GLOBAL STABILITY

IN EPIDEMIC MODELS

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- Stability in nonlinear population models is often established by examining the eigenvalues of the linearized dynamics

- This methods gives only stability relative to infinitesimal perturbations of the initial state.

- Populations on the real word are subjected to large perturbations.

- It is essential that a population model should be stable relative to finite perturbations of its initial state.

In this course we deal with global properties of classic epidemic models using the direct Lyapunov method and topological approaches.

BASIC EPIDEMIOLOGICAL MODEL

(Kermack & Mc. Kendrick, 1927)

- The population is divided into disjoint classes with change with time:
  - a) Susceptible class: individuals who can incur the disease but are not yet infective.
  - b) Infective class: individuals who are transmitting the disease to others.
  - c) Removed class: individuals who are removed form the susceptible-infective interaction by immunity or isolation.
- The fraction of the total population in these classes: $S(t)$, $I(t)$ and $R(t)$.
- The population has constant size N.
- The death removal rate is denoted by μ. The average lifetime is $1/\mu$.
- The average number of contacts per infective per day which result in infection is denoted by λ.
- The average fraction of susceptibles infected by the infective class is λSI.
- Individuals recover from the infective class at a per capita constant rate γ.

$$
\begin{array}{ccccccc}
\xrightarrow{\mu} & S & \xrightarrow{\lambda SI} & I & \xrightarrow{\gamma I} & R \\
 & \downarrow & & \downarrow & & \downarrow \\
 & \mu S & & \mu I & & \mu R
\end{array}
$$

$$
\begin{aligned}
S'(t) &= \mu - \lambda SI - \mu S \\
I'(t) &= \lambda SI - \mu I \\
R'(t) &= \gamma I - \mu R
\end{aligned} \tag{1}
$$

$S(t) + I(t) + R(t) = 1.$

Since $R(t) = 1 - S(t) - I(t)$ it is enough to consider

$$
\begin{aligned}
S'(t) &= \mu - \lambda SI - \mu S \\
I'(t) &= \lambda SI - (\gamma + \mu) I
\end{aligned} \tag{2}
$$

in $T = \{(S, I) | S \geq 0, I \geq 0, S + I \leq 1\}$.

$S = 0 \Rightarrow S'(t) = \mu > 0,$
$I = 0 \Rightarrow I'(t) = 0,$
$S + I = 1 \Rightarrow (S + I)' = -\gamma I \leq 0$

$\Rightarrow$ T is positively invariant (solutions starting in T remains there for $t > 0$).

EQUILIBRIUM POINTS

Disease free equilibrium $E_0 = (1, 0)$.

Endemic equilibrium $E_1 = (S^*, I^*)$

$$S^* = \frac{1}{R_0}, \quad I^* = \frac{\mu}{\lambda}(R_0 - 1),$$

$$R_0 = \frac{\lambda}{\gamma + \mu}.$$

Basic reproduction number: Average number of secondary infections of an infective during the infection period.

LINEAR ANALYSIS

Characteristic roots of the linearization around E_0: $-\mu$, $(\gamma + \mu)(R_0 - 1)$.

$\Rightarrow E_0$ is a stable node if $R_0 < 1$ and a saddle if $R_0 > 1$.

Characteristic equation of the linearization around E_1:

$$s^2 + \mu R_0 s + \mu\lambda(R_0 - 1).$$

Routh Hurwitz criteria (Gantmacher, 1959) $\Rightarrow E_1$ is l.a.s for $R_0 > 1$.

GLOBAL STABILITY

Poincarè-Bendixon Theorem (Coddington & Levinson, 1955).

For two dimensional systems, bounded paths approach

a) an equilibrium point,

b) a limit cycle or,

c) a cycle graph.

Limit cycles must contain alt least one equilibrium in their interior.

Cyclic graphics are not possible from a stable equilibrium.

Bendixon-Dulac test (Hethcote, 1976).

$$\begin{aligned} x'(t) &= F(x,y) \\ y'(t) &= G(x,y) \end{aligned}$$

$(x,y) \in D$ simply connected, $F(x,y)$, $G(x,y) \in C^1(D)$

$\partial(HF)/\partial x + \partial(HG)/\partial y$ sign stable in D for some $H(x,y) \in C^1(D) \Rightarrow$

there is no periodic solution or cyclic graphs in D.

$R_0 \leq 1$:

$E_0 \in \partial T$ is the only equilibrium point in T.

There is not limit cycle in T.

There is not cyclic graph in T.

$\Rightarrow$ All paths in T approach E_0.

$R_0 > 1$:

E_0 is a saddle, $(S, 0) \Rightarrow E_0$ for $0 \leq S \leq 1$.

$E_1 \in \text{int } T$ is l.a.s.

$H = 1/I \Rightarrow$

$$\frac{\partial}{\partial S}(-\lambda S + \mu(1-S)/I) + \frac{\partial}{\partial I}(\lambda S - \gamma - \mu) = -\lambda - \mu/I$$

$\Rightarrow$ all paths in T except the S axis approach E_1.

DIRECT METHOD OF LYAPUNOV

(Hale, 1969)

$$V : U \subseteq R^n \rightarrow R; \quad \bar{0} \in U \quad V \in C^1(U)$$

is *positive definite* on U if

(i)$V(\bar{0}) = 0$

(ii) $V(\bar{x}) > 0, \bar{x} \neq \bar{0} \in U$.

V is *negative definite* if $-V$ is positive definite.

$$\bar{x}(t)' = f(\bar{x})$$

$\bar{x} = (x_1, x_2, ...x_n) \in R^n$,

$f(\bar{x}) = (f_1(\bar{x}), f_2(\bar{x}), ..., f_n(\bar{x})) \in C^1(R^n)$.

The *orbital derivative* of V along the trajectory $\bar{x}(t)$

$$\dot{V}(\bar{x}(t)) = \Sigma_{i=1}^n \frac{\partial V(\bar{x}(t))}{\partial x_i} x_i'(t)$$

Theorem 1 (Lyapunov). Let $\bar{0}$ an equilibrium point of $\bar{x}' = f(\bar{x})$, V positive definite on a neighborhood U of $\bar{0}$.

(i) If $\dot{V}(\bar{x}) \leq 0$ for $\bar{x} \in U - \{\bar{0}\} \Rightarrow \bar{0}$ is stable.

(ii) If $\dot{V}(\bar{x}) < 0$ for $\bar{x} \in U - \{\bar{0}\} \Rightarrow \bar{0}$ is asymptotically stable.

(iii) If $\dot{V}(\bar{x}) >$ for $\bar{x} \in U - \{\bar{0}\} \Rightarrow \bar{0}$ is unstable.

V is a Lyapunov function if V is positive definite, and $\dot{V}(\bar{x}) \leq 0$.

$M \subseteq R^n$ is an *invariant set* under the flow of $\bar{x}' = f(\bar{x})$ if for any $\bar{x}^0 \in M$, the solution trajectories through $\bar{x}^0$ belong to M for all $t \in R$.

