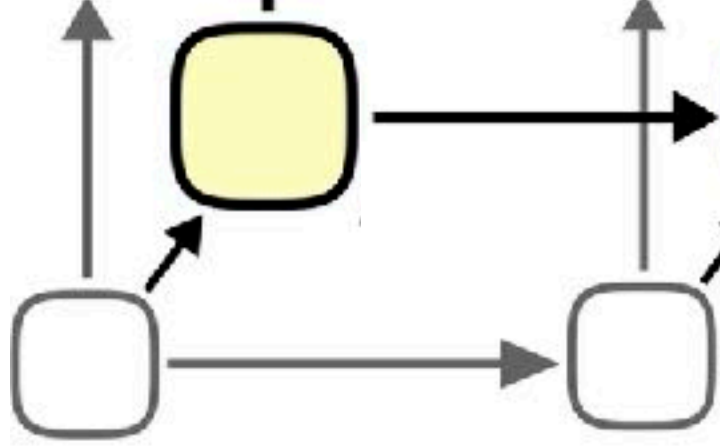
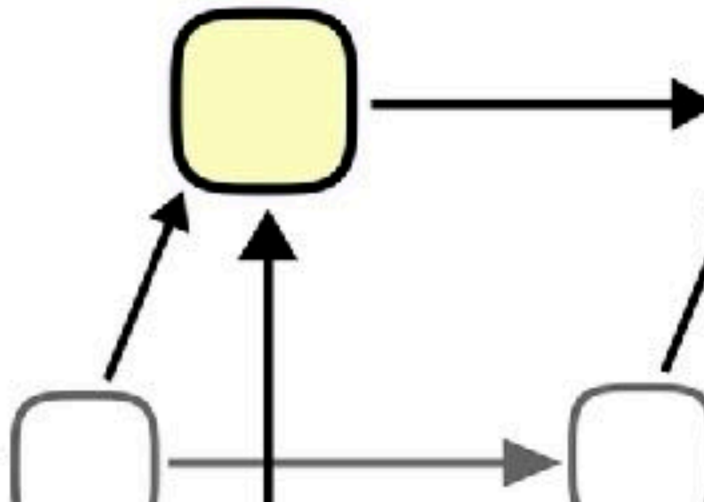


