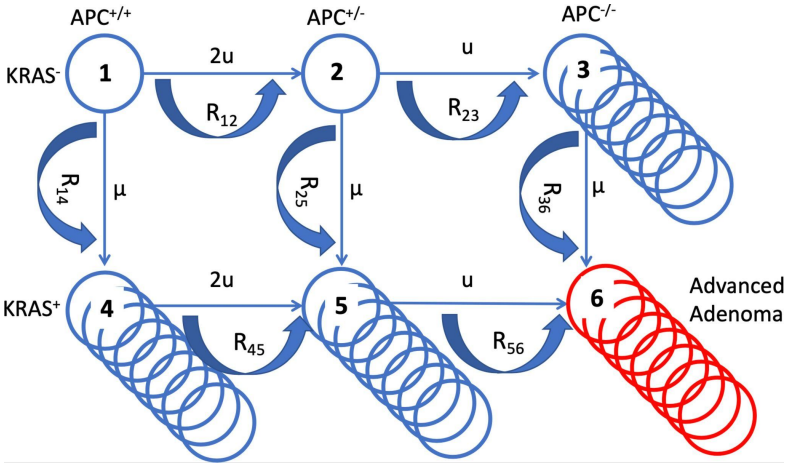
Modelling Aspirin's Effect on Colorectal Cancer Initiation

(Y. Wang et al., 2022)

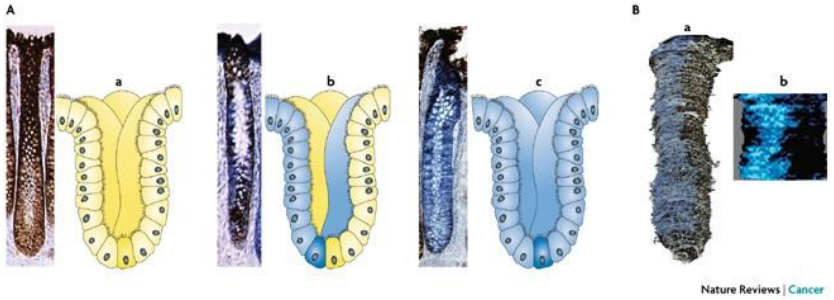
Presented By: Benji Brown, Dora Layanto, Julien Goldstick, & Yuan Gao
AMATH 422/522 Case Study

Introduction

- >150,000 new colorectal cases in the US in 2024 (American Cancer Society)
- Accumulation of specific mutations in colonic crypt stem cells → colorectal cancer
- Underlying model Assumptions:
  - 2 APC LOF (tumor suppressor) and 1 KRAS GOF (division rate) mutations are necessary
  - Crypt competition occurs
  - Aspirin affects cellular process
- Study tracks 5 populations of crypts leading to A.A
  - APC or KRAS first?
  - Effect of aspirin on cancer progression?
- How is this studied mathematically?
  - Deterministic vs. stochastic models
  - Next slide!



(above) Figure 1, model schematic of cancer initiation, Wang et. al, 2022
(below) Figure 2, crypt conversion, Humphries and Wright, 2008



