Application of M–matricies for study a high–dimension models in biology and medicine: stability and asymptotic behavior of solutions

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The author was supported by the Interdisciplinary Project of the Siberian Division of the Russian Academy of Sciences «Differential, Difference and Integro–Differential Equations. Applications to the Natural Science Problems» (Grant N. 80, 2012–2014 years)

1. Nonsingular M–matrix.

Matrix $S = (s_{ij})$, $1 \le i, j \le m$, with elements $s_{ij} \le 0$, $i \ne j$, is called to be a nonsingular M–matrix,

if S satisfies $\approx$ 50 equivalent properties (see, Berman and Plemons; Kuznetsov and Voevodin), for example:

- S^{-1} exists and has nonnegative elements;
- all corner (diagonal) minors of S are positive;
- all eigenvalues λ_S of S are such, that $Re(\lambda_S) > 0$;
- $\exists\, z \in R^m$, $z > 0$, such that $Sz > 0$,

$$z > 0 \Longleftrightarrow z_i > 0, \quad z \ge 0 \Longleftrightarrow \; z_i \ge 0, \quad 1 \le i \le m.$$

2. Systems of linear differential equations (LDE) and stability of trivial solutions.

Let us consider the system of LDE:

$$x = x(t) \in R^m, \quad \dot{x} = Qx, \tag{2.1}$$

$m \times m$ matrix $Q = (q_{ij})$ has elements $q_{ij} \geq 0$, $i \neq j$.

Trivial solution $x = 0$ of (2.1) is asymptotically stable $\Longleftrightarrow$ $S = -Q$ is nonsingular M–matrix.

Note: we don't solve the problem of finding eigenvalues λ_Q.

We will check, that the matrix $S = -Q$ satisfies one of the equivalent properties to be a nonsingular M–matrix.

- Original criteria: trivial solution $x = 0$ of (2.1) is asymptotically stable $\Longleftrightarrow$ Q satisfies the Sevast'janov–Kotelj'anskii criteria $(-1)^k M^{(k)} > 0$, $1 \leq k \leq m$, where $M^{(k)}$ — corner (diagonal) minor of Q of order k (see, Gantmakher).

Lets investigate the more general system of LDE

$$x = x(t) \in R^m, \quad \dot{x} = Ax, \tag{2.2}$$

where $A = (a_{ij})$, $a_{ii} < 0$, $1 \le i \le m$, $a_{ij} \in R$, $i \ne j$.

Denote: $A^{(+)} = (a^{+}_{ij})$, $a^{+}_{ij} = |a_{ij}| \ge 0$, $i \ne j$, $a^{+}_{ii} = a_{ii} < 0$.

Suppose, that $S = -A^{(+)}$ is nonsingular M–matrix.

Then solution $x = 0$ of (2.2) is asymptotically stable.

3. Stability of equilibriums in the model of dynamics of a population affected by harmful substances.

We consider a population of individuals whose dynamics is determined by the following factors:

pollutants $C_1, \dots, C_k$ enter the habitat, decay, accumulate in food sources, and are ingested by individuals;

the ingested pollutants $C_1, \dots, C_k$ interact among each other and form a harmpful substance;

individuals bring offspring;

individuals die due to self–limitation and irreversible influence of harmpful substance;

the migration of individuals from the outside is absent.

- Original model: N. Pertsev and G. Tsaregorodtseva, 2011.

Denote: $x = x(t)$ – number of individuals; $c_i = c_i(t)$ – amount of pollutant C_i, $1 \le i \le k$.   The model equations:

$$\dot{c}_i = r_i - \theta_i(c_i)x - \delta_i c_i, \quad 1 \le i \le k, \tag{3.1}$$

$$\dot{x} = \beta x - \gamma x^2 - \theta(c_1, \dots, c_k)x, \quad t > 0, \tag{3.2}$$

$$c_j(0) = c_j^{(0)} \ge 0,\ 1 \le j \le k,\ \ x(0) = x^{(0)} \ge 0, \tag{3.3}$$

$r_i = const > 0$, $\delta_i = const > 0$ – the rates of inflow and decay for pollutant C_i;

$\theta_i(c_i)$ determins ingested rate by one individual of pollutant C_i contained in food;

$\theta(c_1, \dots, c_k) = \sigma \prod_{i=1}^{k} \theta_i^{n_i}(c_i)$ describes the death rate of individuals due to harmpful substance, $\sigma = const > 0$, $n_i = const > 0$;

$\beta = const > 0$ – birth rate of individuals;

$\gamma = const > 0$ – parameter reflecting the intensity of interaction between the individuals.