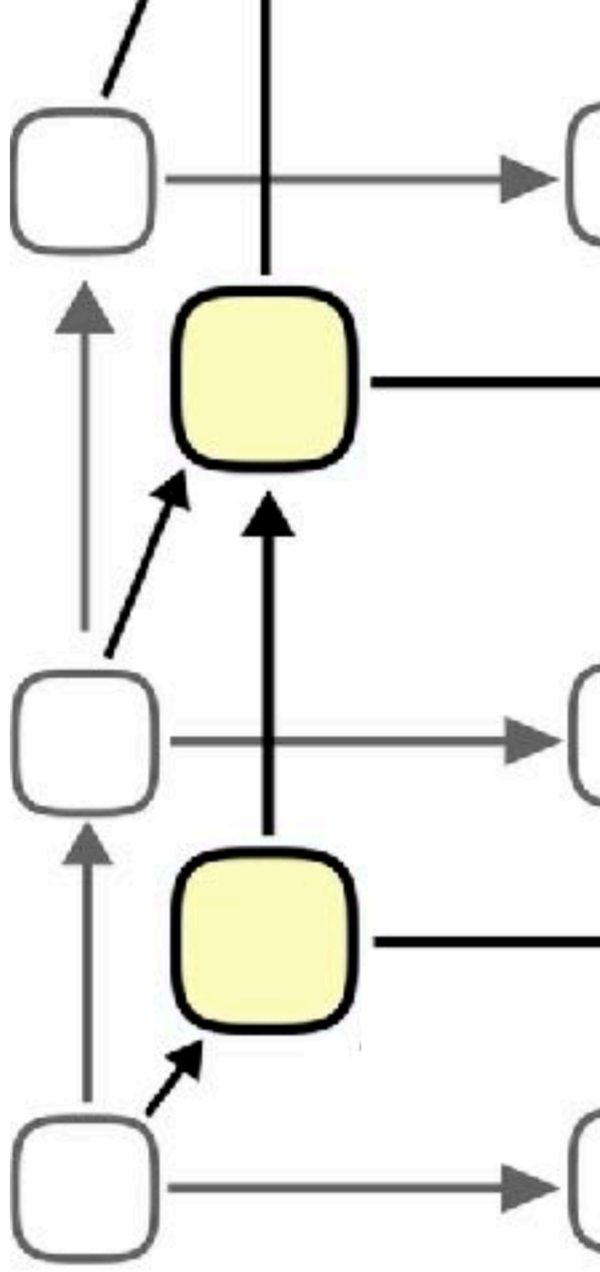
AMATH422 Case Study Presentation



Mathematical model *of*

Colorectal Cancer Initiation

AMATH422 Case Study Presentation



Group Member

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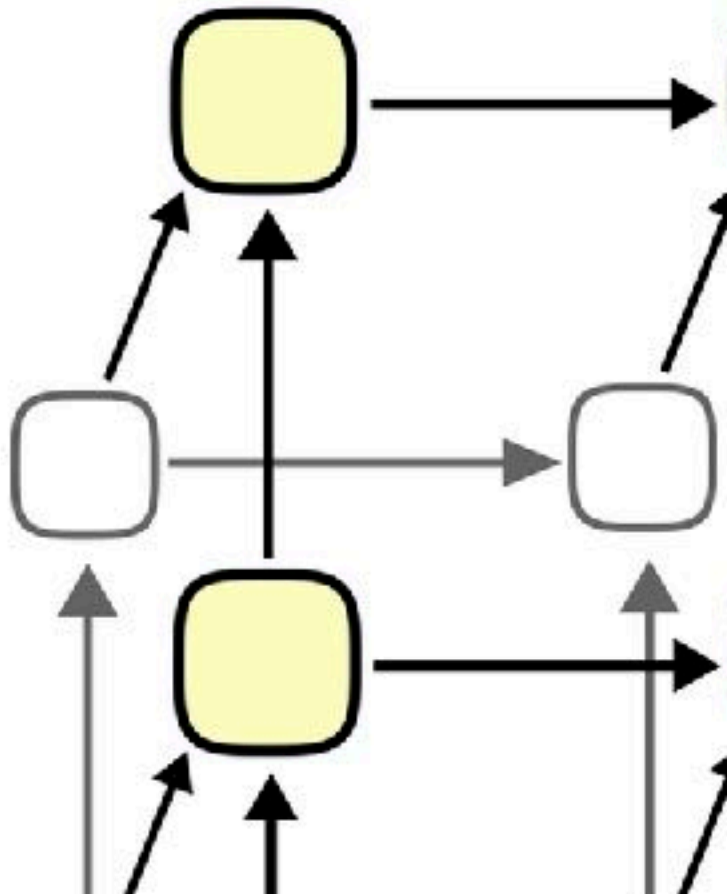
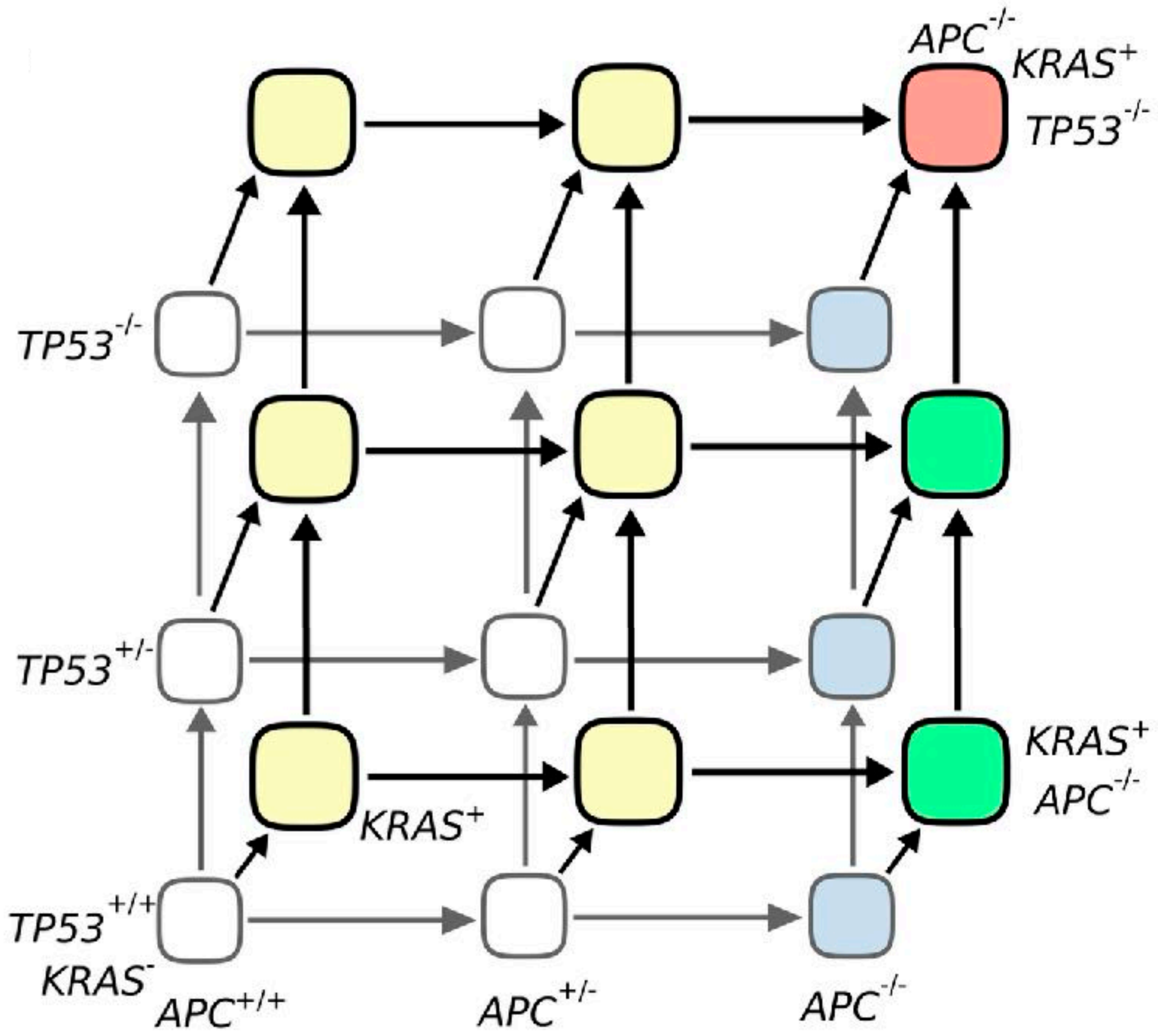