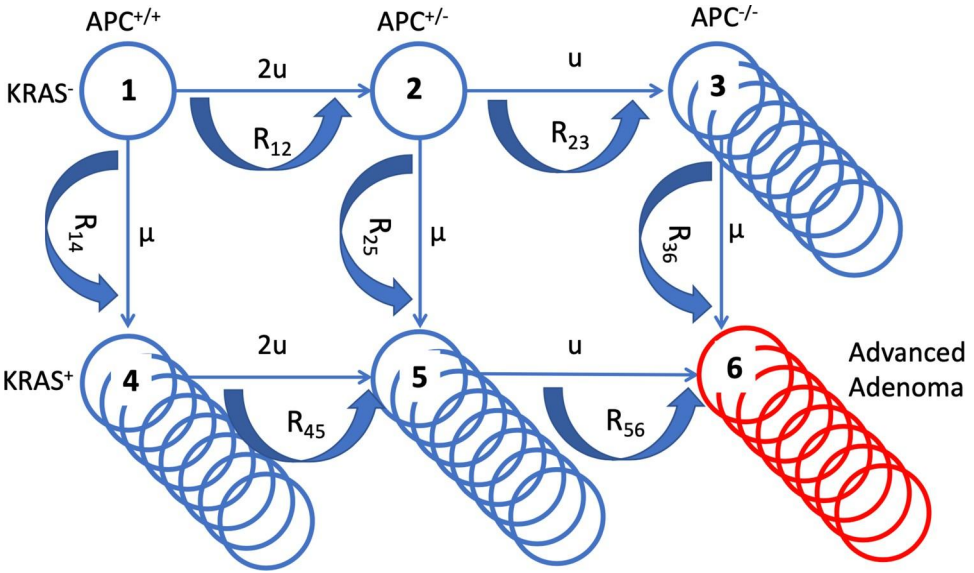
Model

(Population Rate)= immigration - emigration + birth - death

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

The probability of detecting a type 6 crypt

$$\dot{P} = (R_{56}n_5 + R_{36}n_3)(1-P), \quad P(0)=0$$



n_i = number of crypts in state i

R_{ij} = rate at which a crypt changes its mutation state from i to j

K_A, K_R = carrying capacity of APC or KRAS

γ = division rate

δ = death rate

μ, u = rate of mutation of APC and KRAS

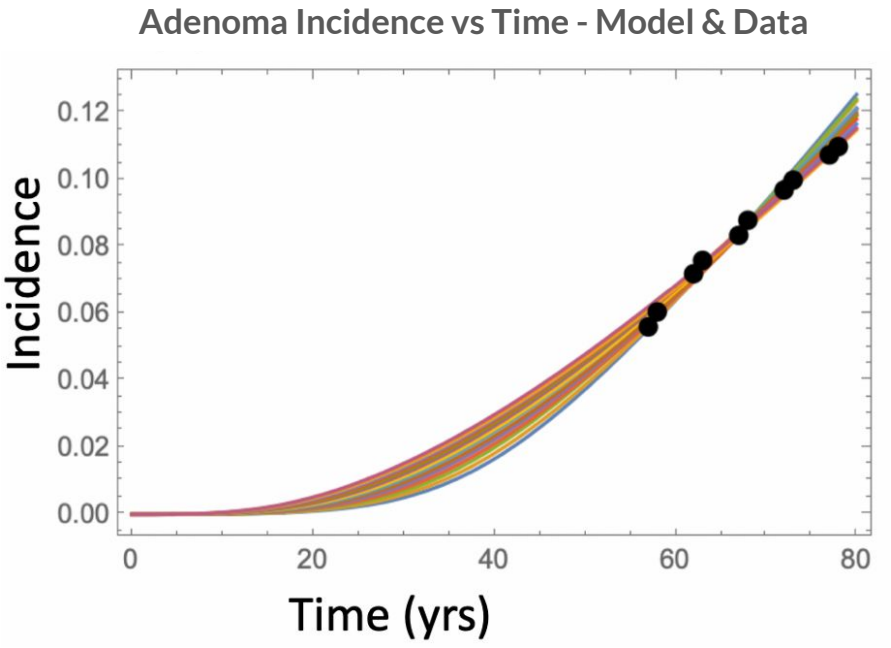
Fitting the ODE model

Determining wild-type parameters:

- Most parameter values referenced from wet-lab data
- Carrying capacity K_a & K_r are:
  - necessary for model to work,
  - and its values are solved in this paper.

Result:

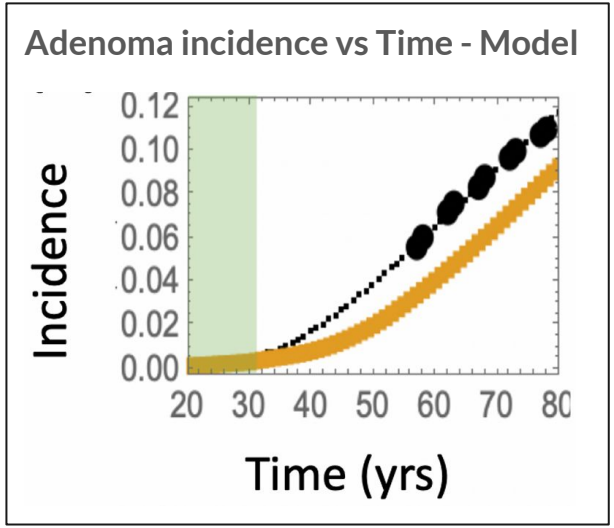
- Age-incidence curve: percent of population with detectable colorectal cancer, at each age
- ODE model (deterministic) **fits the observed age-incidence curve** of advanced adenoma.



