Lecture 2: Heterogeneous Epidemic Models and a Graph-Theoretic Method for Constructing Lyapunov Functions

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Outline

Part I: Lyapunov Functions for Simple Epidemic Models

- Threshold Theorem for Models of Endemic Diseases
- Lyapunov functions for SIR and SEIR models with demography

Part II: Epidemic Models in Heterogeneous Populations

- SEIAR models for COVID-19
- Staged progression models for HIV
- Multi-group models
- Age-group models
- Multi-city models

Outline

Part III: Dynamical Systems on Networks

- A network is described by a digraph
- A simple model defined at each vertex (node)
- Different forms of interactions among vertex systems
- Examples

Part IV: Constructing Lyapunov Functions for Complex Models

- The graph-theoretic approach to the construction of Lyapunov functions
- An application to multi-group SEIR models
- An application to multi-patch predator-prey models

Threshold Theorem for Endemic Diseases

An endemic disease lasts a very long time (years), and the natural birth and death cannot be ignored.

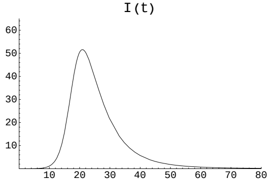
For illustration, we use an SIR model with birth and death to model an endemic disease

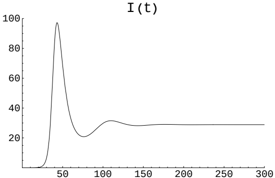
$$\begin{aligned} S' &= \Lambda - \beta IS - d_1 S \\ I' &= \beta IS - \gamma I - d_2 I \\ R' &= \gamma I - \ d_3 R \end{aligned}$$

initial conditions: $S(0) = S_0 > 0, I(0) = I_0 > 0,\ R(0) = R_0 = 0.$

$$\mathcal{R}_0 = \frac{\beta}{\gamma + d_2}\frac{\Lambda}{d_1} = \beta \cdot \frac{1}{\gamma + d_2} \cdot \frac{\Lambda}{d_1}.$$

Two possible disease outcomes:





Threshold Theorem for Endemic Diseases

Threshold Theorem

- If $\mathcal{R}_0 \leq 1$, then the disease-free equilibrium $P_0 = (\bar{S}, 0, 0)$ is globally asymptotically stable, and the disease always dies out irrespective of the initial number I_0.

- If $\mathcal{R}_0 > 1$, then P_0 becomes unstable and a unique endemic (positive) equilibrium $P^* = (S^*, I^*, R^*)$ comes to existence and is always globally asymptotically stable irrespective of the initial number I_0.

Here $\bar{S} = \frac{\Lambda}{d_1}, \quad I^* = 1 - \frac{1}{\mathcal{R}_0}$.

The Threshold Theorem can be illustrated by the bifurcation diagram:

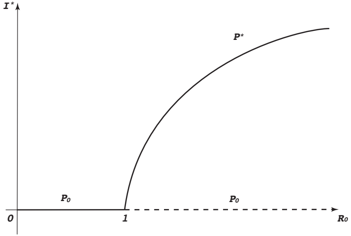


Figure: Bifurcation diagram for SIR model

- Local stability can be proved using linearization or local Lyapunov functions

- Global stability is commonly proved using global Lyapunov functions.

What is a Lyapunov Function for Global Stability

Consider a systems of ODE in $\mathbb{R}^n$

$$x' = f(x), \quad x \in D \subset \mathbb{R}^n,$$

and assume that $f(x)$ is C^1 for $x \in D$.
Let $x = 0 \in D$ is an equilibrium, $U \subset \mathbb{R}^n$ be a neighbourhood of 0, and $V : U \to \mathbb{R}$ is a C^1 real-valued function. The gradient vector of $V(x)$ is

$$\text{grad } V(x) = \left(\frac{\partial V}{\partial x_1}, \cdots, \frac{\partial V}{\partial x_n} \right).$$

The derivative of V in the direction of the vector field f is

$$\overset{*}{V}(x) = \text{grad } V(x) \cdot f(x).$$

$\overset{*}{V}(x)$ is also called the Lyapunov derivative of V.
Let $x(t)$ be a solution that stays in U, then

$$\frac{d}{dt} V(x(t)) = \text{grad } V(x(t)) \cdot x'(t) = \text{grad } V(x(t)) \cdot f(x(t)) = \overset{*}{V}(x(t))$$

If $\overset{*}{V}(x(t)) \leq 0$ for $t > 0$, then $V(x(t))$ decreases along a solution in a neighbourhood of $x = 0$.

Lyapunov Stability Theorem

Theorem 1 Suppose that a function $V(x)$ exists such that

(1) $V(x) \geq 0$ for $x \in U$ and $V(x) = 0$ if and only if $x = 0$; ($V(x)$ is positive definite at 0)

(2) $\overset{*}{V}(x) \leq 0$ for $x \in U$. ($\overset{*}{V}(x)$ is negative semi-definite at 0)

Then the equilibrium $x = 0$ is locally stable.

Theorem 2 Suppose that a function $V(x)$ exists such that

(1) $V(x) \geq 0$ for $x \in U$ and $V(x) = 0$ if and only if $x = 0$; ($V(x)$ is positive definite at 0 in U)

(2) $\overset{*}{V}(x) \leq 0$ for $x \in U$ and $\overset{*}{V}(x) = 0$ if and only if $x = 0$. ($\overset{*}{V}(x)$ is negative definite at 0 in U)

Then the equilibrium $x = 0$ is globally asymptotically stable in U.