C. Paterson, H. Clevers, I. Bozic, Mathematical model of colorectal cancer initiation, Proc. Natl. Acad. Sci. U.S.A.

Brief background: *Pathway from Wild-Type to Malignant Crypt*

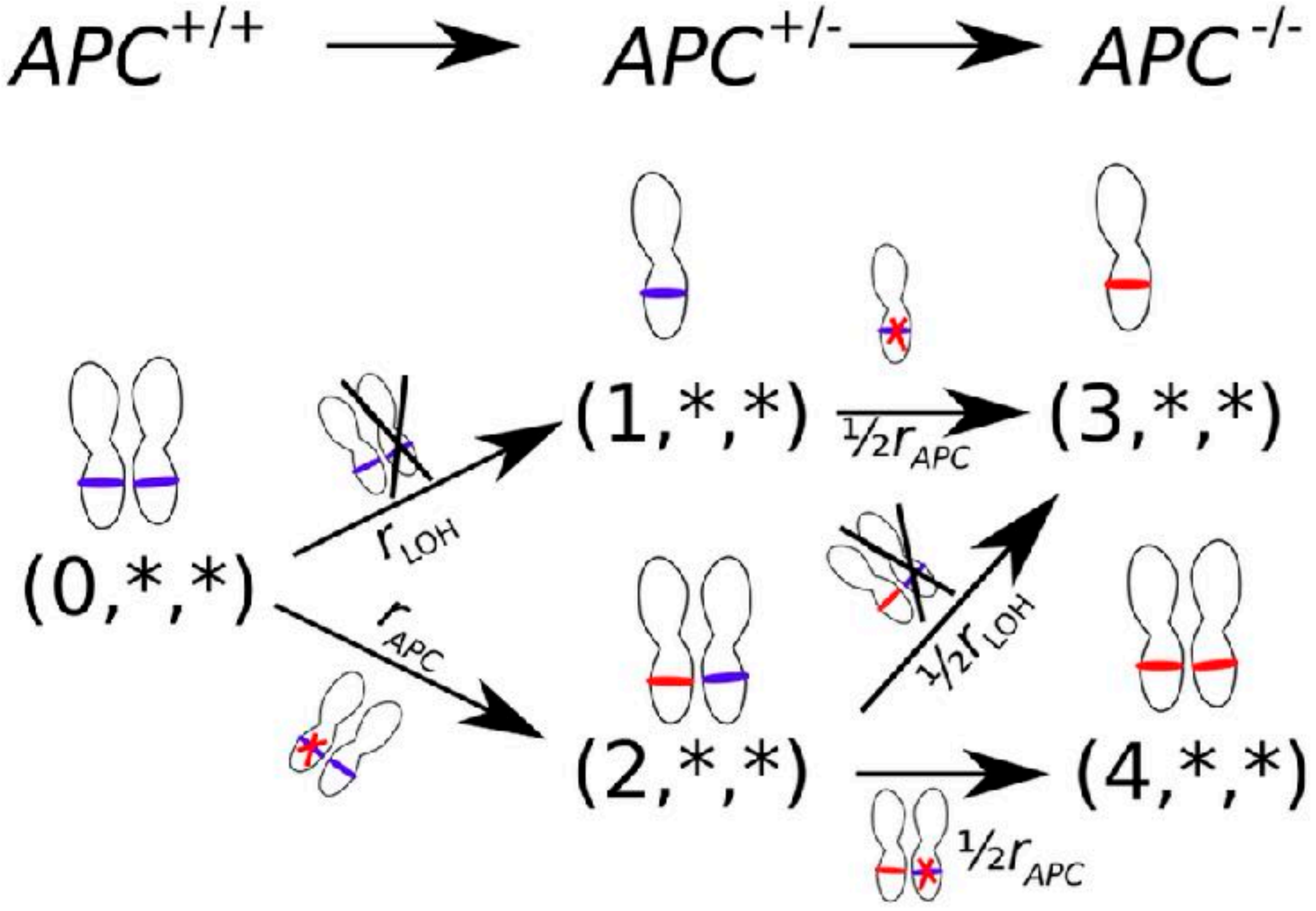
Colorectal Cancer initiation:

A crypt (not a single cell) accumulates the three gene mutations: ***APC***$^{-/-}$, ***TP53***$^{-/-}$, ***KRAS***$^{+}$.

