A Minimal Mathematical Model for Disease Variant Competition

and

Dynamical System Analysis for Systems of 4–6 Components

Glenn Ledder

Department of Mathematics
University of Nebraska-Lincoln
gledder@unl.edu

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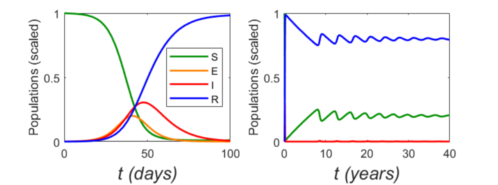
Overview – Two Talks in One

- I will present and analyze a mathematical model I created as a simple setting for competition between disease variants.
  - The model is an endemic SIR model with an added variant.
  - Compared to the resident, the variant is generally less contagious, but better at evading the immune system.

- I will showcase my general method for efficient analysis of medium size dynamical systems (4–6 components).
  - Characteristic polynomial coefficients are calculated more efficiently than the usual $P(\lambda) = \det(J - \lambda I)$.
  - The Routh-Hurwitz conditions are constructed from a Routh array for each specific problem.
  - 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 are negligible (often omitted).
- 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 Research Problem Inspired by COVID-19

- Biological Question: Why did the omicron COVID-19 variant displace the delta variant so quickly?
    1. It could be more contagious.
    2. It could have advantages that offset being less contagious.
- Research Question: What features would a less contagious disease need to outcompete a more contagious one?
- Research Plan: Add a second variant to the **simplest** endemic disease model.
    - Make the new variant less contagious to (S)usceptibles.
    - But give it some compensatory advantage.
        - Inspiration from COVID-19: Maybe immunity to either variant doesn't protect against the new variant.

Variant Competition Model

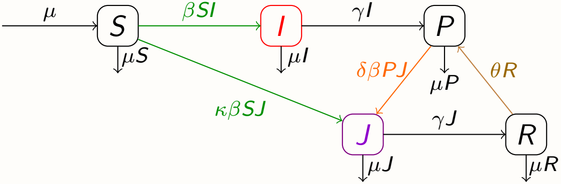


Figure 1: Competing Variant Model

- Equal birth and death rates (μ) yield constant population (1).
- Both variants have the same mean recovery time ($1/\gamma$).
- The invader (J) is less contagious to Susceptibles ($\kappa < 1$).
- Recovery from I confers at most partial immunity against J.
  - $\delta \leq \kappa < 1$.
- Immunity against J wanes with mean time $1/\theta$.

Variant Competition Model – 4 Independent Components

$$\begin{aligned}
\frac{dI}{dT} &= -(\gamma+\mu)I + \beta SI \\
\frac{dJ}{dT} &= -(\gamma+\mu)J + \kappa\beta SJ + \delta\beta PJ \\
\frac{dS}{dT} &= \mu(1-S) - \beta SI - \kappa\beta SJ \\
\frac{dP}{dT} &= \gamma I - \mu P + \theta R - \delta\beta PJ \\
\frac{dR}{dT} &= \gamma J - \mu R - \theta R \\
1 &= S + I + J + P + R
\end{aligned} \tag{1}$$

- Parameters and Scaling:

$$\epsilon = \frac{\mu}{\gamma+\mu} \ll 1, \quad b = \frac{\beta}{\gamma+\mu} > 1, \quad h = \frac{\theta}{\mu}, \qquad \frac{d}{dT} = \mu\frac{d}{dt}.$$

  - b is the basic reproduction number for the resident (I).

Rescaling Infectious Populations

$$
\begin{aligned}
\epsilon I' &= -I + bSI \\
\epsilon J' &= -J + b(\kappa S + \delta P)J \\
S' &= 1 - S - \epsilon^{-1} bS(I + \kappa J) \\
P' &= (\epsilon^{-1} - 1)I - P + hR - \epsilon^{-1}\delta bPJ \\
R' &= (\epsilon^{-1} - 1)J - (h+1)R \\
1 &= S + I + J + P + R
\end{aligned}
\tag{2}
$$

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

    $$bS(I + \kappa J) = O(\epsilon) \quad \Rightarrow \quad I, J = O(\epsilon).$$

  - I and J should be rescaled with $I = \epsilon Y$ and $J = \epsilon Z$.