A Lyapunov Function for a Simple SIR Model

Consider a SIR model:

$$S' = b - \beta IS - bS, \quad I' = \beta IS - \gamma I - bI, \quad R' = \gamma I - bR.$$

Since $(S + I + R)' = b(1 - S - I - R)$, the total population is constant and is equal to 1. For proof of GAS of the disease-free equilibrium $P_0 = (1, 0)$, we use A Lyapunov function (A. Korobeinikov, 2004)

$$V(S, I) = S - 1 - \log S + I,$$

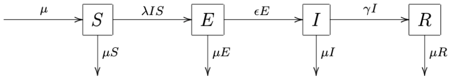
We can check that $V(S, I)$ is positive-definite at $P_0 = (1, 0)$ (Exercise)

$$\overset{*}{V}(S(t), I(t)) = S' - \frac{S'}{S} + I' = b - \beta IS - bS - \frac{1}{S}(b - \beta IS - bS) + \beta IS - \gamma I - bI$$
$$= b - \beta IS - bS - \frac{b}{S} + \beta I + b + \beta IS - \gamma I - bI$$
$$= 2b - bS - \frac{b}{S} = b\left(2 - S - \frac{1}{S}\right) \leq 0, \quad \text{for } (S, I) \in \Gamma.$$

and $\overset{*}{V}(S(t), I(t)) = 0$ only at P_0. Therefore, $\overset{*}{V}(S(t), I(t))$ is negative definite at P_0, and we proved global stability of P_0.

A Lyapunov Function for a Simple SEIR Model

Consider a SEIR model:



$$
\begin{aligned}
S' &= \mu - \lambda IS - \mu S \\
E' &= \lambda IS - (\epsilon + \mu)E \\
I' &= \epsilon E - (\gamma + \mu)I \\
R' &= \gamma I - \mu R.
\end{aligned}
\tag{1}
$$

Since $(S + E + I + R)' = b(1 - S - E - I - R)$, the total population is constant and is equal to 1. The model has two possible equilibria:

$$P_0 = (1, 0, 0, 0), \quad P^* = (S^*, E^*, I^*, R^*).$$

The basic reproduction number

$$\mathcal{R}_0 = \frac{\lambda\epsilon}{(\epsilon + b)(\gamma + b)} = \lambda \cdot \frac{\epsilon}{\epsilon + b} \cdot \frac{1}{\gamma + b}.$$

We can check that the global stability of P_0 when $\mathcal{R} \leq 1$ can be shown using the Lyapunov function (Exercise)

$$L(S, E, I) = S - 1 - \ln S + E + \frac{\epsilon + \mu}{\epsilon} I.$$

A Lyapunov Function for a Simple SEIR Model

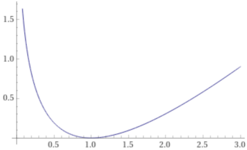
We only consider the SEI equations. R can be determined by $R = 1 - S - E - I$

We want to show that $P^* = (S^*, E^*, I^*)$ is globally asymptotically stable when $\mathcal{R}_0 > 1$ using a Lyapunov function

$$V(S,E,I) = (S - S^*) - S^* \log \frac{S}{S^*} + (E - E^*) - E^* \log \frac{E}{E^*} + \frac{\epsilon + \mu}{\epsilon}\Big((I - I^*) - I^* \log \frac{I}{I^*}\Big).$$

First check that $V(S,E,I)$ is positive-definite at P^*. Consider the function

$$f(x) = x - x^* - x^* \log \frac{x}{x^*}$$



We can show that $f(x)$ is positive definite at $x = x^*$ in $(0, \infty)$.

A Lyapunov Function for a Simple SEIR Model

Next we check $\overset{*}{V}(S, E, I)$ is negative definite at P^*.

$$\overset{*}{V} = S' - \frac{S^*}{S}S' + E' - \frac{E^*}{E}E' + \frac{\epsilon+\mu}{\epsilon}\Big(I' - \frac{I^*}{I}I'\Big)$$

$$= \mu - \mu S - \frac{S^*}{S}(\mu - \lambda IS - \mu S) - (\epsilon+\mu)E - \frac{E^*}{E}(\lambda S - (\epsilon+\mu)E)$$

$$+ \frac{\epsilon+\mu}{\epsilon}(\epsilon E - (\gamma+\mu)I) - \frac{\epsilon+\mu}{\epsilon}\frac{I^*}{I}(\epsilon E - (\gamma+\mu)I)$$

$$= \mu - \mu S - \mu\frac{S^*}{S} - \lambda IS^* + \mu S^* - \frac{\lambda ISE^*}{E} + (\epsilon+\mu)E^* - \frac{(\epsilon+\mu)(\gamma+\mu)}{\epsilon}I$$

$$-(\epsilon+\mu)\frac{EI}{I^*} + \frac{(\epsilon+\mu)(\gamma+\mu)}{\epsilon}I^*.$$

A Lyapunov Function for a Simple SEIR Model

While the expressions in $\overset{*}{V}$ seem complex, we can simplify them using the equilibrium relations satisfied by P^*:

$$\mu = \lambda I^* S^* + \mu S^*, \quad \lambda I^* S^* = (\epsilon + \mu) E^*, \quad \epsilon E^* = (\gamma + \mu) I^*. \tag{2}$$