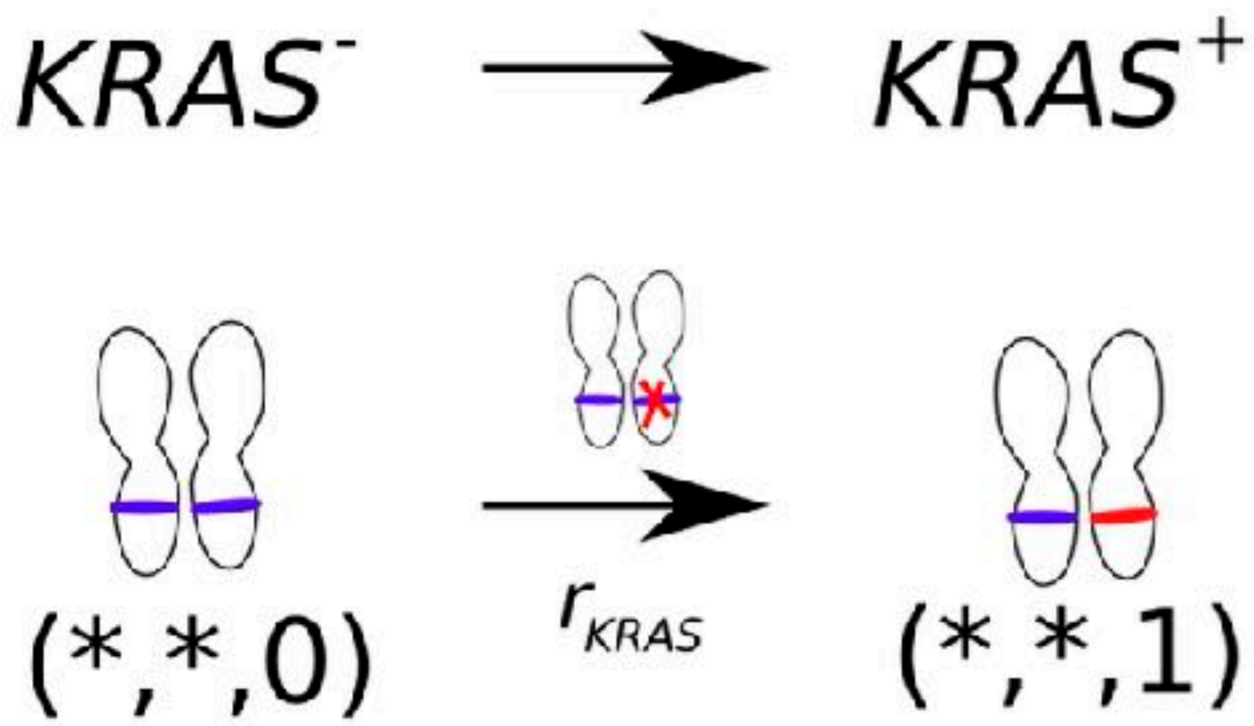


Brief background: *Transition Rates and Genetic Changes in Each Gene*

Gene inactivation:

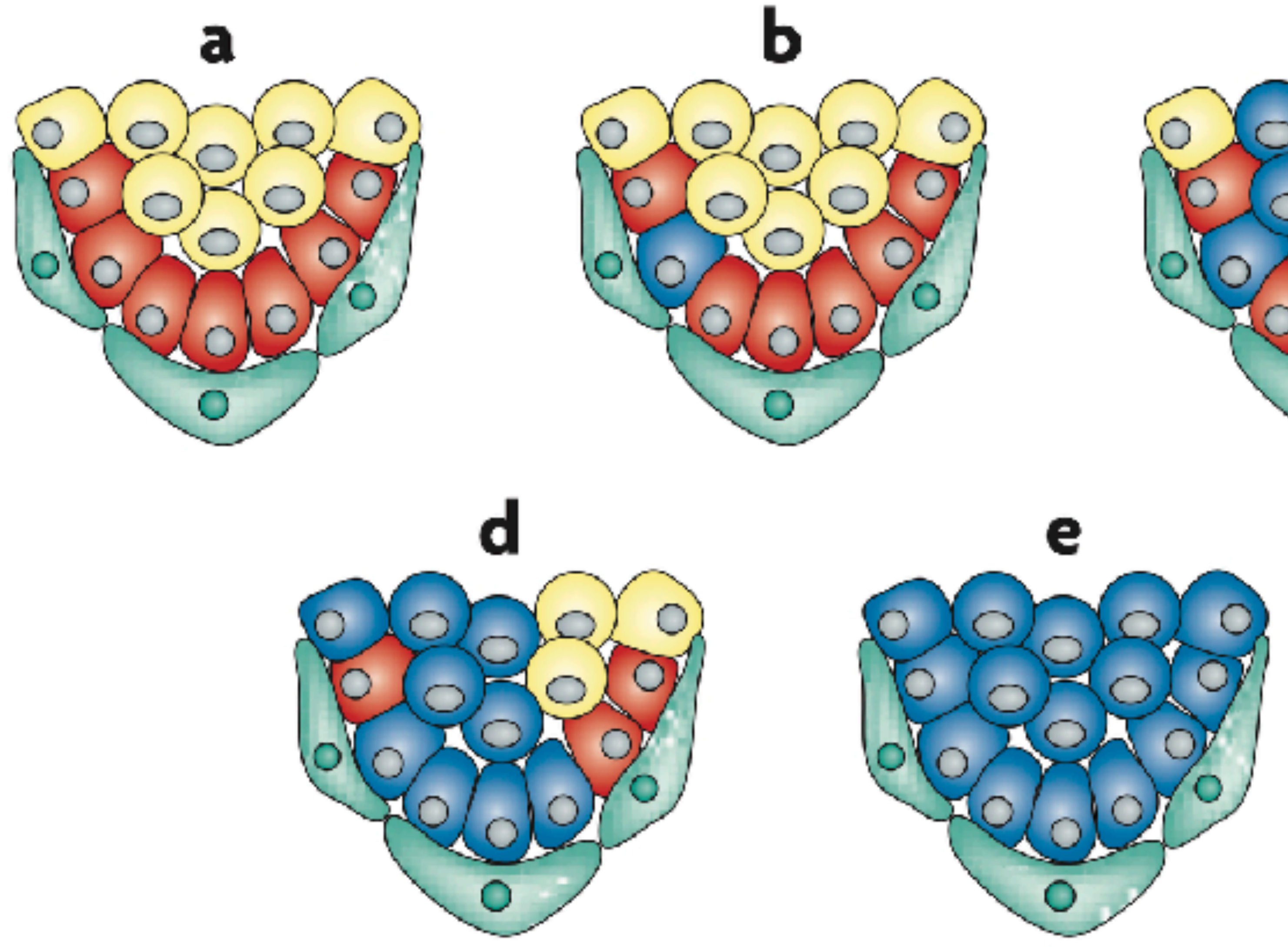


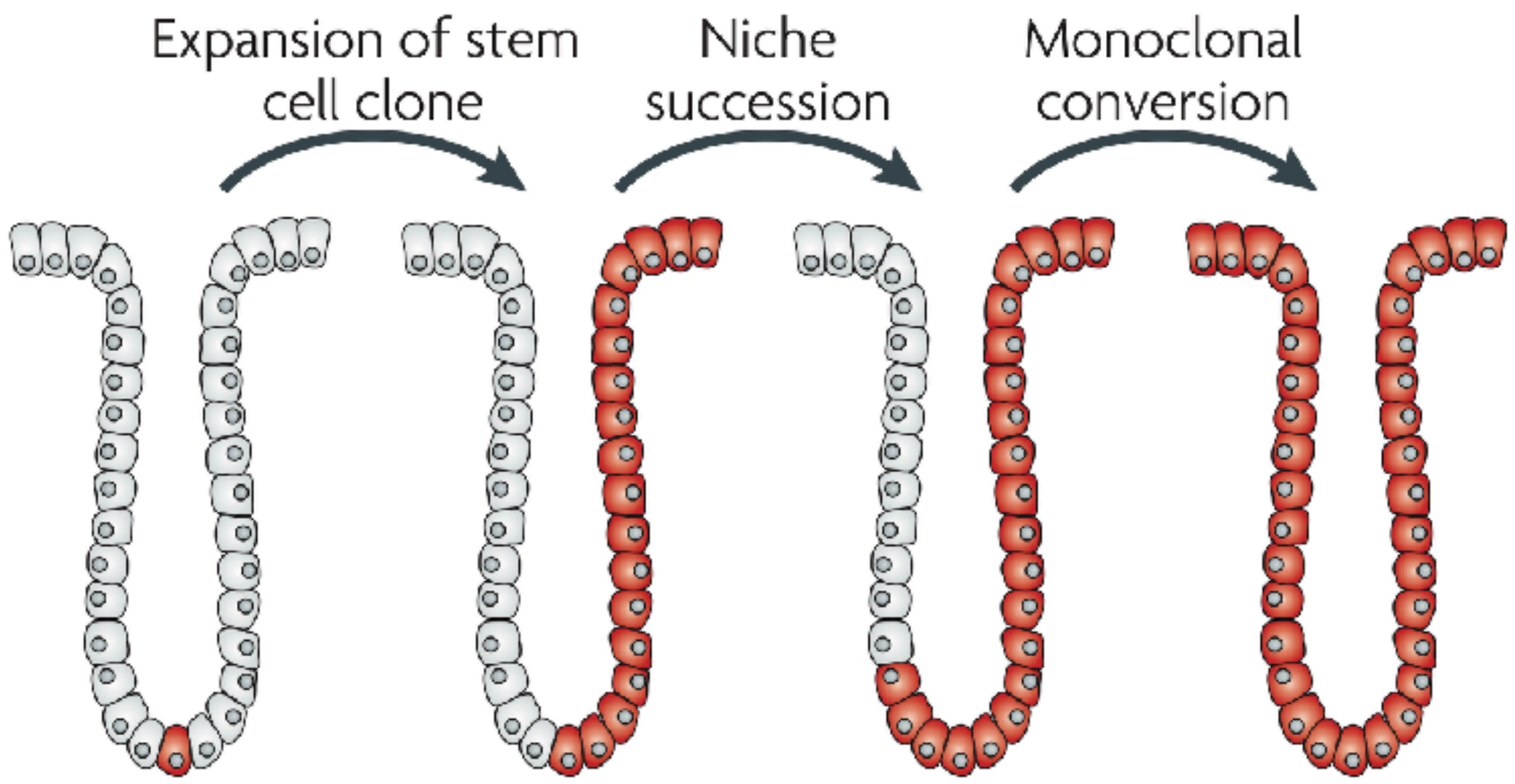
Gene activation:



Gene mutation rate: *r*

Crypt Growth Rates in Colorectal Cancer Progression





APC$^{-/-}$, ***KRAS***$^{+}$ bring growth advantage

N : Crypt number
b : Crypt growth rate

Humphries, A., & Wright, N. A. (2008). *Colonic crypt organization and tumorigenesis.* Nature Reviews Cancer, 8(6), 415–424.

Mathematical Model

Growth Advantage from *APC* and *KRAS* Mutations is Essential for *CRC* Initiation.

