# Sensitivity Analysis of Colorectal Cancer Initiation

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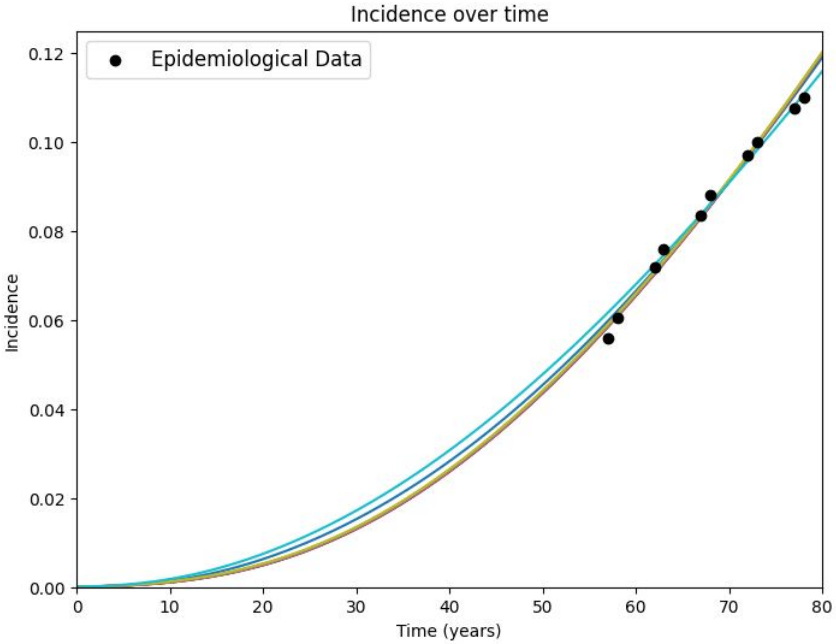
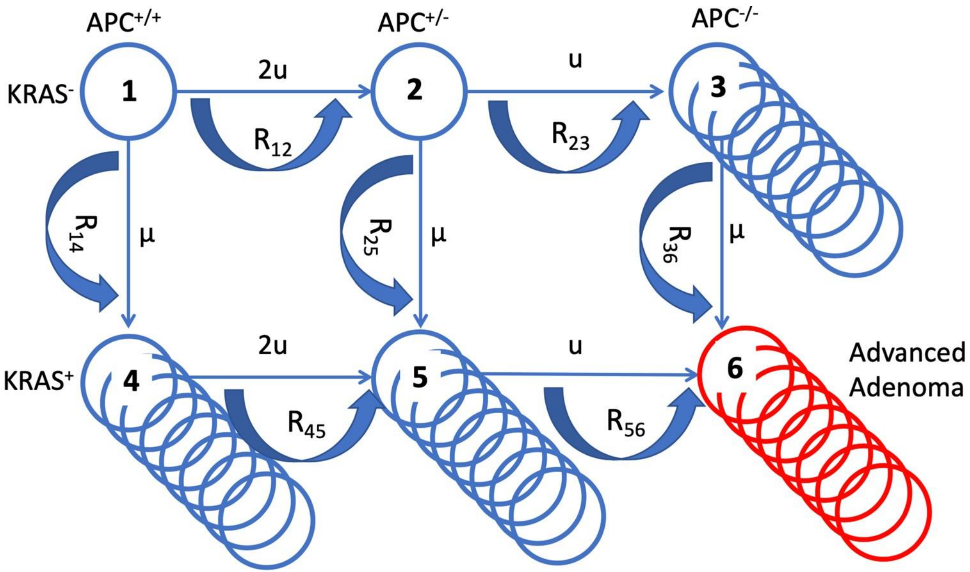
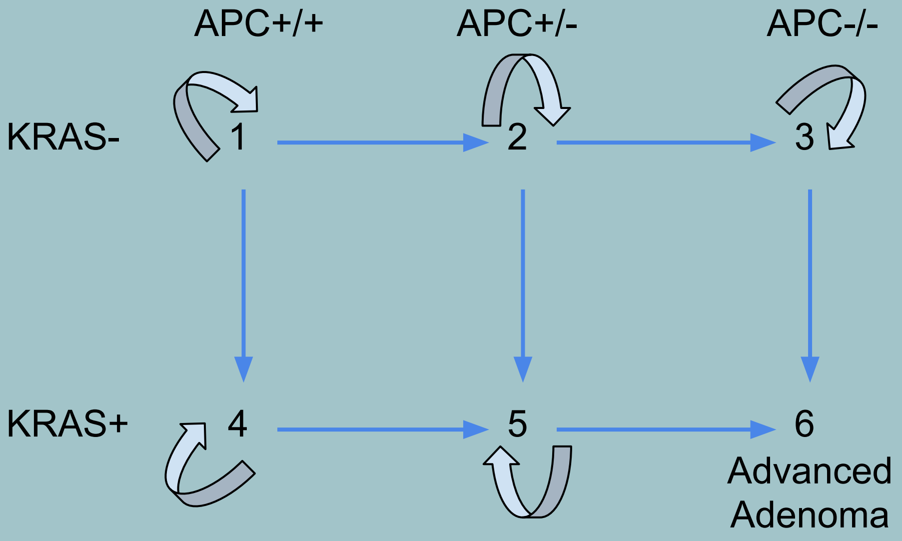
AMATH 422/522 Final Presentation