Rescaled Model

$$
\begin{aligned}
\epsilon Y' &= -Y + bSY \\
\epsilon Z' &= -Z + b(\kappa S + \delta P)Z \\
S' &= 1 - S - bS(Y + \kappa Z) \\
P' &= (1-\epsilon)Y - P + hR - \delta bPZ \\
R' &= (1-\epsilon)Z - (h+1)R \\
1 &= S + P + R + \epsilon Y + \epsilon Z
\end{aligned}
\tag{3}
$$

- 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 safely be neglected.

Final (Rescaled and Approximate) Model

$$
\begin{aligned}
Y' &= \Gamma Y(-1 + bS) \\
Z' &= \Gamma Z(-1 + bQ) \\
S' &= 1 - S(1 + bX) \\
P' &= Y - P + hR - \delta bPZ \\
R' &= Z - \bar{h}R \\
1 &= S + I + J
\end{aligned}
\tag{4}
$$

where

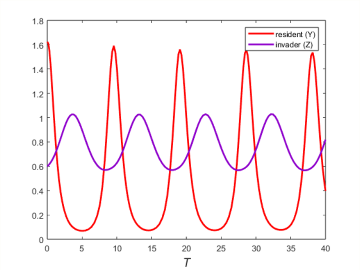
$$
Q = \kappa S + \delta P, \quad X = Y + \kappa Z, \quad \bar{h} = h + 1, \quad \Gamma = \epsilon^{-1}. \tag{5}
$$

- Y is the resident and Z is the invader.
- Tip 1: Better to have extra symbols than messier formulas.

Mathematical Agenda

- Our research began with a biological question. This led to a model. For the analysis, we need a mathematical agenda.
- We have four principal parameters: b, κ, δ, h.
  - Larger b makes both variants more contagious in general.
  - Larger κ decreases the advantage of I for infecting S.
  - Larger δ decreases the value of immunity from I against J.
  - Larger h decreases the value of immunity from J against J.
- Mathematical question: Given b and h, how do the values of κ and δ affect the competition between variants?
- Strategy: Determine the regions in the $\kappa\delta$ plane that produce different outcomes. Plot for different b and h.
  1. Identify possible end states in different regions of the $\kappa\delta$ plane.
  2. Determine which are stable in each region.

The End of the Story



- Hacker's Challenge: Try to guess a point in the 4-D parameter space $(b, \kappa, \delta, h,$ with $\epsilon \to 0)$ that yields a limit cycle.
  - Probability less than 1% even if you know the best b and h.
    - Even in a 4×4 system with 4 parameters, it is important to do a general stability analysis!

Four Equilibria

- There are three possible endemic equilibria:
  1. A resident-only equilibrium (EDE-Y)
  2. An invader-only equilibrium (EDE-Z)
  3. A coexistence equilibrium (EDE-YZ)

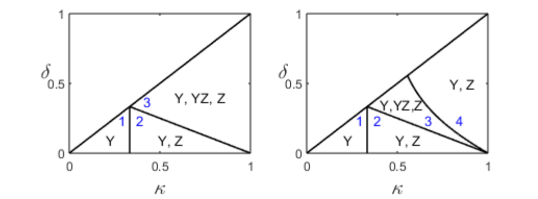


Figure 2: Existence regions for the competition model in the $\kappa\delta$ plane with $b = 3$, $h = 0$ (left) and $b = 3$, $h = 2$

- Region 3 gets smaller as h increases.