We suppose, that $\theta_i(c_i)$ is continuous and increasing, $c_i \in R_+ = [0, \infty)$, $\theta_i(0) = 0$,

$\exists\ \ 0 < \lim_{c_i \to +\infty} \theta_i(c_i) = \bar{\theta}_i < \infty$, $\exists$ continuous $\theta_i'(c_i) \ge 0$, $c_i \in R_+$, $1 \le i \le k$.

For the equilibriums we have to find solutions of the system

$$r_i - \theta_i(c_i)x - \delta_i c_i = 0, \;\; c_i \geq 0, \quad 1 \leq i \leq k, \tag{3.4}$$

$$(\beta - \gamma x - \theta(c_1, \dots, c_k))x = 0, \;\; x \geq 0. \tag{3.5}$$

Nontrivial equilibrium: $x = \bar{x} > 0$. Fix $1 \leq i \leq k$ and consider (3.4) in the form

$$r_i - \delta_i c_i = \theta_i(c_i)x. \tag{3.6}$$

For fixed $x \geq 0$ equation (3.6) has only one root $\bar{c}_i = \bar{c}_i(x) > 0$. Lets introduce the function

$$h(x) = \theta(\bar{c}_1(x), \dots, \bar{c}_k(x)) = \sigma \prod_{i=1}^{k} \theta_i^{n_i}(\bar{c}_i(x)), \;\; x \in R_+. \tag{3.7}$$

For finding the roots $\bar{x}$ we use (3.5) and solve the equation

$$\beta - \gamma x = h(x), \quad 0 \leq x \leq \beta/\gamma. \tag{3.8}$$

If $\bar{x} > 0$ – root of (3.8), then $\bar{c}_i > 0$ one can find from (3.6).

Now we use method of linearization to study the problem of asymptotic stability of nontrivial equilibrium.

Denote $y_i = c_i - \bar{c}_i, \ \ 1 \le i \le k, \ \ y_{k+1} = x - \bar{x}, \ \ m = k+1$ and lets investigate the system of LDE

$$y = y(t) \in R^m, \ \dot{y} = Ay, \tag{3.9}$$

$$A = \begin{pmatrix} a_{11} & 0 & 0 & \dots & 0 & a_{1m} \\ 0 & a_{22} & 0 & \dots & 0 & a_{2m} \\ 0 & 0 & a_{33} & \dots & 0 & a_{3m} \\ \dots & \dots & \dots & \dots & \dots & \dots \\ 0 & 0 & 0 & \dots & -a_{kk} & a_{km} \\ a_{m1} & a_{m2} & a_{m3} & \dots & a_{mk} & a_{mm} \end{pmatrix},$$

$$a_{ii} = -\theta_i'(\bar{c}_i)\bar{x} - \delta_i < 0, \ a_{im} = -\theta_i(\bar{c}_i) \le 0, \ 1 \le i \le k,$$

$$a_{mj} = -\theta_{c_j}'(\bar{c}_1, \dots, \bar{c}_k)\bar{x} \le 0, \ 1 \le j \le k, \ a_{mm} = -\gamma\bar{x} < 0.$$

Eigenvalues $\boldsymbol{\lambda} = \boldsymbol{\lambda}_A$ are roots of characteristic equation

$$\det(\boldsymbol{A} - \boldsymbol{\lambda I}) = (-1)^m \boldsymbol{\lambda}^m + r_1 \boldsymbol{\lambda}^{m-1} + r_2 \boldsymbol{\lambda}^{m-2} + \cdots + r_m = 0,$$

$$r_m = \det(\boldsymbol{A}) = \prod_{i=1}^{k} a_{ii}(a_{mm} - \sum_{j=1}^{k} a_{mj}\, a_{jm}/a_{jj}) =$$

$$= (-1)^m \bar{x} \prod_{i=1}^{k} (\theta_i'(\bar{c}_i)\bar{x} + \delta_i)(h'(\bar{x}) + \gamma).$$

Using well–known results, we have:

- if $h'(\bar{x}) + \gamma < 0$, then equilibrium is unstable;
- inequality $h'(\bar{x}) + \gamma > 0$ gives nesessary condition for asymptotic stability of equilibrium.