# Population Dynamics (ODE Solutions)



Based on the *sensitivity matrix* which stage transition of colonic crypts has the largest effect on cancer incidence?



# To answer this we need to Linearize the ODE

$$\dot n_1 = -(R_{12}+R_{14})n_1$$

$$\dot n_2 = R_{23}n_1 - (R_{23}+R_{25})n_2$$

$$\dot n_3 = R_{23}n_2 - R_{36}n_3 \boxed{+ \gamma_3 n_3\left(1-\frac{n_3+n_4+n_5}{K_A}\right)} - \delta n_3$$

$$\dot n_4 = R_{14}n_1 - R_{45}n_3 \boxed{+ \gamma_4 n_4\left(1-\frac{n_3+n_4+n_5}{K_R}\right)} - \delta n_4$$

$$\dot n_5 = R_{25}n_2 - R_{45}n_4 - R_{56}n_5 \boxed{+ \gamma_5 n_5\left(1-\frac{n_3+n_4+n_5}{K_R}\right)} - \delta n_5$$

Nonlinear term

$$J = \begin{bmatrix} \frac{\partial \dot n_1}{\partial n_1} & \frac{\partial \dot n_1}{\partial n_2} & \frac{\partial \dot n_1}{\partial n_3} & \frac{\partial \dot n_1}{\partial n_4} & \frac{\partial \dot n_1}{\partial n_5} \\ \frac{\partial \dot n_2}{\partial n_1} & \frac{\partial \dot n_2}{\partial n_2} & \frac{\partial \dot n_2}{\partial n_3} & \frac{\partial \dot n_2}{\partial n_4} & \frac{\partial \dot n_2}{\partial n_5} \\ \frac{\partial \dot n_3}{\partial n_1} & \frac{\partial \dot n_3}{\partial n_2} & \frac{\partial \dot n_3}{\partial n_3} & \frac{\partial \dot n_3}{\partial n_4} & \frac{\partial \dot n_3}{\partial n_5} \\ \frac{\partial \dot n_4}{\partial n_1} & \frac{\partial \dot n_4}{\partial n_2} & \frac{\partial \dot n_4}{\partial n_3} & \frac{\partial \dot n_4}{\partial n_4} & \frac{\partial \dot n_4}{\partial n_5} \\ \frac{\partial \dot n_5}{\partial n_1} & \frac{\partial \dot n_5}{\partial n_2} & \frac{\partial \dot n_5}{\partial n_3} & \frac{\partial \dot n_5}{\partial n_4} & \frac{\partial \dot n_5}{\partial n_5} \end{bmatrix}$$

$$f(x) \approx f(x_{\text{eq}}) + \left.\frac{\partial f}{\partial x}\right|_{x_{\text{eq}}} (x - x_{\text{eq}})$$

