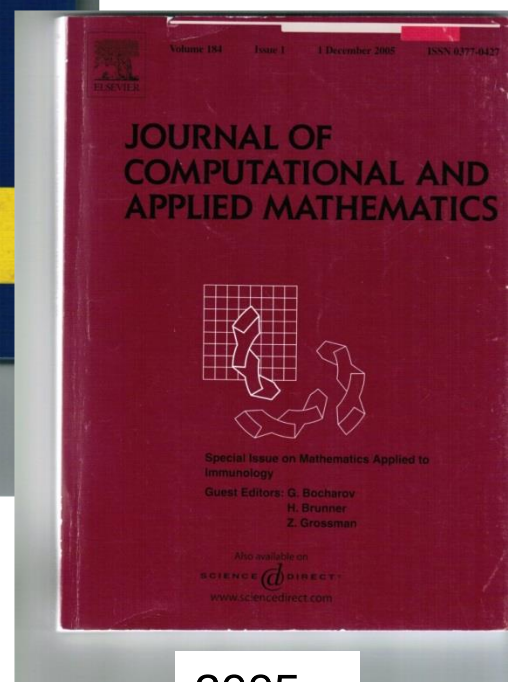
Ronal R. Mohler (Oregon State University, USA)
A.V. Balakrishnan (University of California, Los Angeles, USA)



1978 г.



1983 г.



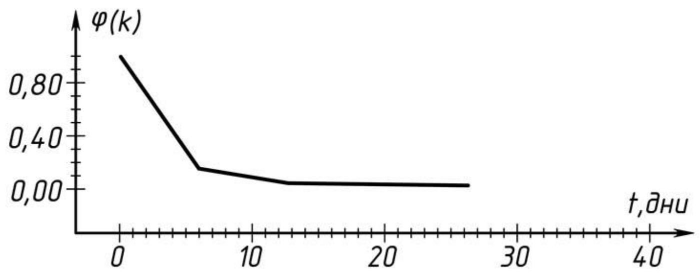
2005 г.

2011 г.

Quantification of the tissue damage and the **individual patient based** assessment of the recovery process for hepatitis virus infection

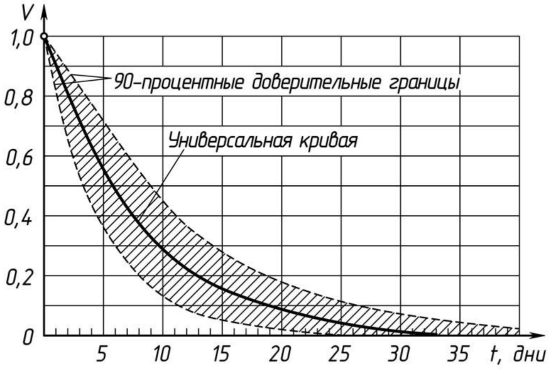
$\varphi(k)$ - disease severity index for *k*-th patient

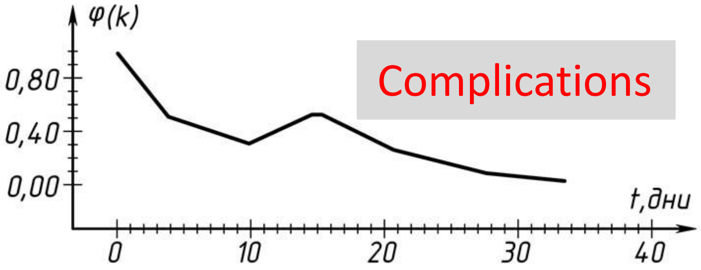
Normal recovery



Academician N.I. Nisevitch, I.I. Zubikova, I.B. Pogozhev

95% normal recovery band





Complications

Quantification of disease severity of the lung infections

Severity index

$$\Pi l = \frac{F-2.50}{4.50}+\frac{C-0.20}{0.30}+\frac{S-16}{30}+\frac{L-5.0\cdot 10^{9}\mathrm{l}^{-1}}{20.0\cdot 10^{9}\mathrm{l}^{-1}} + \frac{Fr-70}{90}+\frac{N-1}{40}+\frac{30-l}{50}+\frac{Cr}{20}.$$

The variables mean here: F, fibrinogen concentration in blood (in g/l); C, seromucoid concentration in blood (in g/l); Cr, concentration of C-reactive protein (quantity of "crosses" by the method of sedimentation in capillaries); S, precipitation rate for erythrocytes (mm/h); L, number of leukocytes in blood (10^9/l); l, percentage content of lymphocytes in blood; Fr, pulse rate per minute; N, neutrophiles (in %).