The analysis of $\boldsymbol{S} = -\boldsymbol{A}^{(+)}$ gives us the sufficient condition:

$$h'(\bar{x}) + \gamma > 0. \tag{3.10}$$

Inequality $h'(\bar{x}) + \gamma > 0$ is nesessary and sufficient for asymptotic stability of equilibrium $\bar{x} > 0$ of simple DE

$$\dot{x} = (\beta - \gamma x - h(x))x.$$

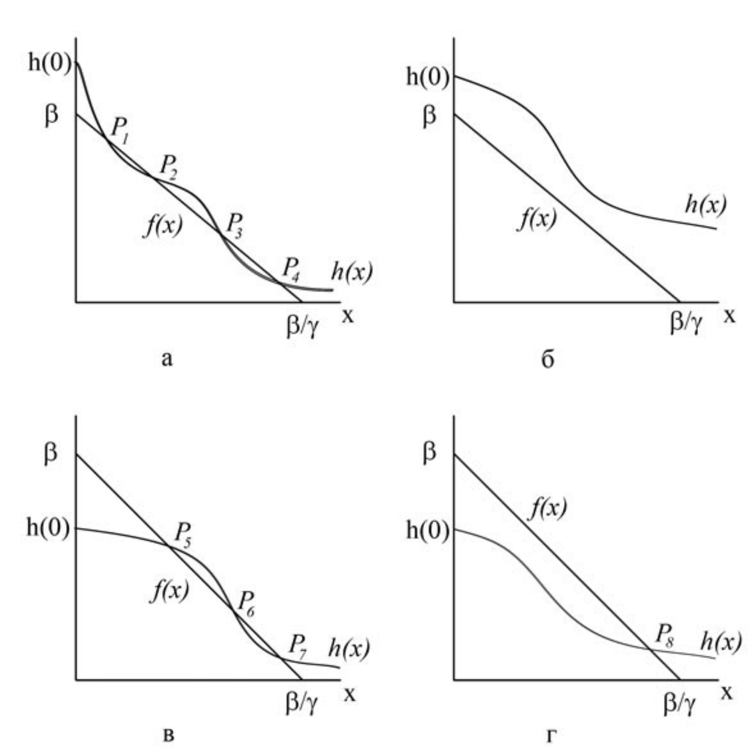

Fig.1. Typical graphs of $f(x) = \beta - \gamma x$ and $h(x)$,
P_1, P_3, P_6 – unstable cases, P_2, P_4, P_5, P_7, P_8 – asymp. stable cases.

SUMMARY. Some properties of solutions of high–dimension model

$$\dot{c}_i = r_i - \theta_i(c_i)x - \delta_i c_i, \quad 1 \le i \le k,$$

$$\dot{x} = \beta x - \gamma x^2 - \theta(c_1, \dots, c_k)x, \quad t > 0,$$

$$c_j(0) = c_j^{(0)} \ge 0,\ 1 \le j \le k, \ \ x(0) = x^{(0)} \ge 0,$$

may be studied by means of one–dimension model

$$\dot{x} = \beta x - \gamma x^2 - h(x)x,\ t > 0,$$

$$x(0) = x^{(0)} \ge 0.$$

Note: we don't use the well–known Tikhonov theorem about «fast» and «slow» variables in biological models.

4. Global stability of trivial equilibrium in the model of spread of HIV–infection.

Let: $S_1, \dots, S_n$ — groups of HIV–susceptible individuals, $I_1, \dots, I_n$ — groups of HIV–infected individuals,

$S_i(t)$, $I_i(t)$ – number of individuals of groups S_i, I_i at time t.

Model equations ($1 \le i \le n$):

$$\dot{S}_i = \sum_{k=1, k\neq i}^{n} \rho_{ki} S_k - \sum_{k=1}^{n} \rho_{ik} S_i - \sum_{j=1}^{n} \beta_{ij} I_j S_i + f_i, \tag{4.1}$$

$$\dot{I}_i = \sum_{k=1, k\neq i}^{n} \alpha_{ki} I_k - \sum_{k=1}^{n} \alpha_{ik} I_i + \sum_{j=1}^{n} \beta_{ij} I_j S_i, \ t > 0, \tag{4.2}$$

$$S_i(0) = S_i^0 \ge 0, \ I_i(0) = I_i^0 \ge 0. \tag{4.3}$$

- Original model: A. Romanyukha and E. Nosova, 2010–2012, for $n = 4$, model equations (4.1)–(4.3): N. Pertsev, 2013.