Substituting into $\overset{*}{V}$, we obtain

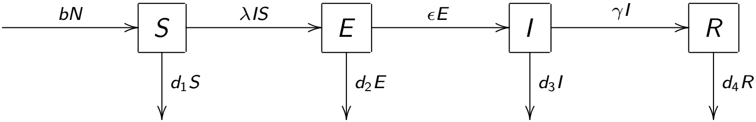
$$\begin{aligned} \overset{*}{V} &= \lambda I^* S^* + \mu S^* - \mu S - \frac{(\lambda I^* S^* + \mu S^*) S^*}{S} + \mu S^* + \lambda I^* S^* \frac{S}{S^*} \frac{E^*}{E} \frac{I}{I^*} \\ &\quad - (\epsilon + \mu) E^* \frac{E^*}{E} \frac{I}{I^*} + (\epsilon + \mu) E^* + \frac{(\epsilon + \mu)(\gamma + \mu)}{\epsilon} I^* \\ &= \mu S^* \left[2 - \frac{S}{S^*} - \frac{S^*}{S} \right] + \lambda I^* S^* \left[3 - \frac{S^*}{S} - \frac{S}{S^*} \frac{E^*}{E} \frac{I}{I^*} - \frac{E}{E^*} \frac{I^*}{I} \right] \\ &\leq 0, \quad \text{for all } (S, E, I) \text{ in the interior of } \Gamma. \end{aligned}$$

$$\overset{*}{V} = 0 \quad \Longrightarrow \quad 2 - \frac{S}{S^*} - \frac{S^*}{S}, \quad 3 - \frac{S^*}{S} - \frac{S}{S^*} \frac{E^*}{E} \frac{I}{I^*} - \frac{E}{E^*} \frac{I^*}{I} = 0$$

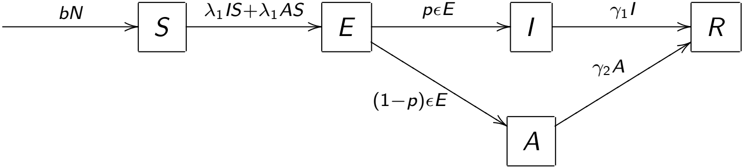
and $S = S^*, E = E^*, I = I^*$.

Part III: Some Examples of More Complex Epidemic Models

I. SEIR Models for diseases with latency:

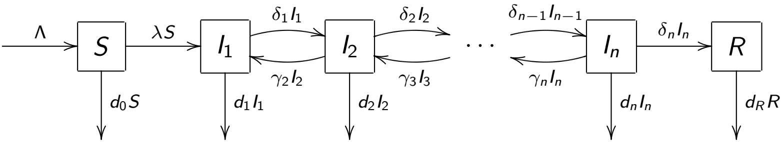


II. SEIAR Models for diseases with latency and asymptomatic state:

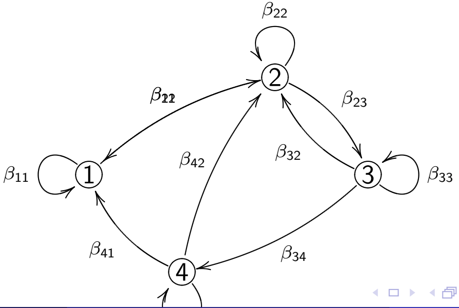


Part III: Some Examples of More Complex Epidemic Models

I. Stated Progression Models for diseases with long infectious period:

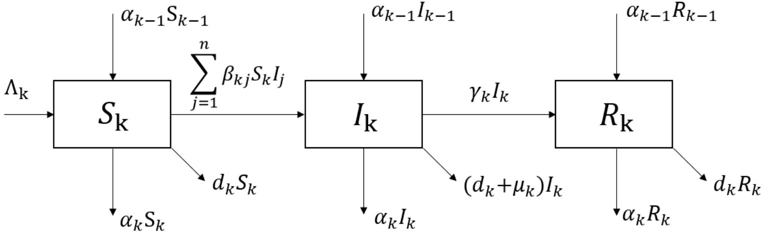


IV. Multi-group Models for diseases in heterogeneous population:



Some Examples of More Complex Epidemic Models

V. Age-Group Models Incorporating age-structure in diseases transmission: Divide the population into n discrete age groups: for each $1 \leq k \leq n$:



Some Examples of More Complex Epidemic Models

VI. Multi-City Models incorporating spatial movement in disease transmission. An example of such a model is:

$$S_i' = \Lambda_i - \beta_i S_i I_i - d_i^S S_i + \sum_{j=1}^{n} a_{ij} S_j - \sum_{j=1}^{n} a_{ji} S_i,$$

$$I_i' = \beta_i S_i I_i - (d_i^I + \gamma_i) I_i + \sum_{j=1}^{n} b_{ij} I_j - \sum_{j=1}^{n} b_{ji} I_i,$$

$$R_i' = \gamma_i I_i - d_i^R R_i + \sum_{j=1}^{n} c_{ij} R_j - \sum_{j=1}^{n} c_{ji} R_i,$$

$$i = 1, 2, \ldots, n.$$

Part III: Dynamical Systems on Networks

Dynamical Systems on Networks – A mathematical framework

- Topic I: Dynamical Systems on Networks
  - A network is described by a digraph
  - A simple model defined at each vertex (node)
  - Different forms of interactions among vertex systems
- Topic II: Global stability – constructing Lyapunov functions
  - Global stability of the disease-free equilibrium P_0.
  - Global stability of the endemic equilibrium P^*
- Topic III: The graph-theoretic method for constructing Lyapunov functions of large-scale models

A Mathematical Framework for Heterogenous Models

Common to both multi-group and multi-region models:

- They are both large-scale systems:
  - large number of variables: difficult to analyze
  - large number of parameters: difficult to identify from data
- The equations for each group or region inherit those of the simple model, together with interaction terms among groups or regions.
- If we remove the interactions among groups (cross-infections) or regions (movements) are removed, each group or region has a simple model, which is well-understood.
- The interactions can be coded on a directed graph.

Directed Graphs, Directed paths, Weight Matrix

- A directed graph (digraph) $\mathcal{G} = (V, E)$:
  - $V = \{1, 2, \ldots, n\}$ is the set of vertices
  - E is the set of arcs (i, j) from vertex i to vertex j.
- A digraph $\mathcal{G}$ is weighted if each arc (i, j) is assigned a weight $a_{ij} > 0$.
- When an arc (i, j) does not exist, we set the weight $a_{ij} = 0$.
- The weight matrix $A = (a_{ij})$ of $\mathcal{G}$ is nonnegative.
- Each nonnegative matrix $A \geq 0$ defines a digraph $\mathcal{G}(A)$.
- A digraph $\mathcal{G}$ is strongly connected if, for each pair of vertices $i \neq j$, there exists a directed path from i to j.
- A nonnegative matrix A is reducible if there exists permutation matrix P such that $P^T AP$ is block triangular.