Theorem 2. (La Salle-Lyapunov). Let V a $C^1(R^n)$ real valued function, $U = \{\bar{x} \in R^n | V(\bar{x}) < k\}$, $k \in R$, and $\dot{V}(\bar{x}) \leq 0$.

M the largest invariant set in $S = \{\bar{x} \in U | \dot{V}(\bar{x}) = 0\}$. Then every path that starts in U and remains bounded approach to M.

Global stability of $(1,0)$ by Lyapunov functions

$V : T \to R$

$V(S,I) = I$

$\dot{V}(S,I) = \lambda SI - (\gamma+\mu)I = (\gamma+\mu)(R_0S-1)I \leq 0$

for $R_0 \leq 1$.

If $R_0 < 1 : \dot{V} = 0 \Leftrightarrow I = 0$.

If $R_0 = 1 : \dot{V} = 0 \Leftrightarrow S = 1$.

In both cases $M = \{E_0\}$.

By La Salle-Lyapunov Theorem, E_0 is g.a.s in T.

Global stability of (S^*, I^*) by Lyapunov functions

$V : T_+ :\longrightarrow R, \quad T_+ = \{(S, I) \in T | S > 0, I > 0\}$

$$V(S, I) = W_1 \left[S - S^* - S^* ln\left(\frac{S}{S^*}\right)\right] + W_2 \left[I - I^* - I^* ln\left(\frac{I}{I^*}\right)\right]$$

for some $W_1 > 0, W_2 > 0$.

$$\begin{aligned} \dot{V} &= W_1(S - S^*)(-\lambda I - \mu + \frac{\mu}{S}) \\ &+ W_2(I - I^*)(\lambda S - (\gamma + \mu)) \end{aligned}$$

From the equations at equilibrium:

$$-\mu = \lambda I^* - \frac{\mu}{S^*}, \quad -(\mu + \gamma) = -\lambda S^*$$

$$\dot{V} = \lambda(W_2 - W_1)(S - S^*)(I - I^*) - W_1 \mu (S - S^*)^2$$

$W_1 = W_2 = 1 \Rightarrow$

$$\dot{V} = -\mu \frac{(S - S^*)^2}{SS^*} \leq 0$$

$\dot{V} = 0 \Leftrightarrow S = S^* \Rightarrow M = \{(S^*, I^*)\}$.

All paths in T_+ approach E_1. Since the vector field on the I axis, and on the line $S + I = 1$ points to the interior of T $\Rightarrow$all paths in $T - \{(S, 0) | 0 \leq S \leq 1\}$ tend to E_1.

- Generalizations of the Kermack and Mc.Kendrick model to introduce more realistic situations.
- Analysis of the asymptotic behavior of more complex systems.
- General ODE system that include a class of epidemiological models (Bereta & Capasso, 1986).

$$\bar{z}'(t) = \mathrm{diag}(\bar{z})\ (\bar{e} + A\bar{z}) + \bar{b}(\bar{z}) \qquad (3)$$

$R^n_+ = \{\bar{z} \in R^n|, z_i \geq 0, i = 1, ...n\}$

(i) $\bar{e} \in R^n$, a constant vector;

(ii) $A = (a_{ij})$, a real constant matrix;

(iii) $\bar{b}(\bar{z}) = \bar{c} + B\bar{z}$, $\bar{c} \in R^n_+$, $B = (b_{ij})$ a constant non negative matrix with $b_{ii} = 0$;

(iv)

$$\Omega = \{\bar{z} \in R^n_+ | \Sigma^n_{i=1} z_i \leq 1\} \quad \text{or} \quad \Omega = \{\bar{z} \in R^n_+ | z_i \leq 1\}$$

are positively invariant under the flow induced by (3).

The vector field $F(\bar{z}) = \text{diag}(\bar{z})\ (\bar{e} + A\bar{z}) + \bar{b}(\bar{z}) \in C^1(\Omega)$

Consider $D^i = \{\bar{z} \in \Omega | z_i = 0\}$.

- If $b_i(\bar{z})|_{D_i} = 0 \Rightarrow F(\bar{z})|_{D_i} = 0 \Rightarrow D_i$ is positively invariant.
- If $b_i(\bar{z}) > 0 \Rightarrow F(\bar{z}) \cdot \bar{n}_i < 0$, $\bar{n}_i$ is the exterior normal to Ω in $D_i \Rightarrow F(\bar{z})$ points inside Ω.
- Fixed point theorem assures the existence of at least one equilibrium solution within Ω.
- If $\bar{c}$ is positive definite, then system (3) has a positive equilibrium $\bar{z}^*$.

Define $\Omega_+ = \{\bar{z} \in \Omega | z_i > 0, i = 1, ...n\}$

A positive equilibrium $\bar{z} \in \Omega_+$ is called an endemic equilibrium.

- If an endemic equilibrium $\bar{z}^*$ is globally asymptotically stable (g.a.s) with respect to $\Omega_+ \Rightarrow \bar{z}$ is unique.

EXAMPLES

I) **Kermack & McKendrick model**

$$\begin{aligned} S'(t) &= \mu - \lambda SI - \mu S \\ I'(t) &= \lambda SI - (\gamma + \mu) I \end{aligned}$$

$$A = \begin{pmatrix} 0 & -\lambda \\ \lambda & 0 \end{pmatrix}, \quad \bar{e} = \begin{pmatrix} -\mu \\ -(\gamma+\mu) \end{pmatrix}, \quad \bar{c} = \begin{pmatrix} \mu \\ 0 \end{pmatrix}, B = 0$$

II) **Multi group SIS model** (Lajmanovich & Yorke, 1979)

$S_i + I_i = 1$, $i = 1, ..n.$

$$I_i' = (1 - I_i)\Sigma_{j=1}^{n} \lambda_{ij} I_j - (\mu_i + \alpha_i) I_i$$

$$A = \begin{pmatrix} -\lambda_{11} & -\lambda_{12} & \cdot & \cdot & -\lambda_{1n} \\ -\lambda_{21} & -\lambda_{22} & \cdot & \cdot & -\lambda_{2n} \\ \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot \\ -\lambda_{n1} & -\lambda_{n2} & \cdot & \cdot & -\lambda_{nn} \end{pmatrix}, \quad \bar{e} = \begin{pmatrix} \lambda_{11} - (\mu_1 + \alpha_1) \\ \lambda_{22} - (\mu_2 + \alpha_2) \\ \cdot \\ \cdot \\ \lambda_{nn} - (\mu_n + \alpha_n) \end{pmatrix}$$

$$\bar{c} = 0, \quad B = \begin{pmatrix} 0 & \lambda_{12} & \cdot & \cdot & \lambda_{1n} \\ \lambda_{21} & 0 & \cdot & \cdot & \lambda_{2n} \\ \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot \\ \lambda_{n1} & \lambda_{n2} & \cdot & \cdot & 0 \end{pmatrix}$$