***P*(*t*)** : The probability that at least one cancerous crypt is present by time.

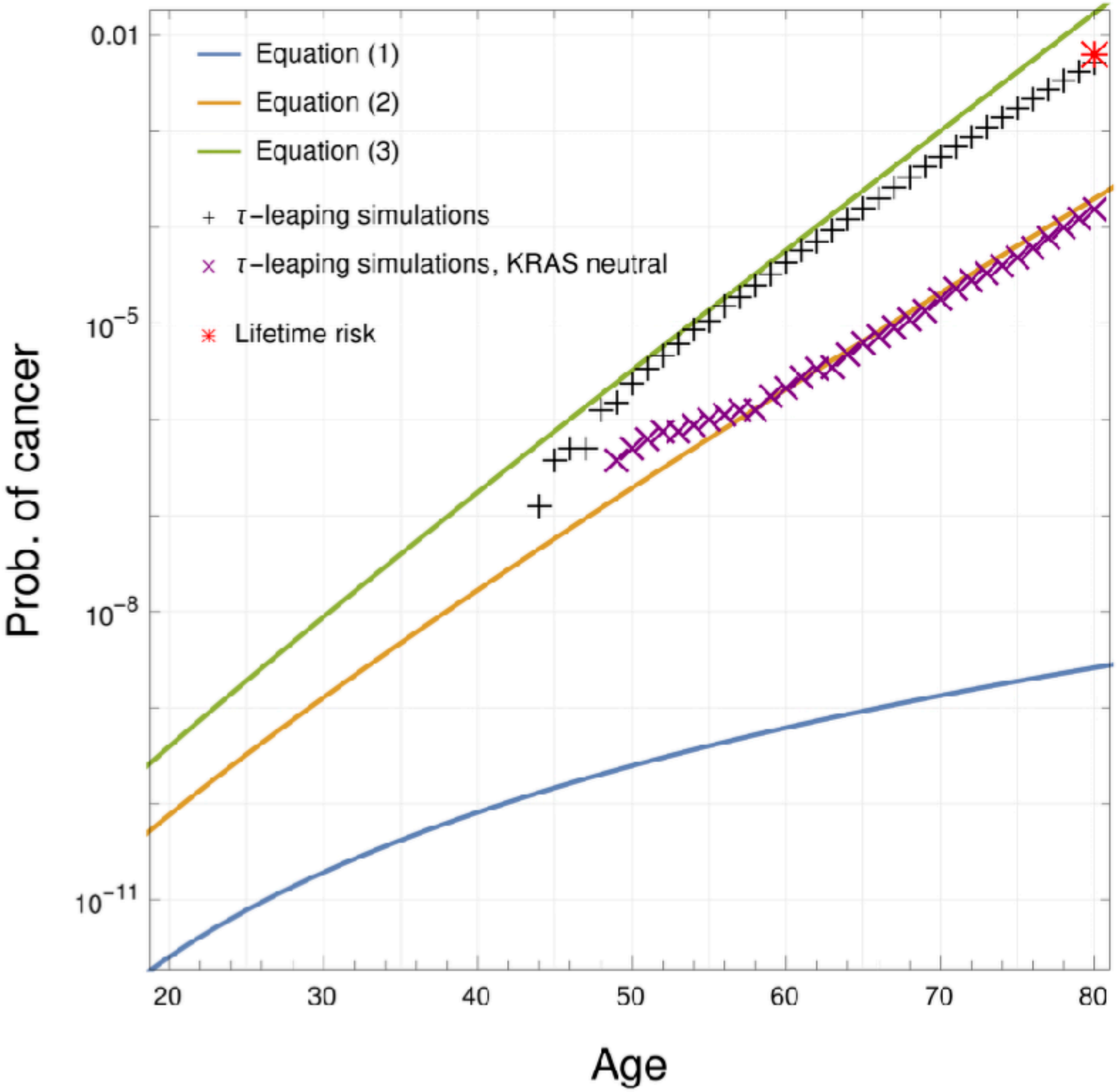
$$P(t) = 1 - \exp\left(-\int \left(\frac{1}{2} r_{LOH} n_{231} + \frac{1}{2} r_{APC} n_{131} + \frac{1}{2} r_{LOH} n_{321} + \frac{1}{2} r_{TP53} n_{311} + r_{KRAS} n_{330}\right) dt\right)$$

Mathematical Model

***P*(*t*)** : The probability that at least one cancerous crypt is present by time.

Equation (1)