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Directed Graphs, Directed paths, Weight Matrix

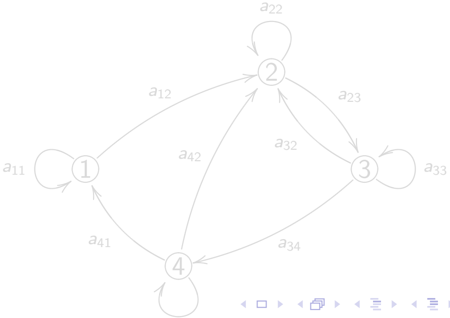
Theorem

Digraph $\mathcal{G}(A)$ is strongly connected $\iff$ matrix A is irreducible.

$$A = \begin{bmatrix} a_{11} & a_{12} & 0 & 0 \\ 0 & a_{22} & a_{23} & 0 \\ 0 & a_{32} & a_{33} & a_{34} \\ a_{41} & a_{42} & 0 & a_{44} \end{bmatrix}$$

Matrix A is irreducible

Digraph $\mathcal{G}(A)$ is strongly connected



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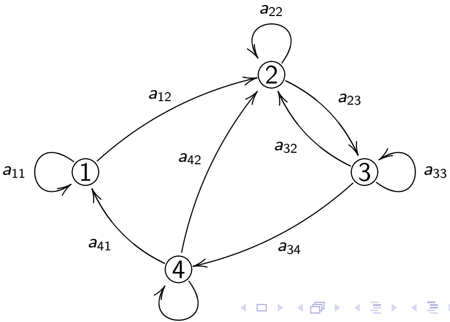

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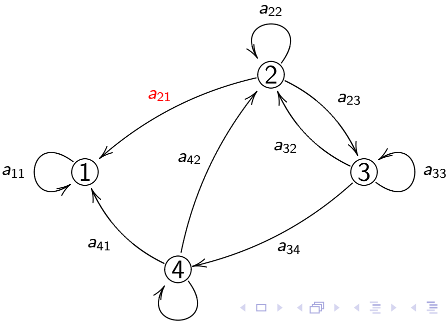
Theorem

Digraph $\mathcal{G}(A)$ is strongly connected $\iff$ matrix A is irreducible.

$$A = \begin{bmatrix} a_{11} & 0 & 0 & 0 \\ a_{21} & a_{22} & a_{23} & 0 \\ 0 & a_{32} & a_{33} & a_{34} \\ a_{41} & a_{42} & 0 & a_{44} \end{bmatrix}$$

Matrix A is reducible

Digraph $\mathcal{G}(A)$ is not strongly connected



Dynamical Systems on Networks

- $\mathcal{G}$: a digraph represents a network
- Dynamics at vertex i is described by an ODE

$$x_i' = f_i(x_i), \quad x_i \in \mathbb{R}^{n_i}, \quad f_i : \mathbb{R}^{n_i} \to \mathbb{R}^{n_i}.$$

- $g_{ij} : \mathbb{R}^{n_i} \times \mathbb{R}^{n_j} \to \mathbb{R}^{n_i}$ represent the influence of vertex j on i
- $g_{ij} \equiv 0$ if arc from j to i is absent.

A dynamical system on network $\mathcal{G}$ is

$$x_i' = f_i(x_i) + \sum_{j=1}^{n} g_{ij}(x_i, x_j), \qquad i = 1, 2, \dots, n.$$

- For multi-group model: $g_{ij}(S_i, I_i, S_j, I_j) = (-\beta_{ij} S_i I_j,\ \beta_{ij} S_i I_j)^T$.
- For multi-region model: $g_{ij}(S_{hi}, I_{hi}, S_{vi}, I_{vi}) = (0, m_{ji} I_{hj} - m_{ij} I_{hi}, 0, 0)^T$.

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Global Stability

Definition

An equilibrium $\bar{x}$ is globally stable in the feasible region Γ if

- $\bar{x}$ is locally stable; and
- All positive solutions in the feasible region converge to $\bar{x}$.

The second property is also called global attractivity.
Important: Global attractivity does not necessarily imply global stability!

Methods for proving global attractivity

- Constructing global Lyapunov functions
- Applying Monotone Dynamical System theory (Hirsch, see H. Smith's book)
- Applying Autonomous Convergence Theorems (R. A. Smith, Li-Muldowney)

For large-scale heterogeneous epidemic models, the most practical and effective method is constructing Lyapunov functions.

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Constructing Lyapunov Functions for Heterogenous Models

An Idea for the framework of dynamical systems on networks

- Each vertex system is well studied and often has a know Lyapunov function $V_i(x_i)$.
- Consider a Lyapunov function for the coupled system

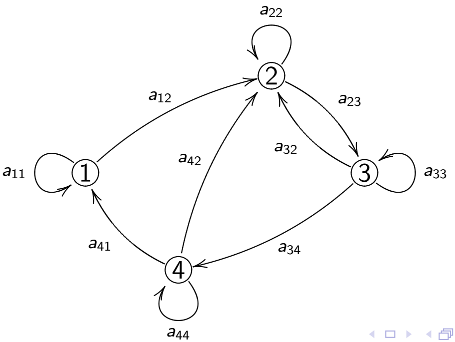
$$V(x) = \sum_{i=1}^{n} c_i V_i(x_i), \quad x = (x_1, x_2, \cdots, x_n).$$

- Key Question: how to choose suitable constants $c_i > 0$ such that V is a global Lyapunov function for the coupled system?