Assume an equilibrium z^* in Ω_+, $z_i^* > 0$

Goh (1978) for a predator prey system

$V : \Omega_+ \rightarrow R$

$$V(\bar{z}) = \Sigma_{i=1}^{n} W_i \left(z_i - z_i^* - z_i^* ln \frac{z_i}{z_i^*} \right) \tag{4}$$

$W = \text{diag}(W_1, ..., W_n), W_i$ positive real numbers.

$$\dot{V}(\bar{z}) = (\bar{z} - \bar{z}^*)^T W A \ \text{diag}(\bar{z}^{-1}) \ \bar{z}' \tag{5}$$

At the equilibrium $\bar{z}^*$:

$$0 = \mathrm{diag}(\bar{z}^*)\ (\bar{e} + A\bar{z}^*) + \bar{b}(\bar{z}^*)$$

$$\bar{e} = -Az^* - \mathrm{diag}(\bar{z}^{*^{-1}})\ \bar{b}(z^*)$$

where $\bar{z}^{*^{-1}} = (1/z_1^*, ..., 1/z_n^*)$.

Substituting $\bar{e}$:

$$z'(t) = \mathrm{diag(z)}\ [A + \mathrm{diag}(\bar{z}^{*^{-1}})\ B](\bar{z} - \bar{z}^*)$$

$$- \mathrm{diag}(\bar{z} - \bar{z}^*)\ \mathrm{diag}(\bar{z}^{*^{-1}})\bar{b}(\bar{z})$$

$\dot{V}$ becomes

$$\dot{V}(\bar{z}) = (\bar{z}-\bar{z}^*)^T W \left[\tilde{A} - \mathrm{diag}\left(\frac{\bar{b}_1(z)}{z_1 z_1^*}, .., \frac{\bar{b}_n(z)}{z_n z_n^*}\right)\right] (\bar{z}-\bar{z}^*) \quad (6)$$

$\tilde{A} = A + \mathrm{diag}(\bar{z}^{*^{-1}})\ B$.

C a real $n \times n$ matrix.

- $C \in S_w \Leftrightarrow$ there exists a positive diagonal real matrix W such that $WC + C^T W$ is positive definite.
- C is W skew-symmetrizable $\Leftrightarrow$ there exists a positive diagonal real matrix W such that WC is skew-symmetric ($a_{ji} = -a_{ij}$, $a_{ii} = 0$).

If

$$-\left[\tilde{A} - \operatorname{diag}\left(\frac{\bar{b}_1(z)}{z_1 z_1^*}, .., \frac{\bar{b}_n(z)}{z_n z_n^*}\right)\right] \in S_W$$

$$\dot{V}(\bar{z}) \leq 0, \qquad \dot{V}(\bar{z}) = 0 \Leftrightarrow \bar{z} = \bar{z}^*$$

$\bar{z}$ is g.a.s within Ω_+.

If $W\tilde{A}$ is skew-symmetric

$$\dot{V}(\bar{z}) = -\Sigma_{i=1}^{n} \frac{W_i b_i(\bar{z})}{z_i z_i^*}(z_i - z_i^*)^2 \leq 0.$$

$\dot{V}(\bar{z}) = 0 \Leftrightarrow$

$$\bar{z} \in R = \{\bar{z} \in \Omega | z_i = z_i^*, i = 1, .., n \text{ s.t. } b_i(\bar{z}) > 0\}.$$

Associate a graph to $\tilde{A}$ in which nodes representing epidemiological classes z_i, and arrows the mutual interactions following the rules

(i) If $b_i(\bar{z}) = 0$, z_i is represented by $\overset{\bullet}{i}$.

(ii) If $b_i(\bar{z}) > 0$, z_i is represented by $\overset{\circ}{i}$.

(iii) Each pair of elements $\tilde{a}_{ij}\tilde{a_j}i < 0$ is represented by an arrow connecting nodes i and j.

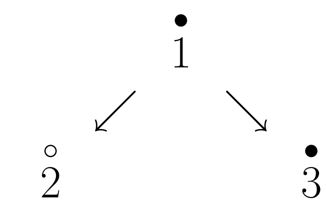
Lemma 1. (Cooke & Yorke, 1973). $\tilde{A}$ W-skew symmetrizable $n \times n$ matrix. If the associated graph is either

a) a tree and $p-1$ of the p terminal nodes are $\circ$,

b) or a chain and two consecutive internal nodes are $\circ$,

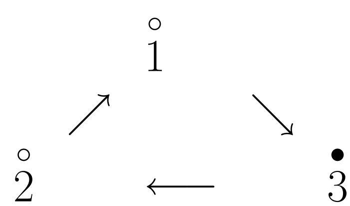
c) or a cycle and two consecutive nodes are $\circ$,

then $M = \{\bar{z}\}$ within R.



a

b



c

If $\tilde{A}$ satisfies a, b or c of Lemma 1 $\Rightarrow$ $\bar{z}^*$ is g.a.s within Ω_+.

I) SIR **model**

$$\begin{aligned} S'(t) &= \mu - \lambda SI - \mu S \\ I'(t) &= \lambda SI - (\gamma + \mu)I \end{aligned}$$

$$\tilde{A} = A = \begin{pmatrix} 0 & -\lambda \\ \lambda & 0 \end{pmatrix}, \quad B = 0, \quad \bar{b}(\bar{z}) = \bar{c} = \begin{pmatrix} \mu \\ 0 \end{pmatrix}$$

$\tilde{A}$ is skew-symmetric. The associated graph $\overset{\circ}{1} \rightarrow \overset{\bullet}{2}$.

II) $SIRS$ **model with temporary immunity** (Hethcote, 1976)

$$\begin{aligned} S'(t) &= \mu - \lambda SI - \mu S + \alpha R \\ I'(t) &= \lambda SI - (\mu + \gamma)I \\ R'(t) &= \gamma I - (\alpha + \mu)R \end{aligned}$$

$S + I + R = 1$

$$\begin{aligned} S'(t) &= (\mu + \alpha) - \lambda SI - (\mu + \alpha)S - \alpha I \\ I'(t) &= \lambda SI - (\mu + \gamma)I \end{aligned}$$

Endemic equilibrium (S^*, I^*)

$$S^* = \frac{1}{R_0}, I^* = \frac{(\delta + \alpha)(R_0 - 1)}{\lambda + \alpha R_0}, R_0 = \frac{\lambda}{\gamma + \mu}$$

$$\tilde{S} = S + \alpha/\lambda$$

$$\begin{aligned} \tilde{S}'(t) &= (\mu+\alpha)(1+\alpha/\lambda) - \lambda\tilde{S}I - (\mu+\alpha)\tilde{S} \\ I'(t) &= \lambda\tilde{S}I - (\mu+\gamma+\alpha)I \end{aligned}$$

$$A = \begin{pmatrix} 0 & -\lambda \\ \lambda & 0 \end{pmatrix}, \bar{e} = \begin{pmatrix} -(\mu+\alpha) \\ -(\gamma+\mu+\alpha) \end{pmatrix}, \bar{c} = \begin{pmatrix} (\mu+\alpha)(1+\alpha/\lambda) \\ 0 \end{pmatrix},$$

$B = 0.$

$\tilde{A} = A$ is skew-symmetric, $\bar{b}(\bar{z}) = \bar{c}$.