Prof. E.P. Berbentsova

Favourable dynamics

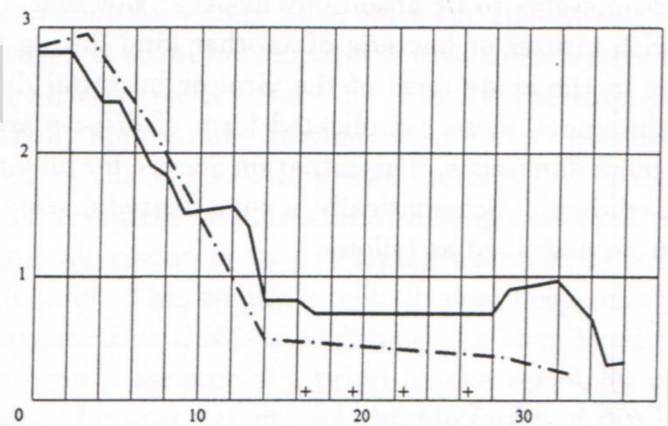
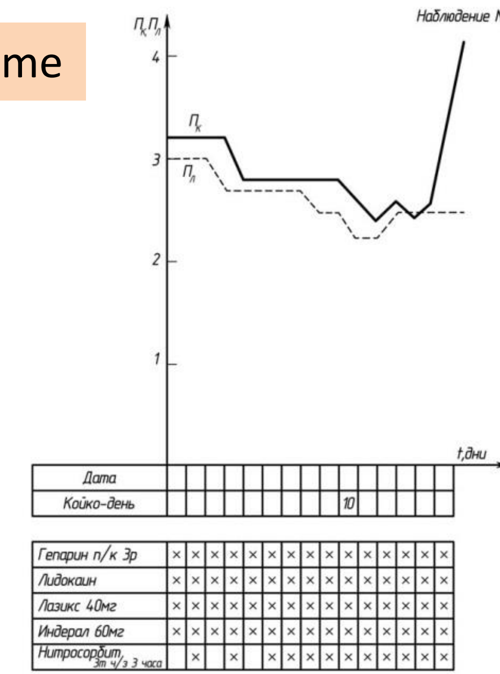


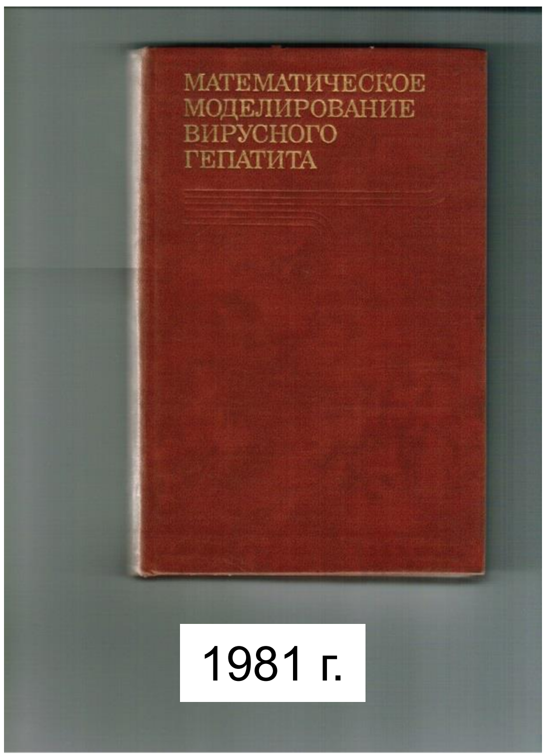
Fig. 13. Clinical observation [198]. Patient C., 38. Dynamics of clinical (Пc, solid line) and laboratory (Пl) severity indices.

Severe outcome



Monographs on Clinical Applications of Mathematical Models

Co-authored with N.I. Nisevitch, I.I. Zubikiva, I.B. Pogozhev



Co-authored with E.P. Berbentsova

Upper respiratory tract and lung infections

Virus Hepatitis

Соратники и ученики научной школы Г.И. Марчука в области математической иммунологии

- **Петров Р.В. (*ИИ МЗ, Москва*)**
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- **Нисевич Н.И., Зубикова И.И. (*2 ММИ, Москва*),**
- **Бербенцова Э.П., Агафонникова К.И., Тамбовцева Л.Г. , Францева Н.М. (*МЗ РСФСР*)**
- **Черешнев В.А. (*ИИФ УрО РАН, Екатеринбург*)**

- **Асаченков А.Л., Белых Л.Н., Зуев С.М., Перцев Н.В., Романюха А.А., Погожев И.Б., *(ВЦ СО АН СССР, Новосибирск)***
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- **Ким А.В. (ИММ, УрО РАН, Екатеринбург)**