Rooted Spanning Trees and Unicyclic Graphs

Given a weighted digraph $\mathcal{G}$ with weight matrix $A = (a_{ij})_{n \times n}$.

- A directed tree is a connected subgraph containing no cycles, directed or undirected.
- A tree $\mathcal{T}$ is rooted at a vertex i if the remaining vertices of $\mathcal{T}$ are connected by directed paths from the root i.
- A tree $\mathcal{T}$ is spanning if it contains all vertices of $\mathcal{G}$.
- A subgraph $\mathcal{H}$ of $\mathcal{G}$ is unicyclic if it contains a unique directed cycle.



Laplacian Matrix and Matrix-Tree Theorem

The Laplacian matrix $L(A)$ of matrix A is

$$L(A) = \operatorname{diag}(d_1, \cdots, d_n) - A$$

where $d_i = \sum_{j=1}^{n} a_{ij}$, the i-th row sum of A.

$$L(A) = \begin{bmatrix} \sum_{k\neq 1} a_{1k} & -a_{12} & \cdots & -a_{1n} \\ -a_{21} & \sum_{k\neq 2} a_{2k} & \cdots & -a_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ -a_{n1} & -a_{n2} & \cdots & \sum_{k\neq n} a_{nk} \end{bmatrix}.$$

Kirchhoff's Matrix-Tree Theorem (1847)

Let C_{ii} be the co-factor of the i-th diagonal element of $L(A)$. Then

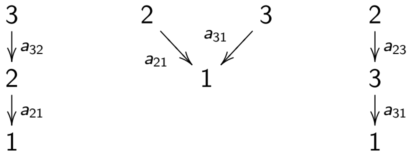
$$C_{ii} = \sum_{\mathcal{T}\in\mathbb{T}_i} w(\mathcal{T}), \quad i = 1, 2, \cdots, n.$$

An Example: $n = 3$

Matrix-Tree Theorem

$$C_{11} = \sum_{T \in \mathbb{T}_1} w(T) = a_{32}a_{21} + a_{21}a_{31} + a_{23}a_{31}$$

All possible spanning trees rooted at vertex 1:



Reordering of a Double Sum: Tree-Cycle Identity

Tree Cycle Identity (Shuai and Li)

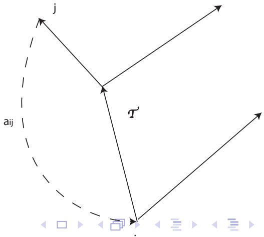
Let $c_i = C_{ii}$ be given by the Matrix-Tree Theorem. Then the following identity holds.

$$\sum_{i,j=1}^{n} c_i \, a_{ij} \, F_{ij}(x) = \sum_{\mathcal{Q} \in \mathbb{Q}} w(\mathcal{Q}) \sum_{(r,s) \in E(\mathcal{C}_{\mathcal{Q}})} F_{rs}(x),$$

where $F_{ij}(x), 1 \leq i, j \leq n$, are arbitrary functions, $\mathbb{Q}$ is the set of all spanning unicyclic graphs $\mathcal{Q}$ of $\mathcal{G}(A)$, $w(\mathcal{Q})$ is the weight of $\mathcal{Q}$, and $\mathcal{C}_{\mathcal{Q}}$ denotes the oriented cycle of $\mathcal{Q}$.

Proof: Note $w(\mathcal{T})\, a_{ij} = w(\mathcal{Q})$,

where $\mathcal{Q}$ is the unicyclic graph obtained by adding an arc (j, i) to $\mathcal{T}$.



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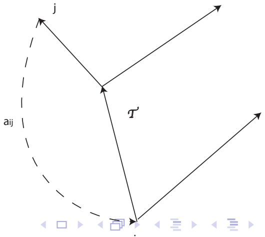

A Graph-Theoretic Approach to Lyapunov Functions

Theorem (Shuai and Li)

Assume

(1) *There exists a family* $\{F_{ij}(x)\}$ *such that*

$$\overset{\bullet}{V}_i(x_i) \le \sum_{j=1}^{n} a_{ij} F_{ij}(x), \quad x \in D = D_1 \times \cdots \times D_n, \quad i = 1, \cdots, n.$$

(2) *Along each directed cycle* $\mathcal{C}$ *of* $\mathcal{G}$,

$$\sum_{(r,s)\in E(\mathcal{C})} F_{rs}(x) \le 0, \quad t > 0,\ x \in D. \quad (\text{Cycle Conditions})$$

Then there exist constants $c_i \ge 0$ *such that* $V(x) = \sum_{i=1}^{n} c_i V_i(x)$ *satisfies*

$$\overset{\bullet}{V}(x) \le 0, \quad x \in D.$$

Proof of Theorem

Let $c_i = C_{ii}$ be given in the Matrix-Tree Theorem. The $A = (a_{ij})$ strongly connected implies $c_i > 0$ for all i.

$$\begin{aligned}\dot{V} &= \sum_{i=1}^{n} c_i \dot{V}_i \le \sum_{i,j=1}^{n} c_i a_{ij} F_{ij}(t,u) \quad \text{(Assumption (1))} \\ &= \sum_{\mathcal{Q} \in \mathbb{Q}} w(\mathcal{Q}) \sum_{(r,s) \in E(\mathcal{C}_{\mathcal{Q}})} F_{rs}(t,u) \quad \text{(Tree-Cycle Identity)} \\ &\le 0. \quad \text{(Cycle Conditions)}\end{aligned}$$

Our Theorem offers a systematic approach to the construction of global Lyapunov functions for the coupled system, using individual Lyapunov functions for the vertex systems.

Is the theorem any good?