The associated graph $\overset{\circ}{1} \rightarrow \overset{\bullet}{2}$.

III) SIS **model for two dissimilar groups**

$$I_1' = [\lambda_{11} I_1 + \lambda_{12} I_2](1 - I_1) - (\mu_1 + \alpha_1) I_1, \;\; I_1 + S_1 = 1$$

$$I_2' = [\lambda_{21} I_1 + \lambda_{22} I_2](1 - I_2) - (\mu_2 + \alpha_2) I_2, \;\; I_2 + S_2 = 1$$

$I_i \leq 1, i = 1, 2.$

$$A = \begin{pmatrix} -\lambda_{11} & -\lambda_{12} \\ -\lambda_{21} & -\lambda_{22} \end{pmatrix}, \quad \bar{e} = \begin{pmatrix} \lambda_{11} - (\mu_1 + \alpha_1) \\ \lambda_{22} - (\mu + \alpha_2) \end{pmatrix}, \bar{c} = 0,$$

$$B = \begin{pmatrix} 0 & \lambda_{12} \\ \lambda_{21} & 0 \end{pmatrix}$$

$$\bar{z} = (I_1, I_2)^T, \qquad \bar{b}(\bar{z}) = (\lambda_{12} I_2, \lambda_{21} I_1)^T$$

$$\tilde{A} = \begin{pmatrix} -\lambda_{11} & \dfrac{\lambda_{12}(1 - I_1^*)}{I_1^*} \\ \dfrac{\lambda_{21}(1 - I_2^*)}{I_2^*} & -\lambda_{22} \end{pmatrix}$$

To show:

$$C = -\left[\tilde{A} - \text{diag}\ \left(\frac{\lambda_{12} I_2}{I_1^* I_1}, \frac{\lambda_{21} I_1}{I_2^* I_2}\right)\right] \in S_W.$$

$$WC \ = \ \begin{pmatrix} W_1\left(\lambda_{11} + \frac{\lambda_{12} I_2}{I_1^* I_1}\right) & W_1\frac{\lambda_{12}(1 - I_1^*)}{I_1^*} \\ \\ W_2\frac{\lambda_{21}(1 - I_2^*)}{I_2^*} & W_2\left(\lambda_{22} + \frac{\lambda_{21} I_1}{I_2^* I_2}\right) \end{pmatrix}$$

Choosing W_1, W_2:

$$\frac{\lambda_{21}(1 - I_2^*)}{I_2^*} W_2 = \frac{\lambda_{12}(1 - I_1^*)}{I_1^*} W_1$$

$\Rightarrow C$ is symmetric

Det(C) $> 0 \Rightarrow C \in S_W$.

$\bar{z}^*$ is g.a.s in $\Omega = \{\bar{z} \in R^2 | I_i \leq 1, i = 1, 2\}$

IV **Host-vector-host model** (Hethcote, 1976)

I_1, and I_3 infected hosts, I_2 infected vector.

$$\begin{aligned} I_1'(t) &= \lambda_{12} I_2 (1 - I_1) - (\gamma_1 + \alpha_1) I_1, && S_1 + I_1 = 1 \\ I_2'(t) &= [\lambda_{21} I_1 + \lambda_{23} I_3](1 - I_2) - (\gamma_2 + \alpha_2) I_2, && S_2 + I_2 = 1 \\ I_3'(t) &= \lambda_{32} I_2 (1 - I_3) - (\gamma_3 + \alpha_3) I_3, && S_3 + I_3 = 1 \end{aligned}$$

$$A = \begin{pmatrix} 0 & -\lambda_{12} & 0 \\ -\lambda_{21} & 0 & -\lambda_{23} \\ 0 & -\lambda_{32} & 0 \end{pmatrix}, \bar{e} = \begin{pmatrix} -(\gamma_1 + \alpha_1) \\ -(\gamma_2 + \alpha_2) \\ -(\gamma_3 + \alpha_3) \end{pmatrix}, \bar{c} = 0,$$

$$B = \begin{pmatrix} 0 & \lambda_{12} & 0 \\ \lambda_{21} & 0 & \lambda_{23} \\ 0 & \lambda_{32} & 0 \end{pmatrix}$$

$$\bar{b}(\bar{z}) = B\bar{z}, \quad \tilde{A} = \begin{pmatrix} 0 & \dfrac{\lambda_{12}(1-I_1^*)}{I_1^*} & 0 \\ \dfrac{\lambda_{21}(1-I_2^*)}{I_2^*} & 0 & \dfrac{\lambda_{23}(1-I_2^*)}{I_2^*} \\ 0 & \dfrac{\lambda_{32}(1-I_3^*)}{I_3^*} & 0 \end{pmatrix}$$

$$C = -W\left[\tilde{A} - \text{diag}\,\left(\frac{b_1(\bar{z})}{I_1 I_1^*}, \frac{b_2(\bar{z})}{I_2 I_2^*}, \frac{b_3(\bar{z})}{I_3 I_3^*}\right)\right] \text{ becomes}$$

$$\begin{pmatrix} \dfrac{\lambda_{12} I_2}{I_1 I_1^*} W_1 & -\dfrac{\lambda_{12}(1-I_1^*)}{I_1^*} W_1 & 0 \\ -\dfrac{\lambda_{21}(1-I_2^*)}{I_2^*} W_2 & \dfrac{(\lambda_{21} I_1 + \lambda_{23} I_3)}{I_2 I_2^*} W_2 & -\dfrac{\lambda_{23}(1-I_2^*)}{I_2^*} W_2 \\ 0 & -\dfrac{\lambda_{32}(1-I_3^*)}{I_3^*} W_3 & \dfrac{\lambda_{32} I_2}{I_3 I_3^*} W_3 \end{pmatrix}$$

is symmetric if

$$W_1 > 0, \quad W_2 = \frac{\lambda_{12}(1-I_1^*) I_2^*}{\lambda_{21}(1-I_2^*) I_1^*} W_1, \quad W_3 = \frac{\lambda_{23}(1-I_2^*) I_3^*}{\lambda_{32}(1-I_3^*) I_2^*} W_2.$$

Sufficient condition for C to be positive definite

$$\det C_{11} > 0, \quad \det C_{22} > 0, \quad \det C_{33} > 0$$

where C_{ii} is the $i \times i$ sub matrix of C taking the first i-rows and the first i columns.

These conditions are always satisfied by an endemic equilibrium $\bar{z}^* \in \Omega_+$.