Equilibrium point = $\{\vec{0}\}$

# Calculated Jacobian

$$J = \begin{bmatrix} -R_{12} - R_{14} & 0 & 0 & 0 & 0 \\ R_{12} & -R_{23} - R_{25} & 0 & 0 & 0 \\ 0 & R_{23} & A & -\frac{\gamma_3 n_3}{K_A} & -\frac{\gamma_3 n_3}{K_A} \\ R_{14} & 0 & -\frac{\gamma_4 n_4}{K_R} & B & -\frac{\gamma_4 n_4}{K_R} \\ 0 & R_{25} & -\frac{\gamma_5 n_5}{K_R} & R_{45} - \frac{\gamma_5 n_5}{K_R} & C \end{bmatrix}$$

$$A = -R_{36} + \gamma_3 - \frac{2\gamma_3 n_3}{K_A} - \frac{\gamma_3 n_4}{K_A} - \frac{\gamma_3 n_5}{K_A} - \delta$$

$$B = -R_{45} + \gamma_4 - \frac{\gamma_4 n_3}{K_R} - \frac{2\gamma_4 n_4}{K_R} - \frac{\gamma_4 n_5}{K_R} - \delta$$

$$C = -R_{56} + \gamma_5 - \frac{\gamma_5 n_3}{K_R} - \frac{\gamma_5 n_4}{K_R} - \frac{2\gamma_5 n_5}{K_R} - \delta$$

# Result Linearized ODE system

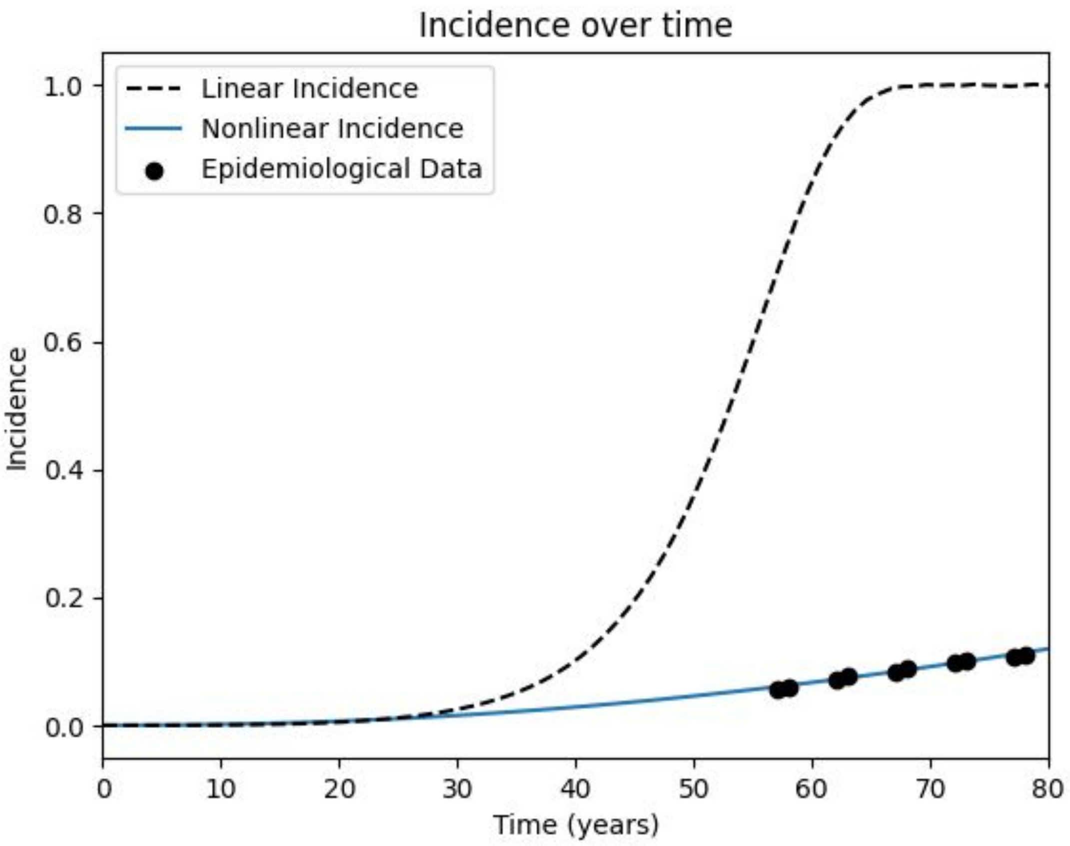
$$
\begin{aligned}
\dot{n}_1 &= -(R_{12} + R_{14})n_1, \\
\dot{n}_2 &= R_{12}n_1 - (R_{23} + R_{25})n_2, \\
\dot{n}_3 &= R_{23}n_2 - R_{36}n_3 + \gamma_3 n_3 - \delta n_3, \\
\dot{n}_4 &= R_{14}n_1 - R_{45}n_4 + \gamma_4 n_4 - \delta n_4, \\
\dot{n}_5 &= R_{25}n_2 + R_{45}n_4 - R_{56}n_5 + \gamma_5 n_5 - \delta n_5 \\
\dot{P} &= R_{36}n_3 + R_{56}n_5(1 - P)
\end{aligned}
$$