Multiple Lines = results of model using limited range of Stem Cell division rates
Black dots = epidemiological data

Extending the model

- Effect of aspirin is represented by **adjusting the birth & death rate** in mutated cells
- Conduct **Gillespie (stochastic) simulations** using the adjusted birth & death rates
  - Avg simulation fits epidem data
- Data also collected & model ran for different decades of aspirin treatment (30s, 40s, etc).
  - Result: model & data always comparable

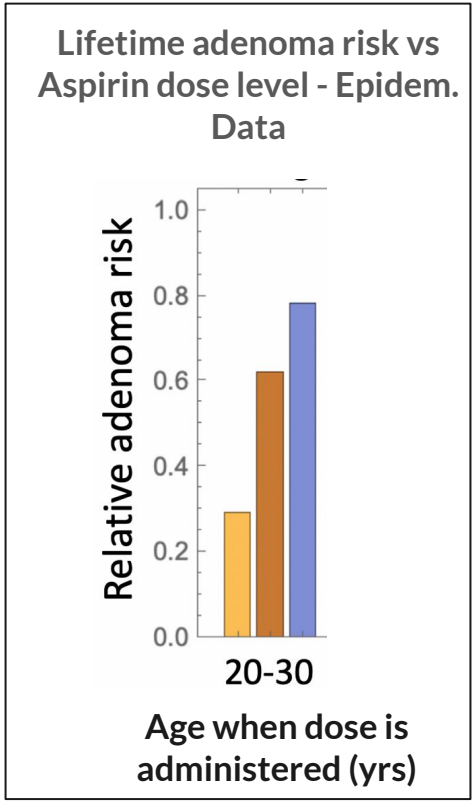


Thin black lines= result of original ODE (WT parameters)

Thick black dots = reference data, no aspirin

Gold curve = average result of stochastic sim (aspirin-adjusted parameters)

Green shade = age of aspirin treatment

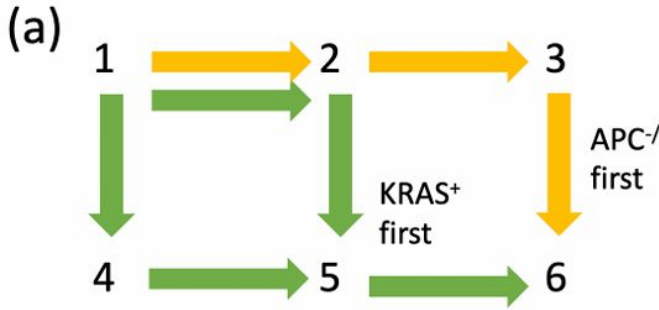


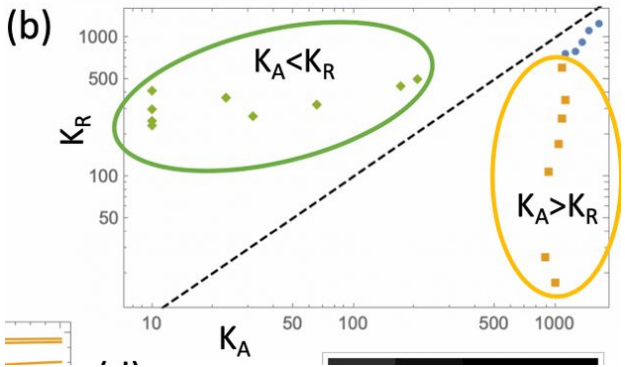
Low aspirin dose
Medium aspirin dose
High aspirin dose

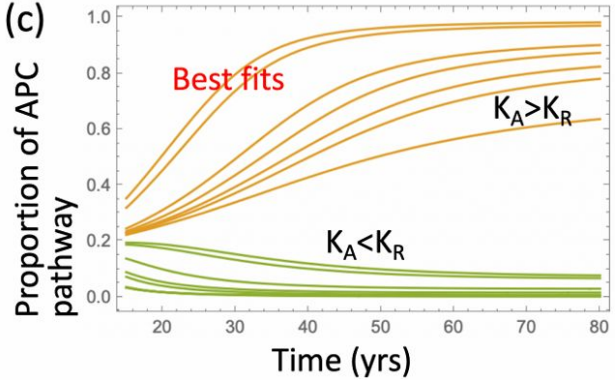
Insight

Question: What is the more likely pathway that leads to creation of type 6 crypts?