- For an epidemiological model with arbitrary n dissimilar groups is difficult to apply the above results.
- Lajmanovich & Yorke (1976) proved existence and stability of the endemic equilibrium for n multigrup SIS model using Lyapunov functions and Perron-Frobenius Theorem for positive and irreducible matrices.

$$I_i' = (1-I_i)\Sigma_{j=1}^{n}\lambda_{ij}I_j-(\mu_i+\alpha_i)I_i, \quad S_i+I_i = 1, i = 1, ..n \tag{7}$$

can be written also as

$$\bar{I}' = A\bar{I} + N(\bar{I}) \tag{8}$$

$$A = \begin{pmatrix} \lambda_{11} - (\mu_1 + \alpha_1) & \lambda_{12} & \cdot\ \cdot & \lambda_{1n} \\ \lambda_{21} & \lambda_{22} - (\mu_2 + \alpha_2) & \cdot\ \cdot & \lambda_{2n} \\ \cdot & \cdot & \cdot\ \cdot & \cdot \\ \cdot & \cdot & \cdot\ \cdot & \cdot \\ \lambda_{n1} & \lambda_{n2} & \cdot\ \cdot & \lambda_{nn} - (\mu_n + \alpha_n) \end{pmatrix}$$

$$N(\bar{I}) = \begin{pmatrix} -\Sigma_{j=1}^{n}\lambda_{1j}I_jI_1 \\ -\Sigma_{j=1}^{n}\lambda_{2j}I_jI_2 \\ \cdot \\ \cdot \\ -\Sigma_{j=1}^{n}\lambda_{nj}I_jI_n \end{pmatrix}$$

Assume for any proper subset S of (1,..,n) there exists $i \in S$ and $j \in S^c$ such that $\lambda_{ij} > 0$ (equivalent to A is irreducible). $\Rightarrow \bar{0}$ is the only invariant set in $\partial\Omega$.

Stability modulus:

$$s(A) = \max_{1 \le i \le n} \text{Re } s_i, \quad s_i \text{ eigenvalues of} A$$

Theorem 3. $s(A) \le 0 \Rightarrow \bar{I}_0 = \bar{0}$ is g.a.s. in Ω.

$s(A) > 0 \Rightarrow$ the system has an endemic equilibrium point $\bar{I}_1$ g.a.s. in $\Omega_+ - \{\bar{0}\}$.

An example: $n = 2$, $\lambda_{11} = \lambda_{22} = 0$ (no homosexual contacts).

$$A = \begin{pmatrix} -(\mu_1 + \alpha_1) & \lambda_{12} \\ \lambda_{21} & -(\mu_2 + \alpha_2) \end{pmatrix}$$

$$\text{Tr } A = -(\mu_1 + \alpha_1 + \mu_2 + \alpha_2) < 0.$$

$s(A) \le 0 \Leftrightarrow \det A = (\mu_1 + \alpha_1)(\mu_2 + \alpha_2) - \lambda_{12}\lambda_{21} \ge 0 \Leftrightarrow$

$$\frac{\lambda_{12}}{(\mu_2 + \alpha_2)} \frac{\lambda_{21}}{(\mu_1 + \alpha_1)} \le 1$$

Proof of Theorem 3.

From Perron-Frobenius Theorem (Varga, 1962) it can be proved the following

Lemma 2. (Lajmanovich & Yorke, 1976.) Let C an irreducible $n \times n$ matrix, and assume $c_{ij} \geq 0$ whenever $i \neq j$. Then, there exists an eigenvector $\bar{w}$ of C such that $\bar{w} > 0$ and the corresponding eigenvalue is $s(A)$.

By Lemma 2, A has an eigenvector $\bar{w} > 0$ with eigenvalue $s(A)$. Assume $s(A) \leq 0$.

Define the Lyapunov function

$$V(\bar{I}) = \bar{w} \cdot \bar{I}$$

$$\begin{aligned} \dot{V}(\bar{I}) &= \bar{w} \cdot \bar{I}'(t) = (\bar{w} \cdot A\bar{I}) + (\bar{w} \cdot N(\bar{I})) \\ &= (A^T\bar{w} \cdot \bar{I}) + (\bar{w} \cdot N(\bar{I})) \\ &= s(A)(\bar{w} \cdot \bar{I}) + (\bar{w} \cdot N(\bar{I})) \leq 0 \end{aligned}$$

$\{\bar{0}\}$ is the only invariant set contained in $M = \{\bar{I} \in \Omega | \dot{V}(\bar{I}) = 0\}$

Assume $s(A) > 0$.

$\bar{I} \in \Omega_\epsilon = \{\bar{I} \mid V(\bar{I}) \geq \epsilon\}$

$\Rightarrow \dot{V} \geq s(A)\epsilon - ||\bar{w}||||N(\bar{I})||$.

$\bar{I} \in \partial\Omega_\epsilon \Rightarrow \epsilon = \bar{w} \cdot \bar{I} \geq r||\bar{I}||, \quad r = \min w_i$

$\Rightarrow ||\bar{I}|| \leq \epsilon/r$

Choose δ such that $s(A) - (||w||/r)\delta > 0$.

Choose ϵ_0 such that $||N(\bar{I})|| \leq \delta||\bar{I}||$ for $||\bar{I}|| \leq \epsilon_0$.

For $\epsilon \in [0, \epsilon_0]$:

$$\dot{V}(\bar{I}) \geq s(A) - \epsilon\delta\frac{||\bar{w}||}{r} = \left(s(A) - \delta\frac{||\bar{w}||}{r}\right)\epsilon > 0.$$

By Fixed Point Theorem Ω_{ϵ_0} contains an endemic equilibrium $\bar{I}^* = (I_1^*, .., I_n^*)$, $I_i > 0$.

Remark.

If $\bar{I} \neq \bar{0}$ then $\bar{I}(t)$ remains remains at a positive distance from the boundary of Ω for $t \geq 0$.

Global stability of $\bar{I}^*$

Remark. For $V(\bar{x})$ continuous Lyapunov Theorem is still true replacing $\dot{V}(\bar{x})$ by

$$\dot{V}_+ = \lim\,\sup_{h\to 0^+} \frac{V(\bar{x}(t+h)) - V(\bar{x}(t))}{h}.$$

Define $M, m : \Omega \to R$

$M(\bar{I}) = \max_{i=1,..,n} (I_i/I_i^*) \qquad m(\bar{I}) = \min_{i=1,..,n} (I_i/I_i^*)$.