Details for EDE-Z

- To simplify EDE notation:
  - Define $w = bW$ for $W \in \{Y, Z, S, P, R\}$.
- Combining all equilibrium equations yields
$$G(s^*) = \bar{h}\kappa(\kappa - \delta){s^*}^2 + \left[\bar{h}\kappa(\delta b - 1) + \delta\right] s^* - \delta b = 0.$$
- The requirement that all variables be nonnegative reduces to
$$bS^* = s^* \leq \kappa^{-1}.$$
- G is increasing for $s > 0$, so $\kappa^{-1} \geq s^*$ is equivalent to
$$G\left(\kappa^{-1}\right) \geq G(s^*) = 0 \quad \Rightarrow \quad \kappa \geq b^{-1}.$$
  - Regions 2, 3, and 4.

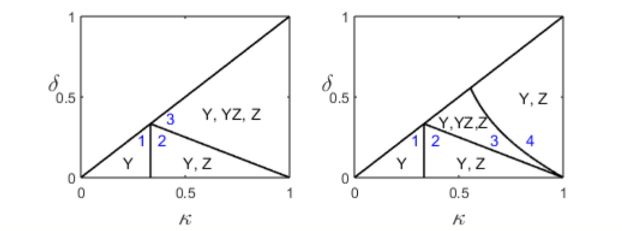
- *This is much better than solving $G = 0$ for s^*.*

Details for EDE-YZ

- The equations decouple to give $s, p > 0$, $z = \bar{h}r$, and

$$\delta r = \delta(b-1) - (1-\kappa), \qquad y = (b-1) - \bar{h}\kappa r.$$

- Region 2 has $r < 0$ and region 4 has $y < 0$.
  - EDE-YZ exists only in region 3.



The Jacobian

The Jacobian for the YZSP system is

$$J = \begin{pmatrix} -(1-s)\Gamma & 0 & y\Gamma & 0 \\ 0 & -(1-q)\Gamma & \kappa z\Gamma & \delta z\Gamma \\ -s & -\kappa s & -\bar{x} & 0 \\ 1 & -\delta p & -h & -\Sigma \end{pmatrix}, \tag{6}$$

where

$$q = \kappa s + \delta p, \quad x = y + \kappa z, \quad \Sigma = \bar{h} + \delta z, \quad \bar{w} = w + 1 \ \ (\forall w).$$

- Tip 2: Better to have extra symbols than messier formulas!

Stability for the DFE

- At the DFE, the Jacobian simplifies to

$$J_{DFE} = \begin{pmatrix} -(1-b)\Gamma & 0 & 0 & 0 \\ 0 & -(1-\kappa b)\Gamma & 0 & 0 \\ -b & -\kappa b & -1 & 0 \\ 1 & 0 & -h & -\bar{h} \end{pmatrix}$$

- The eigenvalues are

$$(b-1)\Gamma, \quad (\kappa b - 1)\Gamma, \quad -1, \quad -\bar{h}.$$

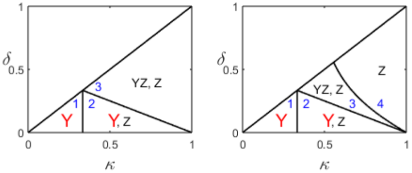
- The DFE is stable when $b < 1$.
  - The basic reproduction numbers are b for Y and $\kappa b < b$ for Z.

Stability for EDE-Y

J_Y is similar to the (lower triangular) block matrix

$$\left(\begin{array}{c|cc|c} -(1-q)\Gamma & 0 & 0 & 0 \\ \hline 0 & 0 & y\Gamma & 0 \\ -\kappa & -1 & -b & 0 \\ \hline -\delta p & 1 & -h & -\bar{h} \end{array}\right) \qquad \begin{aligned} p &= b-1 \\ q &= \kappa + \delta p \end{aligned}$$

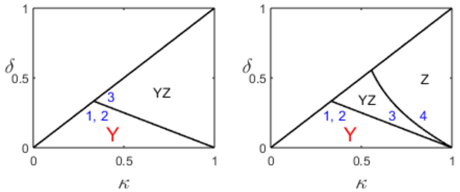
- EDE-Y is stable when $q < 1$, which is regions 1 and 2.