# Nonlinear vs Linear

$$N_{nonlinear} \propto \gamma n\left(1 - \frac{n3 + n4 + n5}{K}\right)$$

$$N_{linear} \not\propto \gamma n\left(1 - \frac{n3 + n4 + n5}{K}\right)$$

- Crypt competition is necessary
- Would predict cancer at age 60 with probability 1
- Continue with sens. analysis



# Derive transition matrix from linear system

$$T = \begin{bmatrix} 1-(R_{12}+R_{14}) & 0 & 0 & 0 & 0 & 0 \\ R_{12} & 1-(R_{23}+R_{25}) & 0 & 0 & 0 & 0 \\ 0 & R_{23} & (1-R_{36})+\gamma_3-\delta & 0 & 0 & R_{35} \\ R_{14} & 0 & 0 & (1-R_{45})+\gamma_4-\delta & 0 & 0 \\ 0 & R_{25} & 0 & R_{45} & (1-R_{56})+\gamma_5-\delta & R_{56} \\ 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$

- Each entry represents the rate of transition from stage i (row#) → stage j (col #)
  - Can assume any non-negative real number

# Compute sensitivities of each entry $t_{ij}$ of T

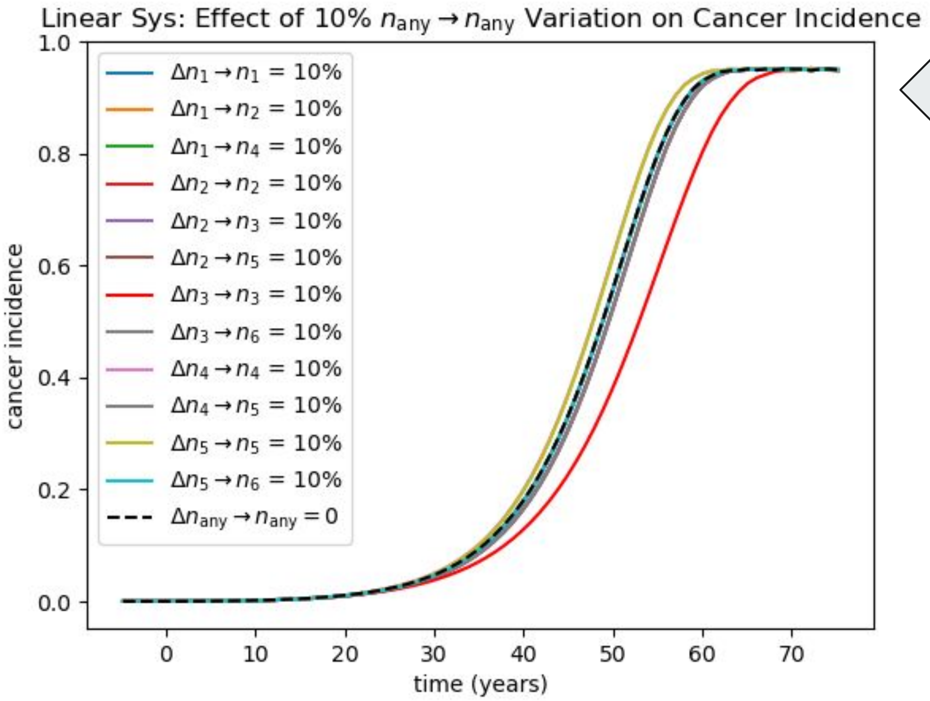
- Calculate dominant eigenvector of T $= v_{right}$
- Calculate dominant eigenvector of $T^T = v_{left}$
- Apply this formula to each entry: $s_{ij} = \dfrac{v_{left,i} * v_{right,j}}{v_{left} \cdot v_{right}}$