Assume: $M(\bar{I}(t)) = I_1(t)/I_1^*$ for $[t_0, t_0+\epsilon]$

$$\Rightarrow \dot{M}_+(I(t_0)) = \frac{I'(t_0)}{I_1^*}$$

From (7):

$$I_1^* \frac{I_1'(t_0)}{I_1(t_0)} = (1 - I_1(t_0)) \Sigma_{j=1}^n \lambda_{1j} \frac{I_j(t_0) I_1^*}{I_1(t_0)} - (\mu_1 + \alpha_1) I_1^*$$

If $M(\bar{I}(t_0)) > 1$:

$$I_1^* \frac{I_1'(t_0)}{I_1(t_0)} < (1 - I_1^*) \Sigma_{j=1}^n \lambda_{1j} I_j^* - (\mu_1 + \alpha_1) I_1^* = 0$$

$\Rightarrow I_1'(t_0) < 0 \Rightarrow \dot{M}_+(\bar{I}(t_0)) < 0$

In the same fashion it can be proved:

- $M(\bar{I}(t_0)) = 1 \Rightarrow \dot{M}_+(\bar{I}(t_0)) \leq 0$
- $m(\bar{I}(t_0)) < 1 \Rightarrow \dot{m}_+(\bar{I}(t_0)) > 0$
- $m(\bar{I}(t_0)) = 1 \Rightarrow \dot{m}_+(\bar{I}(t_0)) \geq 0$

Define

$$V(\bar{I}) = \max[M(\bar{I}) - 1, 0], \qquad W(\bar{I}) = \max[1 - m(\bar{I}), 0].$$

$$V(\bar{I}) \geq 0, W(\bar{I}) \geq 0 \quad \text{and} \quad \dot{V}_+(\bar{I}) \leq 0 \qquad \dot{W}_+(\bar{I}) \leq 0.$$

$$\dot{V} = 0 \text{ in } H_V = \{\bar{I} | 0 \leq I_i \leq I_i^*\}$$
$$\dot{W} = 0 \text{ in } H_W = \{\bar{I} | I_i^* \leq I_i \leq 1\} \cup \{\bar{0}\}$$

By La Salle-Lyapunov Theorem solutions in Ω approach $H_V \cap H_W = \{\bar{I}^*\} \cup \{\bar{0}\}$.

Since $\bar{I}(0) \neq \bar{0} \Rightarrow \liminf_{t\to\infty} ||\bar{I}(t)|| > 0$ then $\bar{I}^*$ is g.a.s. in $\Omega - \{\bar{0}\}$.

- There are fewer mathematical results concerning global stability for epidemic models involving n subpopulations for diseases with immunity.

- Hethcote (1978) analyzed the global behavior of solutions of an SIR model with n subpopulations, but without births and deaths.

- For an $SEIR$ model with n subpopulations, Thieme (1983) proved global asymptotic stability if the latent and removed periods are sufficiently short.

- Esteva & Vargas (1998) proved global asymptotic stability of a host-vector epidemic model with immunity for dengue disease. They use the approach given by Li and Muldowney (1995) for a $SEIR$ model.

DENGUE DISEASE MODEL

(Esteva & Vargas, 1998)

N_h human population size.

N_v mosquito population size.

A mosquito recruitment rate.

μ_h human mortality rate.

μ_v mosquito mortality rate.

$$N_h' = 0 \Rightarrow N_h \quad \text{const.} \qquad N_v' = A - \mu_v N_v \Rightarrow N_v \to \frac{A}{\mu_v}.$$

$S_h(t)$, $I_h(t)$, $R_h(t)$ number of suceptibles, infectives and recovered humans.

$S_v(t)$, $I_v(t)$ number of susceptibles and infectives mosquitoes.

PARAMETERS

b biting rate. Average number of bites per mosquito per day (once every two or three days).

β_h probability that an infectious bite produces a new case in a susceptible human.

β_v probability that an infectious bite produces a new case in a susceptible mosquito.

m number of alternative hosts available as blood sources.

γ_h per capita human recovered rate.

$\frac{1}{\gamma_h}$ infectious period.

INFECTION RATES

$\dfrac{N_h}{N_h+m}$ probability that a mosquito chooses a human as a host.

A human receives $b\dfrac{N_v}{N_h}\dfrac{N_h}{N_h+m}$ bites per day.

A mosquito takes $b\dfrac{N_h}{N_h+m}$ human blood meals per day.

Infection rates per susceptible human and susceptible vector

$$\beta_h b \frac{N_v}{N_h}\frac{N_h}{N_h+m}\frac{I_v}{N_v} = \frac{\beta_h b}{N_h+m} I_v$$

$$\beta_v b \frac{N_h}{N_h+m}\frac{I_h}{N_h} = \frac{\beta_v b}{N_h+m} I_h.$$

$$
\begin{aligned}
S_h'(t) &= \mu_h N_h - \frac{\beta_h b}{N_h + m} I_v S_h - \mu_h S_h \\
I_h'(t) &= \frac{\beta_h b}{N_h + m} I_v S_h - (\gamma_h + \mu_h) I_h \\
R_h'(t) &= \gamma_h I_h - \mu_h R_h \\
S_v'(t) &= A - \frac{\beta_v b}{N_h + m} I_h S_v - \mu_v S_v \\
I_v'(t) &= \frac{\beta_v b}{N_h + m} I_h S_v - \mu_v I_v.
\end{aligned}
\tag{9}
$$

$$
S_h + I_h + R_h = N_h \qquad S_v + I_v = N_v
$$

1. The subset

$$T : S_h + I_h + R_h = N_h, \qquad S_v + I_v = \frac{A}{\mu_v}$$

is invariant under system (9).

2. All solutions of (9) approach T since N_h is constant and $N_v \to \dfrac{A}{\mu_v}$. It is enough to study the asymptotic behavior of solutions of system (9) in T.

3. In T N_h and N_v are constant. Take proportions:

$$s_h = \frac{S_h}{N_h}, \quad i_h = \frac{I_h}{N_h}, \quad r_h = \frac{R_h}{N_h}, \; s_v = \frac{S_v}{A/\mu_v}, \quad i_v = \frac{I_h}{A/\mu_v}.$$

4. Since $r_h = 1 - s_h - i_h$ and $s_v = 1 - i_v$ it is enough to consider only the variables s_h, i_h, i_v.

$$
\begin{aligned}
s_h'(t) &= \mu_h - \frac{\beta_h bA/\mu_v}{N_h+m} i_v s_h - \mu_h s_h \\
i_h'(t) &= \frac{\beta_h bA/\mu_v}{N_h+m} i_v s_h - (\gamma_h + \mu_h) i_h \qquad (10) \\
i_v'(t) &= \frac{\beta_v bN_h}{N_h+m} i_h (1 - s_v) - \mu_v i_v .
\end{aligned}
$$

$$\Omega = \{(s_h, i_h, i_v) |\ 0 \leq i_v \leq 1,\ 0 \leq s_h,\ 0 \leq i_h,\ s_h + i_h \leq 1\}.$$

Ω is positively invariant under the flow induced by system (10).

EQUILIBRIUM POINTS

Define

$$R_0 = \frac{\beta_h \beta_v b^2 N_h A/\mu_v}{(N_h + m)^2 \mu_v (\gamma_h + \mu_h)} \tag{11}$$

$$\beta = \frac{\beta_v b N_h}{\mu_v (N_h + m)}$$

$$M = \frac{\gamma_h + \mu_h}{\mu_h}$$

Disease-free equilibrium $E_1 = (1, 0, 0)$

Endemic equilibrium $E_2 = (s_h^*, i_h^*, i_v^*)$

$$s_h^* = \frac{\beta + M}{\beta + M R_0}, \quad i_h^* = \frac{R_0 - 1}{\beta + M R_0}, \quad i_v^* = \frac{\beta(R_0 - 1)}{R_0(\beta + M)}$$

$R_0 \leq 1 \Rightarrow E_1$ is the only equilibrium in Ω.

