Using Asymptotics for Stability Determination for Systems of ODEs in Epidemiology

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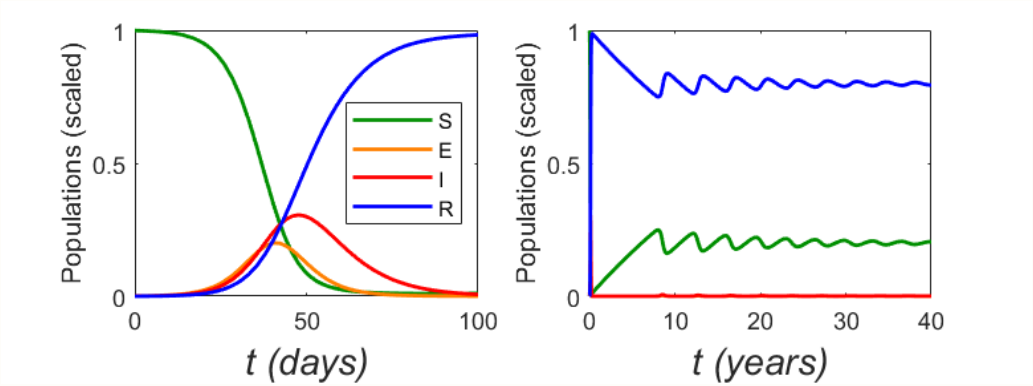
Overview

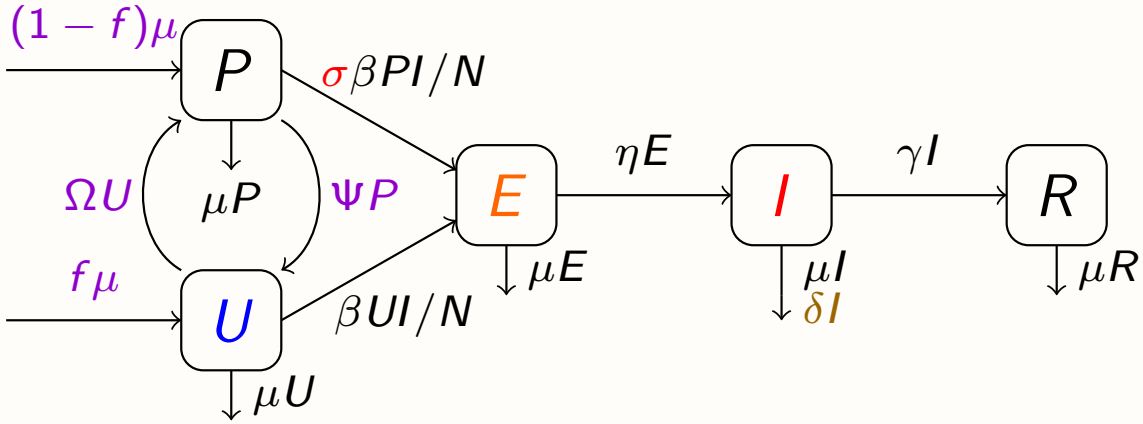
- I will present and analyze a mathematical model I created as a simple setting for a disease with two risk groups.
  - The model is an endemic SEIR model with disease-induced mortality.
- I will showcase my general method for efficient analysis of medium size dynamical systems (4–6 components).
  1. Characteristic polynomial coefficients are calculated more efficiently than the usual $P(\lambda) = \det(J - \lambda I)$.
  2. The Routh-Hurwitz conditions are constructed from a Routh array for each specific problem.
  3. Asymptotic approximations greatly simplify the calculations with minimal effect on stability results.

Two Time Scales in Disease Models



- **The fast time scale (days) shows the epidemic phase.**
  - Infectious population fractions are significant.
  - Plots on the fast time scale show no clue to endemic behavior.
  - Demographic changes (birth, natural death, etc) are negligible.
- **The slow time scale (years) shows the long-term behavior.**
  - Infectious populations are very small.
  - On the slow scale, the epidemic behavior appears at $t = 0$.
  - Both demographics and disease processes are important.