$$S = \begin{bmatrix} 0 & 0 & 2.16 * 10^{-6} & 0 & 0 & 0 \\ 0 & 0 & 1.04 * 10^{-3} & 0 & 0 & 0 \\ 0 & 0 & \boxed{1.00} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1.04 * 10^{-5} & 0 & 0 & 0 \end{bmatrix}$$

Transition from (row # 3) → (column # 3)

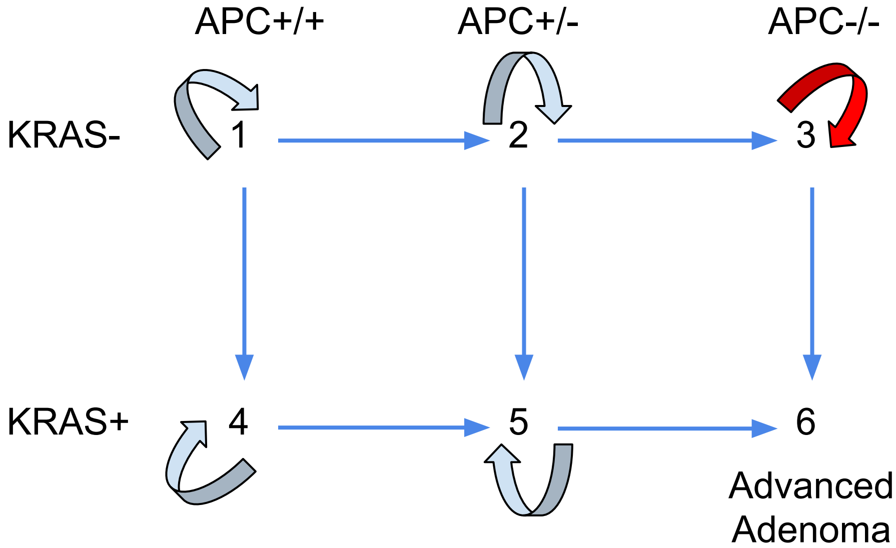
Suggests that magnitude of crypt population btwn $n_1$ to $n_5$ has highest sensitivity to the **$n_3 \rightarrow n_3$ crypt transition**