Stability for EDE-Z – eigenvalue λ_1

$$J_Z = \left(\begin{array}{c|c} -(1-s)\Gamma & 0 \\ \hline \cdots & J_{234} \end{array} \right), \quad J_{234} = \begin{pmatrix} 0 & \kappa z \Gamma & \delta z \Gamma \\ -\kappa s & -\bar{x} & 0 \\ -\delta p & -h & -\Sigma \end{pmatrix}$$

- Stability requires $s < 1$, which is region 4.



  - *Resident persists if variant recovery confers immunity (left).*

Stability for EDE-Z – eigenvalues $\lambda_2, \lambda_3, \lambda_4$

$$J_{234} = \begin{pmatrix} 0 & \kappa z \Gamma & \delta z \Gamma \\ -\kappa s & -\bar{x} & 0 \\ -\delta p & -h & -\Sigma \end{pmatrix}, \quad \cdots \quad \Sigma = \bar{h} + \delta z.$$

- This will require the Routh-Hurwitz conditions.
  - Stability requires $c_j > 0$ and $c_1 c_2 > c_3$, where

$$c_1 = -\sum_k j_{kk}, \qquad c_2 = \sum_{ik} J_{ik}, \qquad c_3 = -\det J_{234}$$

and J_{ik} is the subdeterminant of rows/columns i/k.

$$c_1 = \Sigma + \bar{x} > 0, \qquad c_2 = \kappa^2 sz\Gamma + \delta^2 pz\Gamma + \Sigma\bar{x} > 0.$$

Stability for EDE-Z – eigenvalues $\lambda_2, \lambda_3, \lambda_4$, continued

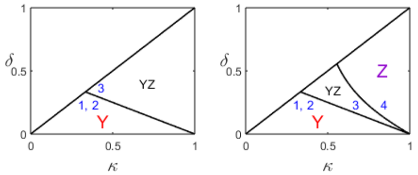
$$c_3 = (\kappa^2 s\Sigma + \delta^2 p\bar{x} - h\delta\kappa s)z\Gamma.$$

$c_3 > 0$ follows from $\Sigma = \bar{h} + \delta z > h$ and

$$\frac{c_3}{z\Gamma} > \kappa^2 s\Sigma - h\delta\kappa s > h\kappa^2 s - h\delta\kappa s > h(\kappa - \delta)\kappa s \geq 0.$$

Meanwhile, $c_1 = \Sigma + \bar{x}$ and $c_2 > \left(\kappa^2 s + \delta^2 p\right) z\Gamma$,

so $$c_1 c_2 > \left(\kappa^2 s\Sigma + \delta^2 p\bar{x}\right) z\Gamma \geq c_3.$$



Stability for EDE-YZ

The Jacobian for EDE-YZ is

$$J_{YZ} = \begin{pmatrix} 0 & 0 & y\Gamma & 0 \\ 0 & 0 & \kappa z\Gamma & \delta z\Gamma \\ -1 & -\kappa & -b & 0 \\ 1 & -\delta p & -h & -\Sigma \end{pmatrix}$$

- There is no decoupling. ☹
- How do we manage a 4×4 characteristic polynomial?
  - The characteristic polynomial theorem! ☺
    - With asymptotics! ☺
- Then what?
  - The Routh-Hurwitz conditions! ☺

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

$$P(\lambda) = \lambda^n + c_1\lambda^{n-1} + c_2\lambda^{n-2} + \cdots + c_{n-1}\lambda + c_n, \tag{7}$$

where

$$c_m = (-1)^m \sum_{|I|=m} J_I, \qquad c_n = (-1)^n |J|. \tag{8}$$

The Characteristic Polynomial for EDE-YZ

$$J_{YZ} = \begin{pmatrix} 0 & 0 & y\Gamma & 0 \\ 0 & 0 & \kappa z\Gamma & \delta z\Gamma \\ -1 & -\kappa & -b & 0 \\ 1 & -\delta p & -h & -\Sigma \end{pmatrix}, \quad \delta p + \kappa = 1.$$