$$\dot{S}_i = \sum_{k=1,k\neq i}^{n} \rho_{ki} S_k - \sum_{k=1}^{n} \rho_{ik} S_i - \sum_{j=1}^{n} \beta_{ij} I_j S_i + f_i, \tag{4.1}$$

$$\dot{I}_i = \sum_{k=1,k\neq i}^{n} \alpha_{ki} I_k - \sum_{k=1}^{n} \alpha_{ik} I_i + \sum_{j=1}^{n} \beta_{ij} I_j S_i, \ t > 0. \tag{4.2}$$

$f_i \geq 0$ — immigration rates for individuals from another regions;

$\rho_{ik} \geq 0$, $\alpha_{jk} \geq 0$, $i, j \neq k$ — transition rates for individuals between the groups;

$\rho_{ii} > 0$, $\alpha_{jj} > 0$ — death rates of individuals;

$\beta_{ij} \geq 0$ — interaction rates between individuals S_i and I_j;

$\beta_{i1} + \cdots + \beta_{in} > 0$, $1 \leq i \leq n$.

Denote: $x = x(t) = (S_1(t), \ldots, S_n(t))^T$,

$y = y(t) = (I_1(t), \ldots, I_n(t))^T$. Model equations:

$$\dot{x} = Ax - D(x)Gy + f, \tag{4.4}$$

$$\dot{y} = By + D(x)Gy, \quad t > 0, \tag{4.5}$$

$$x(0) = x^0 \geq 0, \quad y(0) = y^0 \geq 0, \tag{4.6}$$

$$f = (f_1, \ldots, f_n)^T \geq 0,$$

$$A = (a_{ij}),\ a_{ii} = -\sum_{k=1}^{n} \rho_{ik} < 0,\ a_{ik} = \rho_{ki} \geq 0,\ 1 \leq i, k \leq n,\ \ k \neq i,$$

$$B = (b_{ij}),\ b_{ii} = -\sum_{k=1}^{n} \alpha_{ik} < 0,\ b_{ik} = \alpha_{ki} \geq 0,\ 1 \leq i, k \leq n,\ \ k \neq i,$$

$$G = (g_{ij}),\ g_{ij} = \beta_{ij},\ 1 \leq i, j \leq n,$$

$$D(x) = \mathrm{diag}(x_1, \ldots, x_n).$$

For A and B we have: $(-A)^T \xi > 0,\ (-B)^T \xi > 0$, $\xi = (1, \ldots, 1)^T$. Hence, $(-A)$ and $(-B)$ — are nonsingular M–matrices.

Model equations

$$\dot{x} = Ax - D(x)Gy + f, \quad \dot{y} = By + D(x)Gy,$$

have trivial equilibrium $x^* = (-A)^{-1}f \geq 0, \ \ y^* = 0.$

Now we use method of linearization and investigate the system of LDE for $u = x - x^*$, $w = y - y^*$:

$$\dot{u} = A\,u - D(x^*)G\,w, \tag{4.7}$$

$$\dot{w} = 0\,u + (B + D(x^*)G)\,w. \tag{4.8}$$

Suppose, that $(-1)(B + D(x^*)G)$ is nonsingular M–matrix. Then solution $u = 0$, $w = 0$ of (4.7), (4.8) is asymptotically stable.

If $(-1)(B + D(x^*)G)$ is not nonsingular M–matrix and $\det(B + D(x^*)G) \neq 0$, then solution $u = 0$, $w = 0$ of (4.7), (4.8) is unstable.

More general result for solutions $x(t)$, $y(t)$ of (4.4)–(4.6).

Suppose, that $(-1)(B + D(x^*)G)$ is nonsingular M–matrix.

Then for arbitrary initial data (4.6)

$$\lim_{t\to+\infty} x(t) = x^*, \quad \lim_{t\to+\infty} y(t) = y^* = 0, \tag{4.9}$$

and inequalities are valid

$$0 \le y(t) \le Ce^{-\gamma t}, \ t \ge 0, \tag{4.10}$$

where $C \in R^m$, $C > 0$, $\gamma \in R$, $\gamma > 0$.

SUMMARY. We have sufficient conditions for the extinction of the infection process expressed in terms of M–matrices.

Suppose, for example, that several groups of $S_1, \dots, S_n$ are small enough, $x_i^* \approx 0$, $i = i_1, \dots, i_m$.

Then $(-1)(B + D(x^*)G)$ may be a nonsingular M–matrix.