Modelling in immunology: Experimental and Mathematical

Nobel Prize Laureate
Rolf M. Zinkernagel

Academician
Guri I. Marchuk

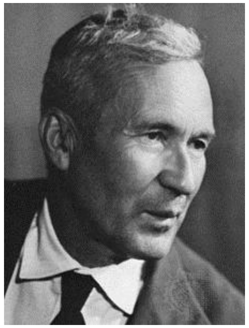
„**The outcome of infection results from the ´ *numbers games*´ between infectious agent and the immune system**.“

Mathematical Biology:
Conceptual Foundations

- *Vito Volterra*

- *Ludwig von Bertalanffy*

- *Andrey Kolmogorov*



- *Norbert Winer*

Mathematical immunology: conceptual foundations set up by G.I. Marchuk

- **Coordinatisation of complex phenomena in immunology of infections**
- **Parameterization of the underlying processes differing in their nature**
- **Informative measures for the severity of disease and protection against infection**
- **Feedback regulation principles of the immune responses during infections**

- **A nested family of relevant mathematical models of the within-host dynamics of infectious diseases formulated with delay-differential equations**
- **Basic model of infectious diseases**
- **Marchuk-Petrov model of antiviral immune response**
- **Models of hemopoiesis**

- **Practical application of mathematical methods to clinics**
- **Clinical and laboratory indices of disease severity**
- **Patient-specific assessment of the disease course**
- ***Hepatitis infection***
- ***Pneumonia***
- ***Myocardial infarction***
- **Methodology for description, explanation and prediction in immunology based on mathematical models**
- **Hepatitis B virus infection**
- **Influenza infection**
- **Viral-bacterial infection**

Credo

“Спрашивается, имеет ли смысл рассматривать столь сложные модели при нынешнем состоянии медицины, когда эти параметры для индивидуального больного пока еще определить невозможно? Мы считаем, что смысл, и большой, имеется по двум причинам, Во-первых, подобные модели позволяют все более глубоко проникать в динамику сложнейших процессов защитных реакций организма от антигенов и выявить общие закономерности в динамике заболевания. С другой стороны, сложные модели ставят проблемы идентификации их параметров и, таким образом, стимулируют как математиков, так и медиков к поиску оптимальных систем оценок параметров моделей для индивидуального больного. Ведь будущее медицины – лечение индивидуального больного на основе слежения за его индивидуальными иммунологическими, эндокринологическими, сосудистыми особенностями с учетом непрерывно приобретаемых с возрастом хронических локусов различной этиологии. Именно такая перспектива всегда двигала автора и его коллег к тщательному и все более усложняющемуся математическому моделированию”.

Future challenges:
Control of infectious disease and the personalized therapy

Управление болезнью.

Рассмотрим упрощенную систему

$$\frac{dV}{dt} - \beta V + \gamma F V = u(t),$$

$$\boxed{\cancel{\frac{dF}{dt} - \rho V(t-\tau)F(t-\tau) + \gamma F V = w(t)}}$$

$$\frac{dC}{dt} - \xi(m)\,\alpha V(t-\tau)F(t-\tau) = 0,$$

$$\frac{dF}{dt} - \rho C + \gamma V F = w(t),$$

$$\frac{dm}{dt} - \sigma V + \mu m = 0, \qquad (1)$$

где $u(t)$ и $w(t)$ — управляющие функции, которые нужно найти из условия

$$J = \int_0^T V^2\,dt = \min \qquad (2)$$

Нач. данные

$$V = V^0, \quad C = C^0, \quad F = F^0, \quad m = m^0. \qquad (3)$$

ИММУНОПАТОЛОГИЯ И КЛИНИЧЕСКАЯ ИММУНОЛОГИЯ

УДК 615.371:578.82/.83].015.46-053.2

Топтыгина А. П.[1, 2], *Азиатцева В. В.*[2], *Савкин И. А.*[3], *Кислицин А. А.*[2], *Семикина Е. Л.*[5], *Гребенников Д. С.*[6], *Алешкин А. В.*[1], *Сулимов А. В.*[3, 4,] *Сулимов А. В.*[3, 4,] *Бочаров Г. А.*[7]

ПРОГНОЗИРОВАНИЕ СПЕЦИФИЧЕСКОГО ГУМОРАЛЬНОГО ИММУННОГО ОТВЕТА НА ОСНОВАНИИ ИСХОДНЫХ ПАРАМЕТРОВ ИММУННОГО СТАТУСА ДЕТЕЙ, ПРИВИТЫХ ПРОТИВ КОРИ, КРАСНУХИ И ЭПИДЕМИЧЕСКОГО ПАРОТИТА

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Thank you for your attention!