A Disease with Two Risk Groups



$$S = P + U, \qquad N = S + E + I + R \leq 1, \qquad \sigma < 1$$

- "Protected" individuals (P) are less susceptible than "Unprotected" individuals (U).
- Susceptible individuals can change risk categories.
- The variables are E, I, S, U, N.
  - Disease mortality makes N variable.

Model Equations

$$\begin{aligned}
\frac{dE}{dT} &= -(\eta+\mu)I + \beta Q\frac{I}{N},\\
\frac{dI}{dT} &= \eta E - (\gamma+\delta+\mu)I,\\
\frac{dS}{dT} &= \mu(1-S) - \beta Q\frac{I}{N},\\
\frac{dU}{dT} &= f\mu + \Psi(S-U) - (\Omega+\mu)U - \beta U\frac{I}{N},\\
\frac{dN}{dT} &= \mu(1-N) - \delta I,
\end{aligned} \tag{1}$$

with

$$Q = (1-\sigma)U + \sigma S. \tag{2}$$

- Parameters and Scaling:

$$\epsilon = \frac{\mu}{\gamma+\mu} \ll 1, \quad b = \frac{\beta}{\gamma+\delta+\mu} > 1, \quad m = \frac{\delta}{\gamma+\delta+\mu},$$
$$\rho = \frac{\eta}{\gamma+\delta+\mu}, \quad \psi = \frac{\Psi}{\mu}, \quad \omega = \frac{\Omega}{\mu}, \quad \frac{d}{dT} = \mu\frac{d}{dt}.$$

  - b is the basic reproduction number for the high risk group.

Rescaling Infectious Populations

$$
\begin{aligned}
\epsilon E' &= -(\rho+\epsilon)I + bQ\tfrac{I}{N},\\
\epsilon I' &= \rho E - I,\\
S' &= 1 - S - \epsilon^{-1} bQ\tfrac{I}{N},\\
U' &= f + \psi S - (\psi+\omega+1)U - \epsilon^{-1} bU\tfrac{I}{N},\\
N' &= 1 - N - \epsilon^{-1} mI,\\
Q &= (1-\sigma)U + \sigma S.
\end{aligned}
\tag{3}
$$

- Long-term behavior with $\epsilon \to 0$ should make sense.
  - Here, $\epsilon \to 0$ reduces the N equilibrium equation to

$$I = O(\epsilon) \qquad \Rightarrow\!\!\!\!\!\!\not\Leftarrow .$$

  - E and I should be rescaled with $E = \epsilon X$ and $I = \epsilon Y$.

Rescaled Model

$$
\begin{aligned}
\epsilon X' &= -(\rho + \epsilon)X + bQ\tfrac{Y}{N}, \\
\epsilon Y' &= \rho X - Y, \\
S' &= 1 - S - bQ\tfrac{Y}{N}, \\
U' &= f + \psi S - (\psi + \omega + 1)U - bU\tfrac{Y}{N}, \\
N' &= 1 - N - mY, \\
Q &= (1 - \sigma)U + \sigma S.
\end{aligned}
\tag{4}
$$

- Factors of ϵ on the left side of an equation signify a fast variable. These factors are used for asymptotic approximation.
- Terms of $O(\epsilon)$ on the right side of an equation signify a small perturbation. These terms can *usually* be neglected.

Endemic Equilibria

- The equations for endemic disease equilibria eventually reduce to a single quadratic equation for Y.
- Other authors have found that the system can have a backward bifurcation, with two endemic disease equilibria, but we can show this is possible only if $m > 0.75$.
  - A mortality fraction greater than 0.75 would require a different set of model assumptions.
- Our principal analytical task is to show that the endemic disease equilibrium for the standard case $m < 0.75$ is always stable.

The Jacobian

The Jacobian for the XYSUN system is

$$J = \begin{pmatrix} -(\rho\Gamma + 1) & \Gamma & \kappa y\Gamma & hy\Gamma & -y\Gamma \\ \rho\Gamma & -\Gamma & 0 & 0 & 0 \\ 0 & -1 & -\overline{\kappa y} & -hy & y \\ 0 & -bu & \psi & -\bar{w} & buy \\ 0 & -m & 0 & 0 & -1 \end{pmatrix}, \qquad (5)$$

where

$$\Gamma = \epsilon^{-1}, \qquad y = \frac{Y}{N}, \qquad w = \psi + \omega + z, \qquad \bar{x} = x + 1 \ \ (\forall x).$$

- Tip: Better to have extra symbols than messier formulas!