# Empirical Verification

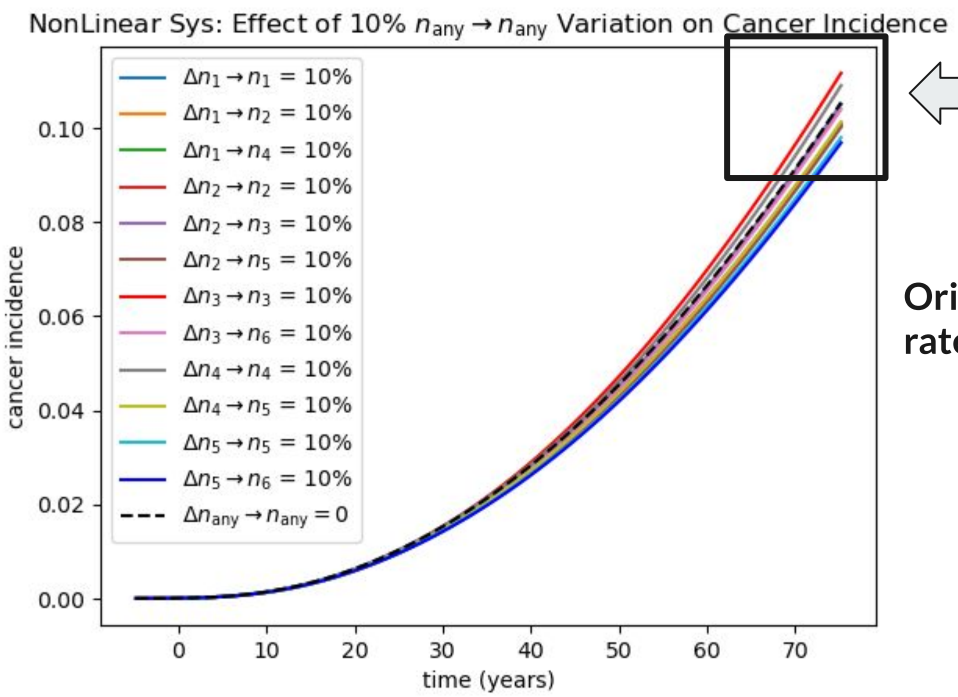


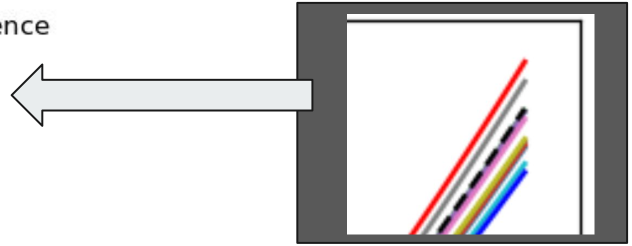

Linear approximation: varying the $n_3 \to n_3$ transition rate has the greatest impact on cancer incidence

(as predicted by sensitivity analysis)

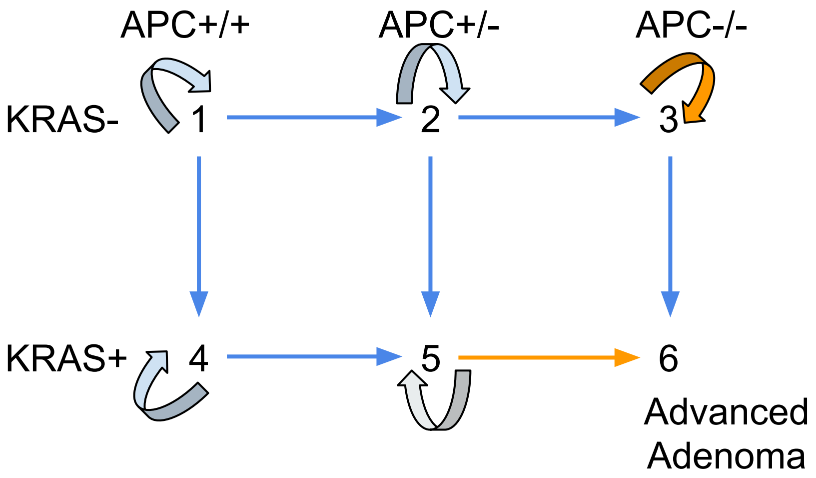


# Empirical Verification - in the nonlinear model



Original NonLinear model: $n_3 \rightarrow n_3$ and $n_5 \rightarrow n_6$ transition rates have the largest relative impact on cancer incidence




*results are dependent on variable parameter values (carrying capacities, stem cell division rate, etc)

# Thank you for listening