$$P(t) \approx N r_{APC} r_{TP53} r_{KRAS} r_{LOH}^{2} \frac{t^5}{4}$$

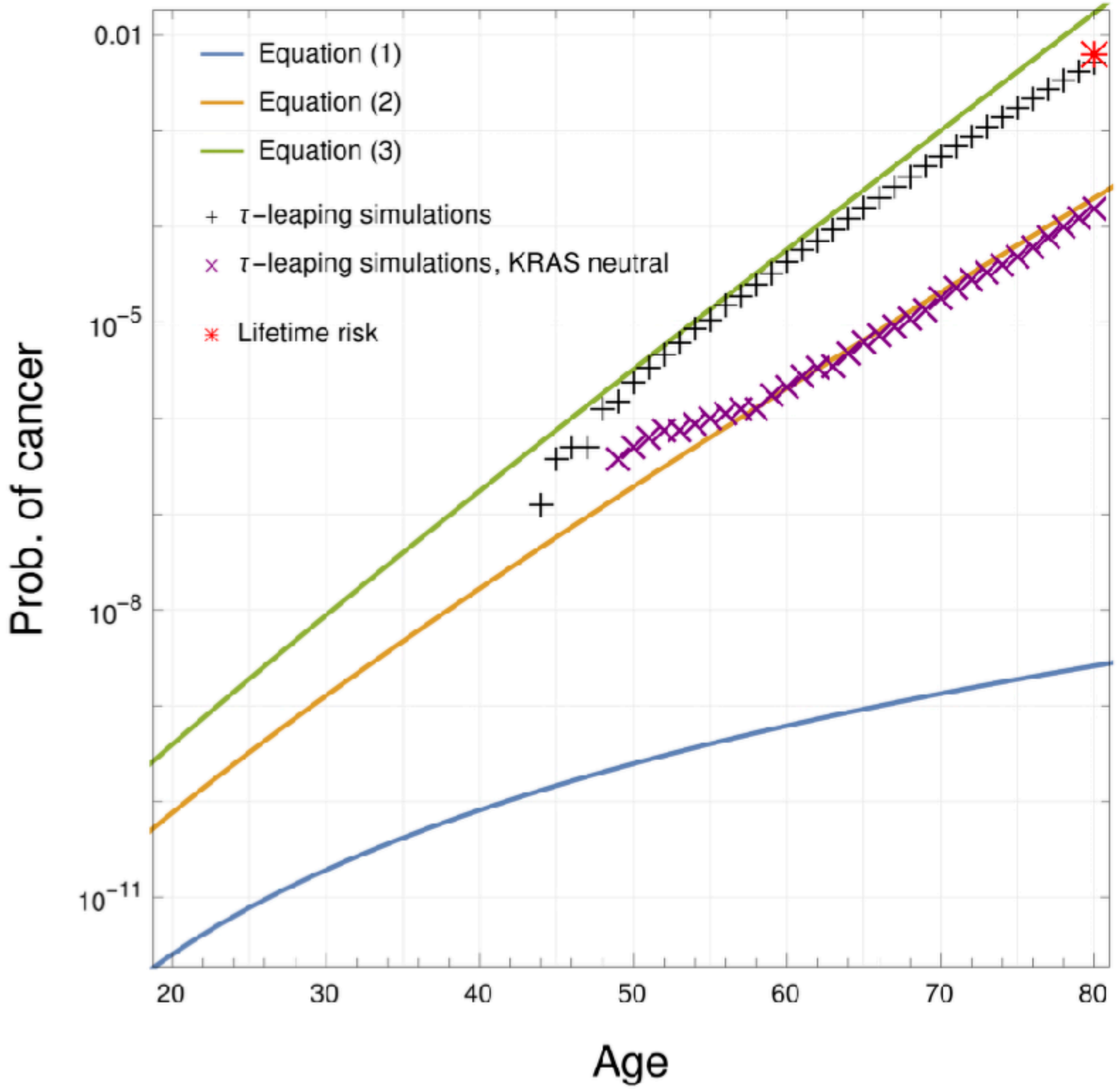


Mathematical Model

***P*(*t*)** : The probability that at least one cancerous crypt is present by time.

Equation (2)

$$P(t) \approx \frac{3}{2}\frac{N r_{APC} r_{KRAS} r_{LOH}^{2} r_{TP53} t^{2} e^{b_1 t}}{b_1^3}$$