The Stability Problem

$$J = \begin{pmatrix} -(\rho\Gamma + 1) & \Gamma & \kappa y\Gamma & hy\Gamma & -y\Gamma \\ \rho\Gamma & -\Gamma & 0 & 0 & 0 \\ 0 & -1 & -\overline{\kappa y} & -hy & y \\ 0 & -bu & \psi & -\bar{w} & buy \\ 0 & -m & 0 & 0 & -1 \end{pmatrix}$$

- There is no decoupling. ☹
- How do we manage a 5×5 characteristic polynomial?
  - The characteristic polynomial theorem! ☺
    - With asymptotics! ☺

The Characteristic Polynomial Theorem

Theorem

For an $n \times n$ matrix J, let I be any nonempty subset of the set of integers $1, 2, \ldots, n$. For each possible I, let J_I be the determinant of the submatrix of J that contains the entries in the rows and columns indicated by the index set I. Then the characteristic polynomial of J is

$$P(\lambda) = \lambda^n + c_1\lambda^{n-1} + c_2\lambda^{n-2} + \cdots + c_{n-1}\lambda + c_n, \qquad (6)$$

where

$$c_m = (-1)^m \sum_{|I|=m} J_I, \qquad c_n = (-1)^n |J|. \qquad (7)$$

The Characteristic Polynomial for the EDE

$$J = \begin{pmatrix} -(\rho\Gamma + 1) & \Gamma & \kappa y\Gamma & hy\Gamma & -y\Gamma \\ \rho\Gamma & -\Gamma & 0 & 0 & 0 \\ 0 & -1 & -\overline{\kappa y} & -hy & y \\ 0 & -bu & \psi & -\bar{w} & buy \\ 0 & -m & 0 & 0 & -1 \end{pmatrix}$$

- Details for c_3: Of the 10 3×3 subdeterminants, only the three of form J_{12j} are $O(\Gamma^2)$. Each is of the form

$$(-1)^3 J_{12j} = F(D, E) = -\begin{vmatrix} -\rho\Gamma & \Gamma & D\Gamma \\ \rho\Gamma & -\Gamma & 0 \\ 0 & -E & -F \end{vmatrix} = \rho DE\Gamma^2,$$

$$c_3 \sim \rho(D \cdot E)\Gamma^2 = \rho y[\kappa + bhu - m]\Gamma^2 \equiv k_3\Gamma^2$$

The Characteristic Polynomial for the EDE

- The characteristic polynomial is

$$P(\lambda) = \lambda^5 + c_1\lambda^4 + c_2\lambda^3 + c_3\lambda^2 + c_4\lambda + c_5$$

- Retaining only the largest terms in each coefficient yields the form

$$P(\lambda) = \lambda^5 + k_1\Gamma\lambda^4 + k_2\Gamma\lambda^3 + k_3\Gamma^2\lambda^2 + k_4\Gamma^2\lambda + k_5\Gamma^2$$

- How do we find Routh-Hurwitz conditions for a degree 5 characteristic polynomial?
  - The Routh array!  With asymptotics!  

The Routh Array, Step 1

$$P(\lambda) = \lambda^5 + k_1\Gamma\lambda^4 + k_2\Gamma\lambda^3 + k_3\Gamma^2\lambda^2 + k_4\Gamma^2\lambda + k_5\Gamma^2$$

1. We begin the Routh array by writing the coefficients of the characteristic polynomial in two rows.
   - The coefficients with even subscripts (including $k_0 = 1$) go in the top row.
   - The odd coefficients go in the second row.

$$\begin{array}{ccc} 1 & k_2\Gamma & k_4\Gamma^2 \\ k_1\Gamma & k_3\Gamma^2 & k_5\Gamma^2 \end{array}$$

The Routh Array, Step 2

$$\begin{array}{lll} 1 & k_2\Gamma & k_4\Gamma^2 \\ k_1\Gamma & k_3\Gamma^2 & k_5\Gamma^2 \end{array}$$