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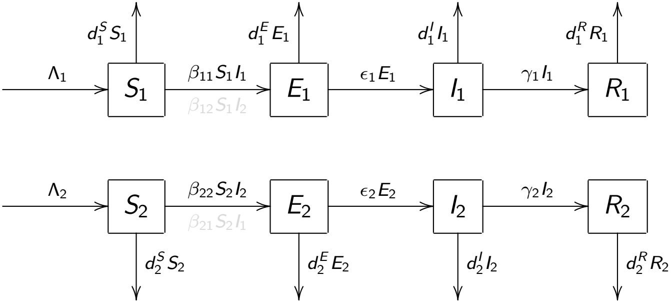
An Application to Multi-Group SEIR Models

A 2-group SEIR model:



Incidence terms:

- Group 1: $\beta_{11} S_1 I_1 + \beta_{12} S_1 I_2$
- Group 2: $\beta_{21} S_2 I_1 + \beta_{22} S_2 I_2$

β_{ij} : transmission coefficient between S_i and I_j

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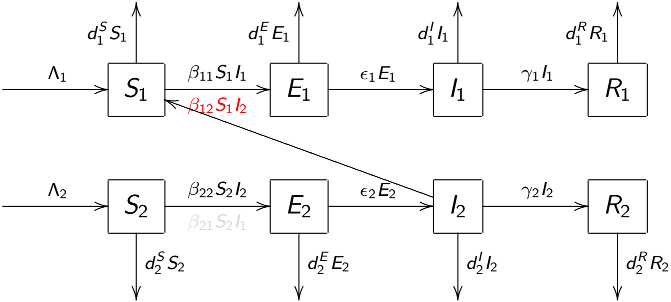

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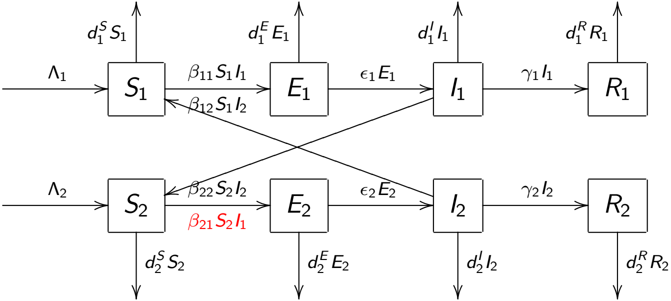

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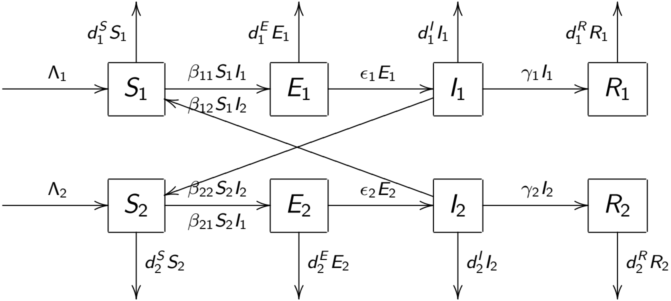

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An n-Group SEIR Model

$$\begin{cases} S_k' = \Lambda_k - d_k^S S_k - \sum_{j=1}^{n} \beta_{kj} S_k I_j \\ E_k' = \sum_{j=1}^{n} \beta_{kj} S_k I_j - (d_k^E + \epsilon_k) E_k \\ I_k' = \epsilon_k E_k - (d_k^I + \gamma_k) I_k \end{cases} \qquad k = 1, \cdots, n$$

Feasible region:

$$\Gamma = \Big\{ (S_1, E_1, I_1, \cdots, S_n, E_n, I_n) \in \mathbb{R}_+^{3n} \quad | \quad S_k \leq \frac{\Lambda_k}{d_k^S}, \\ S_k + E_k + I_k \leq \frac{\Lambda_k}{d_k^*}, \ k = 1, 2, \cdots, n \Big\}$$

An n-Group SEIR Model

Equilibria:

$$P_0 = (S_1^0, 0, 0, \cdots, S_n^0, 0, 0), \quad S_k^0 = \frac{\Lambda_k}{d_k^S}, \quad 1 \leq k \leq n$$

$$P^* = (S_1^*, E_1^*, I_1^*, \cdots, S_n^*, E_n^*, I_n^*) \in \mathring{\Gamma}$$

Basic reproduction number (using the van den Driessche-Watmough method)

$$R_0 = \rho(B) = \rho \begin{bmatrix} \frac{\beta_{11}\epsilon_1 S_1^0}{(d_1^E+\epsilon_1)(d_1^I+\gamma_1)} & \cdots & \frac{\beta_{1n}\epsilon_n S_1^0}{(d_n^E+\epsilon_n)(d_n^I+\gamma_n)} \\ \vdots & \ddots & \vdots \\ \frac{\beta_{n1}\epsilon_1 S_n^0}{(d_1^E+\epsilon_1)(d_1^I+\gamma_1)} & \cdots & \frac{\beta_{nn}\epsilon_n S_n^0}{(d_n^E+\epsilon_n)(d_n^I+\gamma_n)} \end{bmatrix},$$

$\rho(A)$ is the spectral radius of A.

An n-Group SEIR Model

Threshold Theorem (Guo, Li, Shuai, 2006) Assume that B is irreducible.

- If $\mathcal{R}_0 \leq 1$, then P_0 is the unique equilibrium in $\mathbb{R}^{3n}_+$ and is globally asymptotically stable in $\bar{\Gamma}$.
- If $R_0 > 1$, then P_0 is unstable. A unique endemic equilibrium P^* exists and is GAS in $\overset{\circ}{\Gamma}$.