- $c_1 = -[0 + 0 + (-b) + (-\Sigma)] = b + \Sigma.$
- $J_{13} = y\Gamma,\ J_{23} = \kappa^2 z\Gamma,\ J_{24} = \delta^2 pz\Gamma,\ J_{34} = O(1),\ J_{12} = J_{14} = 0.$
  - $c_2 \sim (y + \kappa^2 z)\Gamma + \delta^2 pz\Gamma.$
- $J_{134} = -\Sigma J_{13},\quad J_{234} = -\Sigma J_{23} - bJ_{24} + h\kappa\delta z\Gamma,\quad J_{123} = J_{124} = 0.$
  - $c_3 = \Sigma(y + \kappa^2 z)\Gamma + b\delta^2 pz\Gamma - h\kappa\delta z\Gamma.$
- $c_4 = |J_{YZ}| = (y\Gamma)(\delta z\Gamma).$

The Routh-Hurwitz Conditions

- The characteristic polynomial is

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

$$k_1 = b + \Sigma, \quad k_2 = \eta + \pi, \quad k_3 = \Sigma\eta + b\pi - \delta^{-1}\psi, \quad k_4 = \delta yz,$$

$$\Sigma = \bar{h} + \delta z, \quad \eta = y + \kappa^2 z, \quad \pi = \delta^2 pz, \quad \psi = h\kappa\delta^2 z.$$

- The Routh-Hurwitz conditions are

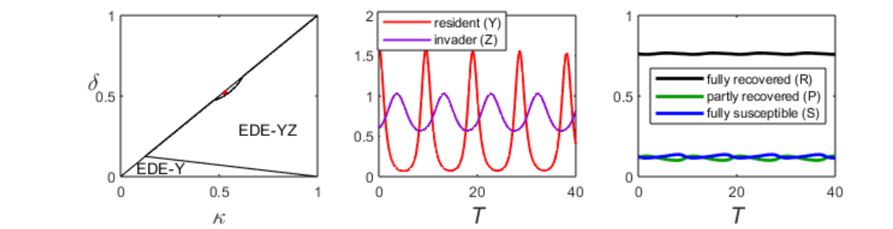
$$k_1 > 0, \quad k_4 > 0, \quad q_1 > 0, \quad q_2 > 0,$$

$$q_1 = k_1 k_2 - k_3, \quad q_2 = k_3 q_1 - k_4 k_1^2.$$

- Tip 3: Better to have extra symbols than messier formulas!!

Summary of Results

- All but one of the RH conditions are automatically satisfied.
- The other is not!
  - There is a tiny region where we find a stable limit cycle.
    - There is a tinier border where the asymptotic approximation gives the wrong result.



A Disease with Two Risk Groups

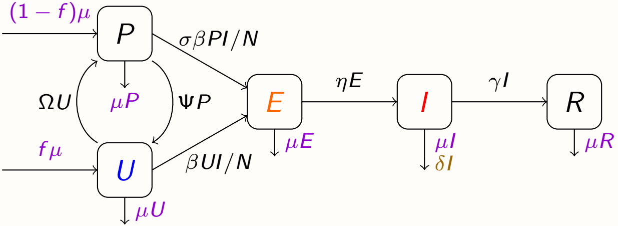


Figure 3: Two Risk Group Model

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

- The variables are $X = E/\epsilon$, $Y = I/\epsilon$, S, U, N.
  - Disease mortality makes N variable.

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

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

- 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

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

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

$$\frac{k_1 k_2 \Gamma^2 - k_3 \Gamma^2}{k_1 \Gamma} = \frac{\Gamma}{k_1}(k_1 k_2 - k_3),$$

so the array is now

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

The Routh Array, Step 3

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

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]

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

The Routh Array, Step 4

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

.

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

where

$$q_1 = k_1 k_2 - k_3, \qquad q_2 = k_3 q_1 - k_1^2 k_4.$$

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 the RH conditions was $k_4 > 0$.
  - Without asymptotics ☹ , it would have been

$$c_1 c_2 c_3 c_4 + c_2 c_3 c_5 + 2 c_1 c_4 c_5 - c_3^2 c_4 - c_1^2 c_4^2 - c_1 c_2^2 c_5 - c_5^2 > 0$$

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