2. The 3-1 element is the red product minus the violet product, divided by the 2-1 element.

$$\frac{k_1k_2\Gamma^2 - k_3\Gamma^2}{k_1\Gamma} = \frac{\Gamma}{k_1}(k_1k_2 - k_3),$$

so the array is now

$$\begin{array}{lll} 1 & k_2\Gamma & k_4\Gamma^2 \\ k_1\Gamma & k_3\Gamma^2 & k_5\Gamma^2 \\ q_1\frac{\Gamma}{k_1} & & \end{array}, \qquad q_1 = k_1k_2 - k_3$$

The Routh Array, Step 3

$$\begin{array}{lll} 1 & k_2\Gamma & k_4\Gamma^2 \\ k_1\Gamma & k_3\Gamma^2 & k_5\Gamma^2 \\ q_1\frac{\Gamma}{k_1} & & \end{array}$$

3. The 3-2 element is the red product minus the blue product, divided by the 2-1 element.

$$\frac{(k_1\Gamma)(k_4\Gamma^2)-(1)(k_5\Gamma^2)}{k_1\Gamma} = k_4\Gamma^2 + O(\Gamma);$$

the array is now [to leading order]

$$\begin{array}{lll} 1 & k_2\Gamma & k_4\Gamma^2 \\ k_1\Gamma & k_3\Gamma^2 & k_5\Gamma^2 \\ q_1\frac{\Gamma}{k_1} & k_4\Gamma^2 & \end{array}$$

The Routh Array, Step 4

4. All subsequent rows follow the same pattern, with blank entries treated as 0.

.

$$
\begin{array}{ll}
1 & k_2\Gamma \quad k_4\Gamma^2 \\
k_1\Gamma & k_3\Gamma^2 \quad k_5\Gamma^2 \\
\frac{q_1}{k_1}\Gamma & k_4\Gamma^2 \\
\frac{q_2}{q_1}\Gamma^2 & k_5\Gamma^2 \\
k_4\Gamma^2 & \\
k_5\Gamma^2 &
\end{array}
$$

where

$$q_1 = k_1k_2 - k_3, \qquad q_2 = k_3q_1 - k_1^2k_4.$$

The Routh Theorem

Theorem (Routh)

The critical point with characteristic polynomial $P(\lambda)$ is locally asymptotically stable if and only if the column 1 entries of the Routh array are all positive.

In our example, we need $k_1, k_4, k_5, q_1, q_2 > 0$. We have

- $k_1 > 0$.
- $k_3 > 0$ and $q_2 > 0$ guarantee $q_1 > 0$.
  - We can replace $q_1 > 0$ with $k_3 > 0$.
- $k_3 > 0$ and $k_5 > 0$ guarantee $k_4 > 0$.
- This leaves three non-trivial conditions:

$$k_3 > 0, \quad k_5 > 0, \quad q_2 > 0$$

Principal Result and Conclusions

- A mortality fraction less than 0.75 is sufficient for EDE stability.
- One of our RH conditions is $k_4 > 0$.
  - Without asymptotics ☹ , the corresponding condition is

$$c_1c_2c_3c_4 + c_2c_3c_5 + 2c_1c_4c_5 - c_3^2c_4 - c_1^2c_4^2 - c_1c_2^2c_5 - c_5^2 > 0$$

  - *In the event, we don't even have to check this condition because we already need* $k_3, k_5 > 0$ *and* $k_4 = k_3 + k_5$*!* ☺ ☺
- **Combining the characteristic polynomial theorem, the Routh array, and asymptotics can make otherwise intractable stability calculations feasible.**

Shameless Self Promotion

- My new book, *Mathematical Modeling for Epidemiology and Ecology*, is now available from Springer (call your school librarian). Features include
  1. empirical modeling, mechanistic modeling, and dynamical systems analysis
  2. a LOT of epidemiology models and many ecology models
  3. case studies, such as onchocerciasis models and analysis of linearization methods for fitting the Michaelis-Menten model
  4. linked problem sets that are like projects, but distributed across multiple sections
  5. original models (eg, vaccination population dynamics) and methods (eg, asymptotic simplification for dynamical systems analysis)

- Contact me at gledder@unl.edu with questions or comments. If anyone wants to have me visit, I'm interested.