Strategies of the proof:

- Prove GAS of any P^* by a Lyapunov function
- GAS $\Longrightarrow$ uniqueness

Lyapunov Functions for the GAS of P^*

Consider the class of Lyapunov functions:

$$V = \sum_{k=1}^{n} v_k \Big[(S_k - S_k^* \ln S_k) + (E_k - E_k^* \ln E_k) + \frac{d_k^E + \epsilon_k}{\epsilon_k} (I_k - I_k^* \ln I_k) \Big]$$

Challenges in the proof:

- Choose a suitable set of $v_k > 0$.
- Show $\frac{dV}{dt} \leq 0$ in $\overset{\circ}{\Gamma}$ (with the help of graph theory)

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Derivative of V

$$V' =$$

$$\sum_{k=1}^{n} v_k \Big[(S_k' - \frac{S_k^*}{S_k} S_k') + (E_k' - \frac{E_k^*}{E_k} E_k') + \frac{d_k^E + \epsilon_k}{\epsilon_k} (I_k' - \frac{I_k^*}{I_k} I_k') \Big]$$

$$= \sum_{k=1}^{n} v_k \Big[d_k^S S_k^* \Big(2 - \frac{S_k^*}{S_k} - \frac{S_k}{S_k^*} \Big) \Big]$$

$$+ \sum_{k=1}^{n} v_k \Big[\sum_{j=1}^{n} \beta_{kj} S_k^* I_j - \frac{(d_k^E + \epsilon_k)(d_k^I + \alpha_k + \gamma_k)}{\epsilon_k} I_k \Big]$$

$$+ \sum_{j,k=1}^{n} v_k \, \beta_{kj} S_k^* I_j^* \Big(3 - \frac{S_k^*}{S_k} - \frac{S_k}{S_k^*} \frac{I_j}{I_j^*} \frac{E_k^*}{E_k} - \frac{I_k^*}{I_k} \frac{E_k}{E_k^*} \Big)$$

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&= \sum_{k=1}^{n} v_k \Big[d_k^S S_k^* \Big(2 - \frac{S_k^*}{S_k} - \frac{S_k}{S_k^*} \Big) \Big] \\
&+ \sum_{k=1}^{n} v_k \Big[\sum_{j=1}^{n} \beta_{kj} S_k^* I_j - \frac{(d_k^E + \epsilon_k)(d_k^I + \alpha_k + \gamma_k)}{\epsilon_k} I_k \Big] \\
&+ \sum_{j,k=1}^{n} v_k \, \beta_{kj} S_k^* I_j^* \Big(3 - \frac{S_k^*}{S_k} - \frac{S_k}{S_k^*} \frac{I_j}{I_j^*} \frac{E_k^*}{E_k} - \frac{I_k^*}{I_k} \frac{E_k}{E_k^*} \Big)
\end{aligned}
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$$H_n := \sum_{j,k=1}^{n} v_k \, \bar{\beta}_{kj} \Big(3 - \frac{S_k^*}{S_k} - \frac{S_k}{S_k^*} \frac{I_j}{I_j^*} \frac{E_k^*}{E_k} - \frac{I_k^*}{I_k} \frac{E_k}{E_k^*} \Big)$$

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Choose v_k so that

$$\sum_{k=1}^{n} v_k \Big[\sum_{j=1}^{n} \beta_{kj} S_k^* I_j - \frac{(d_k^E + \epsilon_k)(d_k^I + \alpha_k + \gamma_k)}{\epsilon_k} I_k \Big] \equiv 0$$

for all $I_1, \cdots, I_n > 0$. This is equivalent to

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since, at P^*,

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Choosing Constants v_k

Choose v_k so that

$$\sum_{k=1}^{n} v_k \Big[\sum_{j=1}^{n} \beta_{kj} S_k^* I_j - \frac{(d_k^E + \epsilon_k)(d_k^I + \alpha_k + \gamma_k)}{\epsilon_k} I_k \Big] \equiv 0$$

for all $I_1, \cdots, I_n > 0$. This is equivalent to

$$\begin{bmatrix} \beta_{11} S_1^* I_1^* & \cdots & \beta_{n1} S_n^* I_1^* \\ \vdots & \ddots & \vdots \\ \beta_{1n} S_1^* I_n^* & \cdots & \beta_{nn} S_n^* I_n^* \end{bmatrix} \begin{bmatrix} v_1 \\ \vdots \\ v_n \end{bmatrix} = \begin{bmatrix} \sum_{j=1}^{n} \beta_{1j} S_1^* I_j^* v_1 \\ \vdots \\ \sum_{j=1}^{n} \beta_{nj} S_n^* I_j^* v_n \end{bmatrix}$$

since, at P^*,

$$\frac{(d_k^E + \epsilon_k)(d_k^I + \alpha_k + \gamma_k)}{\epsilon_k} = \sum_{j=1}^{n} \beta_{kj} S_k^* I_j^* .$$

Choosing Constants v_k ...

Set $\bar{\beta}_{kj} = \beta_{kj} S_k^* I_j^*$, and

$$\overline{B} = \begin{bmatrix} \sum_{l\neq 1} \bar{\beta}_{1l} & -\bar{\beta}_{21} & \cdots & -\bar{\beta}_{n1} \\ -\bar{\beta}_{12} & \sum_{l\neq 2} \bar{\beta}_{2l} & \cdots & -\bar{\beta}_{n2} \\ \vdots & \vdots & \ddots & \vdots \\ -\bar{\beta}_{1n} & -\bar{\beta}_{2n} & \cdots & \sum_{l\neq n} \bar{\beta}_{nl} \end{bmatrix}$$

Then $v = (v_1, \ldots, v_k)^T$ satisfies linear system

$$\overline{B}\, v = 0.$$

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Each column sum of $\overline{B}$ is 0. $\Rightarrow$ Solutions exist. .

Choosing Constants v_k . . .

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Matrix $\overline{B}$ is the Laplacian Matrix of $(\bar{\beta}_{ij})$.