- The APC (tumor suppressor) pathway a LOF mutation from type 3
- The KRAS (proto oncogene) pathway a GOF mutation from type 5
- Model parameters where Carrying Capacity KA>KR is best supported b/c it
  - Has the lowest fitting error to epidemiological data
  - Corresponds with APC-/-KRAS- having a larger carrying capacity.
  - Consistent with APC-/- KRAS- being a more advanced stage of cancer than APC-/+KRAS+







(c) The probabilities P_APC and P_KRAS are plotted as functions of time for these two groups of fits

Future directions?

Evaluating preventative therapies targeted to specific cell types (1-5):

(1) Create the stage-structured matrix describing transitions between cell types 1-6
(2) Calculate sensitivities
(3) Compare the potential of different targeted interventions to lower cancer risk.

Intervention could mean:

- Increasing crypt death rate
- Decreasing crypt fission rate

Targeting means:

- Which cell type (1, 2, 3, 4, 5) should we focus our interventions on?

Challenge:

- To linearize the ODE, we would need to manipulate/remove the carrying capacity term.
- Question: is it even worth exploring a system that doesn't include this important parameter?

Future directions?

Modeling space-dependent crypt competition:

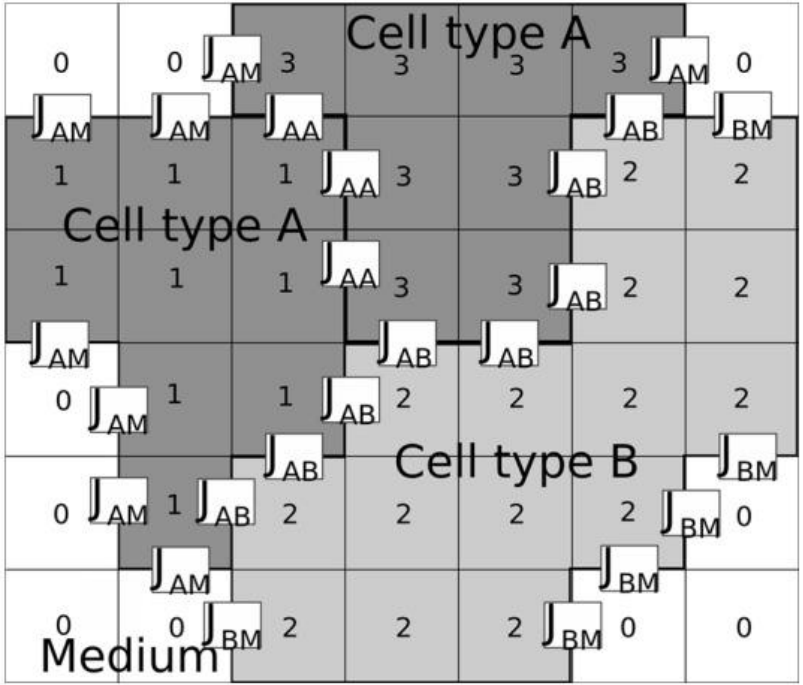
(1) Model the colon's spatial structure with a 2D matrix, where each entry represents a crypt.

- Entry value = dominant cell type in the crypt

(2) Create another matrix that represents the rate of transitions to the next cell type in the crypt

(3) How does introducing a space-dependent parameter for crypt competition affect the model's fit to epidemiological data?

Challenge: How would we represent crypt fission? Cannot simply insert a new entry in a matrix of specified dimensions. How would we quantify the variation in transition rate caused by intercrypt competition?



Note: schematic of 2D matrix representing a neighborhood of cells. Reprinted from Voss-Böhme A. (2012). Multi-Scale Modeling in Morphogenesis: A Critical Analysis of the Cellular Potts Model. *PLOS ONE 7*(9), e42852.

References

Wang, Y. (2022). Aspirin's effect on kinetic parameters of cells contributes to its role in reducing incidence of advanced colorectal adenomas, shown by a multiscale computational study. *eLife*, *11*, e71953. https://doi.org/10.7554/eLife.71953

Voss-Böhme A. (2012). Multi-Scale Modeling in Morphogenesis: A Critical Analysis of the Cellular Potts Model. *PLOS ONE 7*(9), e42852. https://doi.org/10.1371/journal.pone.0042852