$R_0 > 1 \Rightarrow E_2$ will also lie in Ω.

BASIC REPRODUCTIVE NUMBER

For dengue disease

$N_1 = \frac{\beta_v bA/\mu_v}{(N_h + m)} \frac{1}{(\gamma_h + \mu_h)}$ number of secondary infections produced by a single human in a susceptible mosquito population.

$N_2 = \frac{\beta_h b N_h}{(N_h + m)} \frac{1}{\mu_v}$ number of secondary infections produced by a single infectious mosquito during its lifespan.

The basic reproductive number is the geometric mean of N_1 and N_2

$$\tilde{R}_0 = \sqrt{N_1 N_2} = \sqrt{R_0}$$

STABILITY ANALYSIS

Linearizing around the disease-free equilibrium E_1

$$DF(E_1) = \begin{pmatrix} -\mu_h & 0 & -\frac{\beta_h bA/\mu_v}{N_h+m} \\ 0 & -(\gamma_h + \mu_h) & \frac{\beta_h bA/\mu_v}{N_h+m} \\ 0 & \frac{\beta_v b N_h}{N_h+m} & -\mu_v \end{pmatrix}$$

Eigenvalues of $DF(E_1)$:

$$-\mu_h$$

$$\frac{-(\gamma_h + \mu_h + \mu_v) \pm \sqrt{(\gamma_h + \mu_h + \mu_v)^2 - 4\mu_v(\gamma_h + \mu_h)(1 - R_0)}}{2}$$

E_1 is locally asymptotically stable for $R_0 < 1$ and unstable for $R_0 > 1$.

Global stability of E_1 for $R_0 \leq 1$:

$$V = \left(\frac{b\beta_h A/\mu_v}{(N_h + m)\mu_v} \right) i_v + i_h$$

Orbital derivative

$$\dot{V} = -\frac{b\beta_h A/\mu_v}{N_h + m}(1-s_h)i_v - (\gamma_h+\mu_h)[1-R_0(1-i_v)]i_h \leq 0$$

$\dot{V} = 0 \Rightarrow$

$$(1 - s_h)i_v = 0, \quad i_h = 0 \quad \text{if} \;\; R_0 < 1$$

$$(1 - s_h)i_v = 0, \quad i_v i_h = 0 \quad \text{if} \;\; R_0 = 1.$$

La Salle-Lyapunov Theorem $\Rightarrow$ trajectories in Ω approach the maximal invariant set contained in $\dot{V} = 0$.

$\{E_1\}$ is the only invariant set contained in $\dot{V} = 0$.

The eigenvalues of $DF(E_2)$ are the roots of the characteristic equation

$$p(\lambda) = \lambda^3 + A\lambda^2 + B\lambda + C = 0$$

$$\begin{aligned}
A &= \mu_h \frac{\beta + MR_0}{\beta + M} + \mu_h M + \mu_v R_0 \frac{(\beta + M)}{\beta + MR_0} \\
B &= \mu_h^2 M \frac{\beta + MR_0}{\beta + M} + \mu_v \mu_h r_0 + \mu_v \beta \frac{\mu_h M(R_0 - 1)}{\beta + MR_0} \\
C &= \mu_v \mu_h^2 M(R_0 - 1).
\end{aligned}$$

Routh-Hurwitz criterion (Gantmacher 1959), : all eigenvalues of $p(\lambda)$ have negative real parts if and only if $A > 0$, $B > 0$, $C > 0$, and $AB > C$.

- $R_0 > 1 \Rightarrow B > 0, C > 0$.
- $AB > C$ easy to verify.

E_2 is locally asymptotically stable for $R_0 > 1$.

Global stability of E_1 follows from the following result.

Theorem 4. Assume $\bar{x}' = \bar{F}(\bar{x})$ is an autonomous system in a convex, bounded subset D of R^3 which is competitive, persistent and has the property of stability of periodic orbits. If $\bar{x}_0$ is the only equilibrium point in int Ω, and it is locally asymptotically stable, then it is globally stable in int Ω.

(Li & Muldowney, 1995).

COMPETITIVE AND COOPERATIVE SYSTEMS

(Smith, 1995)

$$\bar{x}' = \bar{F}(\bar{x}) \tag{12}$$

$\bar{x} = (x_1, x_2, .., x_n) \in D \subset R^n$,

$\bar{F} = (f_1(\bar{x}), f_2(\bar{x}), ..., f_n(\bar{x})) : D \to R^n$.

- Cooperative system.

  Solutions preserve lexicographic partial order in R^n for $t \geq 0$:

  $\bar{x}_1(0) \leq \bar{x}_2(0) \Rightarrow \bar{x}_1(t) \leq \bar{x}_2(t)$, $t \geq 0$.

- Competitive system.

  Solutions preserve lexicographic partial order in R^n for $t \leq 0$:

  $\bar{x}_1(0) \leq \bar{x}_2(0) \Rightarrow \bar{x}_1(t) \leq \bar{x}_2(t)$, $t \leq 0$.

For D a convex set and $\bar{F}$ a C^1 function:

System (12) is *cooperative* in D if $\dfrac{\partial f_i(\bar{x})}{\partial x_j} \geq 0, i \neq j.$

System (12) is *competitive* in D if $\dfrac{\partial f_i(\bar{x})}{\partial x_j} \leq 0, i \neq j.$

n-dimensional cooperative and competitive systems behave like a dynamical flow in a (n-1)-dimensional space.

For $n = 3$

The solutions of a cooperative or competitive system in a closed convex set $D \subset R^3$ that contains no equilibria are closed or approach a closed orbit when $t \geq 0$.

The definitions and results above can be generalized:

System (12) is *cooperative* in D if for some diagonal matrix

$$H = diag(\epsilon_1, \epsilon_2, ..., \epsilon_n)$$

ϵ_i is either -1 or 1, $H^{-1}DF(\bar{x})H$ has non-negative off-diagonal elements for $\bar{x} \in D$

$$\epsilon_i \epsilon_j \frac{\partial f_i}{\partial x_j}(\bar{x}) \geq 0, \quad i \neq j.$$

System (12) is *competitive* in D if

$$\epsilon_i \epsilon_j \frac{\partial f_i}{\partial x_j}(\bar{x}) \leq 0, \quad i \neq j.$$

The flow of a cooperative (competitive) system preserves for $t > 0$ ($t < 0$) the partial order $\leq_m$ generated by $K_m = \{\bar{x} \in R^n \mid \epsilon_i x_i \geq 0, 1 \leq i \leq n\}$

$$\bar{x} \ \leq_m \bar{y} \Longleftrightarrow \bar{y} - \bar{x} \in K_m$$

By looking at its derivative DF and choosing

$$H = \begin{pmatrix} 1 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & 1 \end{pmatrix}$$

it can be seen that system (10) is competitive in Ω with respect to the partial order defined by the orthant

$$K = \{(s_h, i_h, i_v) \in R^3 \mid s_h \geq 0,\ i_h \leq 0,\ i_v \geq 0\ \}$$

PERSISTENCE

(Butler & Waltman, 1986)

- System (12) is persistent $\Longleftrightarrow$ the solutions starting in int D remains at a positive distance from the boundary of Ω.