Proving $H_n \leq 0$

Recall

$$H_n = \sum_{j,k=1}^{n} v_k \, \bar{\beta}_{kj} \Big(3 - \frac{S_k^*}{S_k} - \frac{S_k}{S_k^*} \frac{I_j}{I_j^*} \frac{E_k^*}{E_k} - \frac{I_k^*}{I_k} \frac{E_k}{E_k^*} \Big)$$

and

$$v_k = \sum_{T \in \mathbb{T}_k} \prod_{(j,h) \in E(T)} \bar{\beta}_{jh}$$

Using the Tree Cycle Identity, terms in H_n are naturally grouped based on unicyclic cycles!

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Re-Grouping the Terms in H_n According to Unicyclic Cycles

$$H_n = \sum_{j,k=1}^{n} v_k\, \bar{\beta}_{kj} \Big(3 - \frac{S_k^*}{S_k} - \frac{S_k}{S_k^*}\frac{I_j}{I_j^*}\frac{E_k^*}{E_k} - \frac{I_k^*}{I_k}\frac{E_k}{E_k^*} \Big)$$

$$= \sum_{Q} w(Q) \sum_{(p,q)\in E(CQ)} \left[3 - \frac{S_p^*}{S_p} - \frac{S_p I_q E_p^*}{S_p^* I_q^* E_p} - \frac{E_p I_p^*}{E_p^* I_p} \right]$$

$$= \sum_{Q} w(Q) \cdot \Big[3r - \sum_{(p,q)\in E(CQ)} \Big(\frac{S_p^*}{S_p} + \frac{S_p I_q E_p^*}{S_p^* I_q^* E_p} + \frac{E_p I_p^*}{E_p^* I_p} \Big) \Big]$$

Finally, because CQ is a cycle,

$$\prod_{(p,q)\in E(CQ)} \frac{S_p^*}{S_p} \cdot \frac{S_p I_q E_p^*}{S_p^* I_q^* E_p} \cdot \frac{E_p I_p^*}{E_p^* I_p} = \prod_{(p,q)\in E(CQ)} \frac{I_q I_p^*}{I_q^* I_p} = 1.$$

Re-Grouping the Terms in H_n According to Unicyclic Cycles

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\begin{aligned}
H_n &= \sum_{j,k=1}^{n} v_k \, \bar{\beta}_{kj} \Big(3 - \frac{S_k^*}{S_k} - \frac{S_k}{S_k^*} \frac{I_j}{I_j^*} \frac{E_k^*}{E_k} - \frac{I_k^*}{I_k} \frac{E_k}{E_k^*} \Big) \\
&= \sum_{Q} w(Q) \sum_{(p,q)\in E(CQ)} \Big[3 - \frac{S_p^*}{S_p} - \frac{S_p I_q E_p^*}{S_p^* I_q^* E_p} - \frac{E_p I_p^*}{E_p^* I_p} \Big] \\
&= \sum_{Q} w(Q) \cdot \Big[3r - \sum_{(p,q)\in E(CQ)} \Big(\frac{S_p^*}{S_p} + \frac{S_p I_q E_p^*}{S_p^* I_q^* E_p} + \frac{E_p I_p^*}{E_p^* I_p} \Big) \Big]
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\end{aligned}
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Further Applications

The graph-theoretic approach was used to prove global stability problems for:

- Network of coupled oscillators
- Multi-patch models of single species
- Multi-patch models of predator-prey models
- Multi-patch SIR models
- Multi-stage models for HIV infection
- Multi-group epidemic models with time delays

Application II: An *n*-Patch Predator-Prey Model

$$\begin{aligned} x_i' &= x_i(r_i - b_i x_i - e_i y_i) + \sum_{j=1}^{n} d_{ij}(x_j - \alpha_{ij} x_i), \\ y_i' &= y_i(-\gamma_i - \delta_i y_i + \epsilon_i x_i), \end{aligned} \qquad i = 1, 2, \ldots, n. \tag{3}$$

Theorem [Z. Shuai and ML (2009)] Assume that (d_{ij}) is irreducible, and that $\exists\ k$ such that $b_k \delta_k > 0$. Then the positive equilibrium E^*, whenever it exists, is unique and globally asymptotically stable in $\mathbb{R}^{2n}_{+}$.

Kuang and Tacheuchi (1994) proved the two-patch case.

$$V_i(x_i, y_i) = \epsilon_i(x_i - x_i^* \ln x_i) + e_i(y_i - y_i^* \ln y_i)$$

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Application III: A Multi-group Delayed Epidemic Model

$$\begin{aligned} S_i' &= \Lambda_i - d_i^S S_i - \sum_{j=1}^{n} \beta_{ij} S_i I_j(t-\tau_j), \\ I_i' &= \sum_{j=1}^{n} \beta_{ij} S_i I_j(t-\tau_j) - (d_i^I + \gamma_i) I_i, \end{aligned} \qquad i = 1, 2, \cdots, n. \tag{4}$$

Theorem [Z. Shuai and ML (2009)] Assume that $B = (\beta_{ij})$ is irreducible. If $R_0 > 1$, then the unique endemic equilibrium P^* for system (4) is globally asymptotically stable in the feasible region $\overset{\circ}{\Theta}$.

When $n = 1$, C. McCluskey proved the global stability with Lyapunov function

$$V_i = (S_i - S_i^* + S_i^* \ln \frac{S_i}{S_i^*}) + (I_i - I_i^* - I_i^* \ln \frac{I_i}{I_i^*}) + \sum_{j=1}^{n} \beta_{ji} S_i^* \int_0^{\tau_j} \left(I_j(t-r) - I_j^* - I_j^* \ln \frac{I_j(t-r)}{I_j^*} \right) dr.$$

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