- For system (10) the vector field points to the interior of Ω except in the s_h axis. In this axis $s_h' = \mu_h(1-s_h)$ $\Rightarrow s_h(t) \to 1$ as $t \to \infty \Rightarrow E_1$ is the only equilibrium in the boundary.

$$V = i_v + \frac{\mu_v(N_h + m)(1 + R_0)}{2b\beta_h A/\mu_v} i_h$$

- For $R_0 > 1$ there exists a neighborhood U of E_1 such that $\dot{V} > 0$ along orbits starting in $U \bigcap$ int Ω $\Rightarrow$ they go away from $E_1 \Rightarrow$ system (10) is persistent for $R_0 > 1$.

STABILITY OF PERIODIC ORBITS

- $\gamma(t)$ a periodic solution of system (12) with period ω and orbit $\gamma = \{\gamma(t) : 0 \leq t \leq \omega\}$.

- γ is *orbitally stable* $\Longleftrightarrow$ for each $\epsilon > 0$, there exists δ such that, any solution $\bar{x}(t)$ for which the distance from $\bar{x}(0)$ from γ is less than δ, remains at a distance less than ϵ from γ, for all $t \geq 0$. It is *asymptotically orbitally stable*, if the distance of $\bar{x}(t)$ from γ also tends to zero as t goes to infinity.

- System (12) has the property of *stability of periodic orbits* $\Longleftrightarrow$ the orbit of any periodic solution $\gamma(t)$ is asymptotically orbitally stable.

COMPOUND MATRICES

(J.S. Muldowney, 1990)

$A = n \times m$ matrix. Let $a_{i_1..i_k,j_1...j_k}$ determinant defined by the rows $(i_1, .., i_k)$ and the columns $(j_1, ..., j_k)$, $1 \leq i_1 < i_2 < \cdots < i_k \leq n$, $1 \leq j_1 < j_2 < \cdots < j_k \leq m$.

- The *kth multiplicative compound* $A^{(k)}$ of A is the $C_k^n \times C_k^m$ matrix whose entries in lexicographic order are $a_{i_1..i_k,j_1...j_k}$, where C_k^n denotes the number of combinations of n elements in groups of k elements.

- For $n \times k$ matrix with columns $a_1, a_2, .., a_n$

  $A^{(k)} = a_1 \wedge a_2 \wedge \cdots \wedge a_k.$

- If A is a $n \times n$ matrix the *kth additive compound* $A^{[k]}$ of A is the $C_k^n \times C_k^n$ matrix

$$A^{[k]} = \frac{d}{dh}(I + hA)^{(k)} \mid_{h=0}$$

- $A^{[1]} = A, \quad A^{[n]}$=Traza$(A)$.

For $A = (a_{ij})$ 3×3 matrix:

$$A^{[1]} = A,$$

$$A^{[2]} = \begin{pmatrix} a_{11} + a_{22} & a_{23} & -a_{13} \\ a_{32} & a_{11} + a_{33} & a_{12} \\ -a_{31} & a_{22} & a_{21} + a_{33} \end{pmatrix},$$

$$A^{[3]} = a_{11} + a_{22} + a_{33}.$$

- Criterion for asymptotic orbital stability of a periodic orbit γ:

  If the zero solution of

  $$\bar{X}(t) = (DF^{[2]}(\gamma(t)))\bar{X}(t)$$

  is asymptotically stable $\Rightarrow$ $\gamma(t)$ is asymptotically orbitally stable, where $DF^{[2]}$ is the second additive compound matrix of the derivative DF.

For system (10)

$\bar{X}(t) = (DF^{[2]}(\gamma(t)))\bar{X}(t)$ becomes

$$
\begin{aligned}
X' &= -(\mu_h + a_h b\beta_h i_v + \gamma_h + \mu_h)X + a_h b\beta_h s_h Y + a_h b\beta_h s_h Z \\
Y' &= a_v b\beta_v(1 - i_v)X - (\mu_h + a_h b\beta_h i_v + \mu_v + a_v b\beta_v i_h)Y \\
Z' &= a_h b\beta_h i_v Y - (\mu_v + a_v b\beta_v i_h + \gamma_h + \mu_h)Z
\end{aligned}
$$

$$a_h = \frac{A/\mu_v}{N_h + m},\ a_v = \frac{N_h}{N_h + m}$$

Lyapunov function:

$$V(X(t), Y(t), Z(t), s_h(t), i_h(t), i_v(t)) = \left|\left|((X(t), \frac{i_h(t)}{i_v(t)}Y(t), \frac{i_h(t)}{i_v(t)}Z(t)\right|\right|$$

$$||(X, Y, Z)|| = sup\{|X|, |Y| + |Z|\}$$

- $V(X(t), Y(t), Z(t), s_h(t), i_h(t), i_v(t)) \geq K||(X, Y, Z)||.$

Along solutions:

- $V(t) = sup\{|X(t), \frac{i_h(t)}{i_v(t)}(|Y(t)| + |Z(t)|)\}$

- $D_+V(t) \leq sup\{h_1(t), h_2(t)\}V(t)$

$$
\begin{aligned}
h_1(t) &= -(\mu_h + a_h b\beta - hi_v + \gamma_h + \mu_h) + a_h b\beta_h s_h \frac{i_v}{i_h}, \\
h_2(t) &= \frac{h}{i_v} a_v b\beta_v(1 - i_v) + \frac{i_h'}{i_h} - \frac{i_v'}{i_v} - \mu_h - \mu_v - a_v b\beta_v i_h
\end{aligned}
$$

$$
a_h b\beta_h s_h \frac{i_v}{i_h} = \frac{i_h'}{i_h} + \gamma_h + \mu_h \quad \text{and} \quad \frac{h}{i_v} a_v b\beta_v(1 - i_v) = \frac{i_v'}{i_v} + \mu_v
$$

$\Rightarrow$

- $D_+V(t) \leq \left(-\mu_h + \frac{i_h'}{i_h}\right) V(t)$

- $V(t) \leq V(0) i_h(t) e^{-\mu_h t} \leq V(0) e^{-\mu_h t} \longrightarrow 0$ as $t \to \infty$

- $(X(t), Y(t), Z(t)) \to 0$ as $t \to \infty \Rightarrow$ system (10) has the property of stability of periodic orbits.

- $\Rightarrow E_2$ is globally asymptotically stable for $\Omega - \{(s_h, 0, 0) : 0 \leq s_h \leq 1\}$.

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