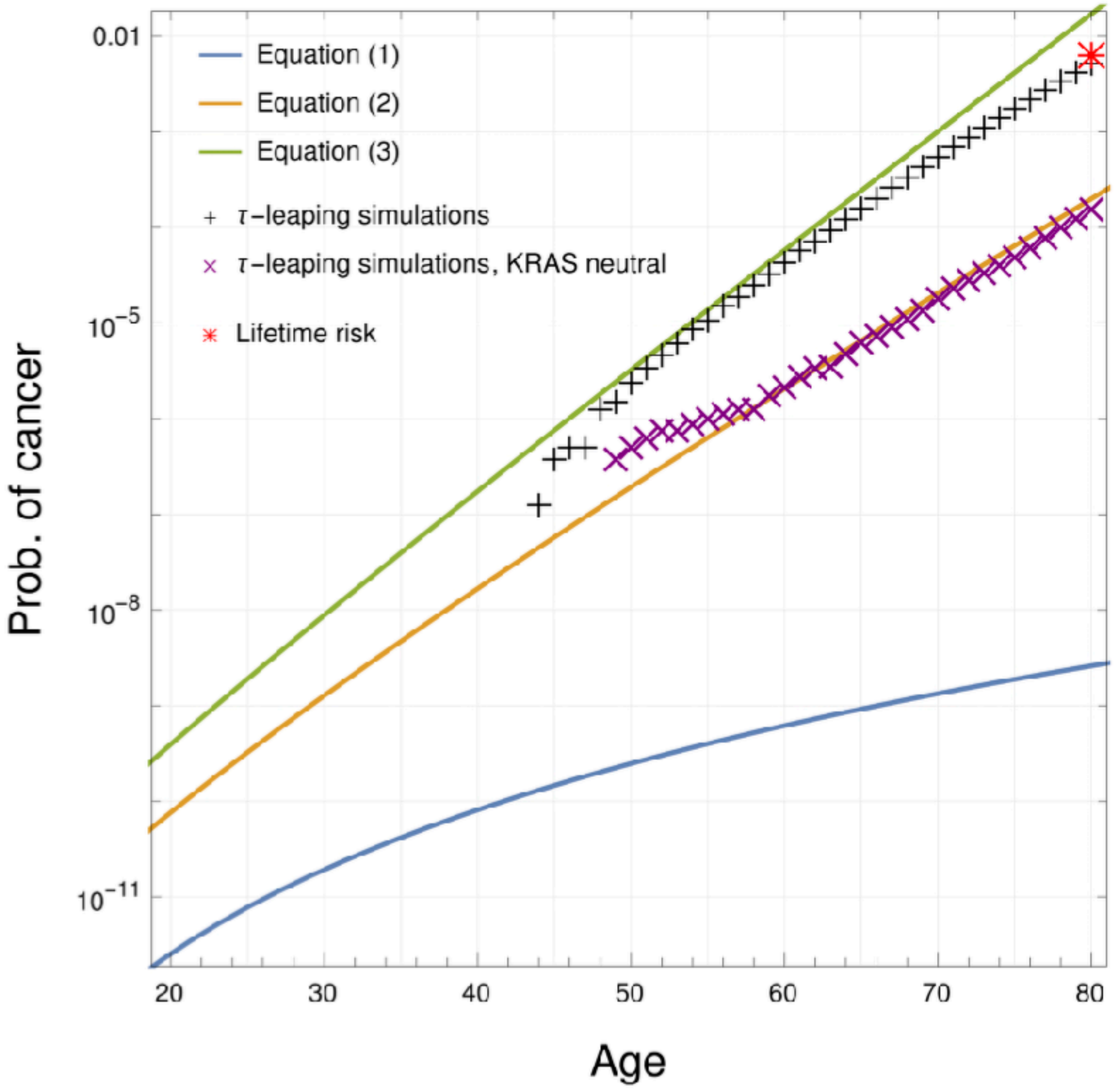
Mathematical Model

***P*(*t*)** : The probability that at least one cancerous crypt is present by time.

Equation (3)

$$P(t) \approx cNr_{APC}r_{TP53}r_{KRAS}r_{LOH}^2$$

$$\left(\frac{1}{b_{12}^3(b_{12}-b_1)}+\frac{1}{b_{12}^3(b_{12}-b_2)}+\frac{1}{b_{12}^2(b_{12}-b_2)^2}\right)te^{b_{12}t}$$



Mathematical Model

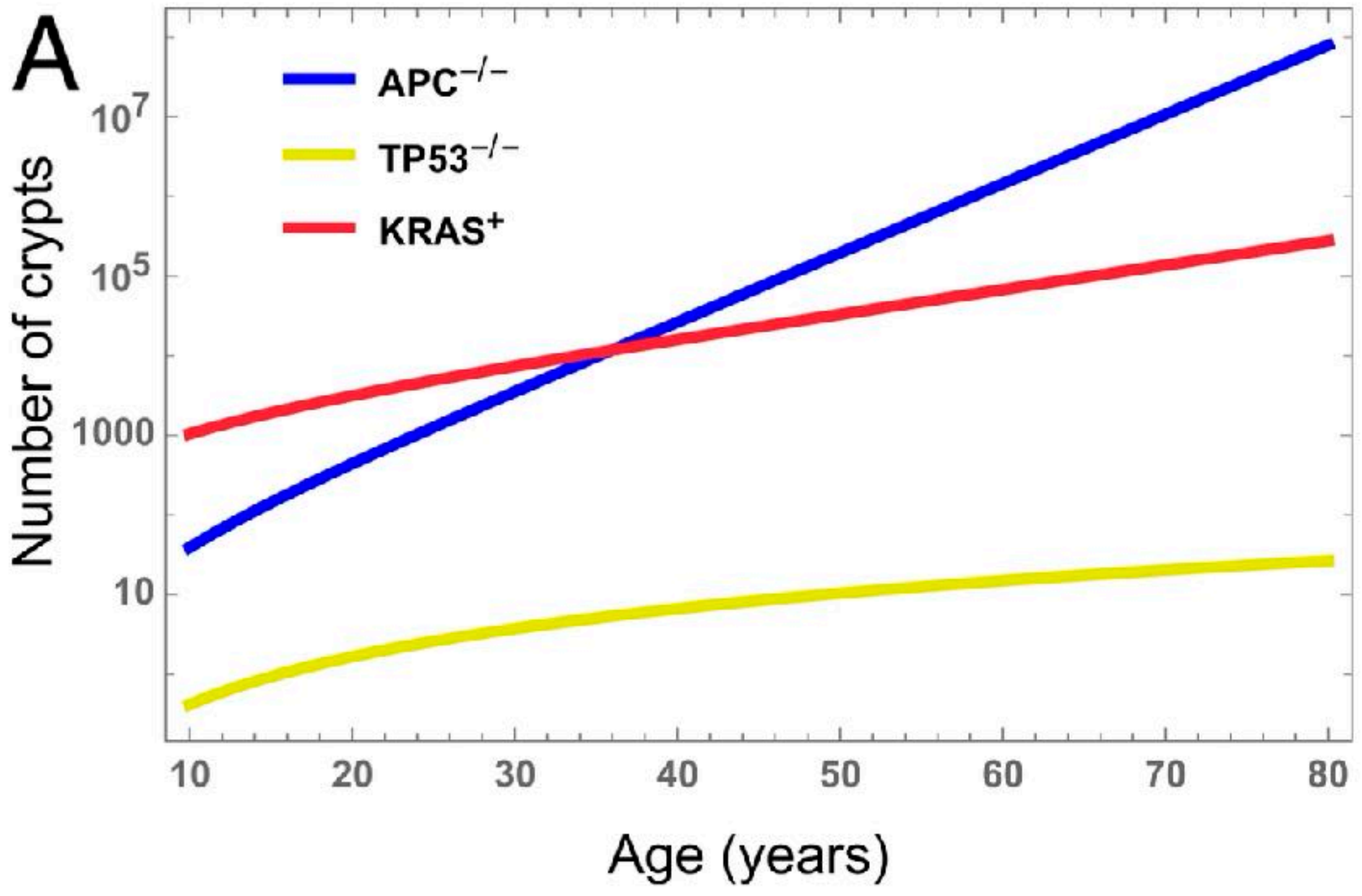
Number of Mutated crypts

of crypts for single-mutant:

$$C_{APC^{-/-}} \approx \frac{c_1 N r_{APC} r_{LOH}(e^{b_1 t} - b_1 t - 1)}{b_1^2}$$

$$C_{TP53^{-/-}} \approx \frac{N r_{TP53} r_{LOH} t^2}{2}$$

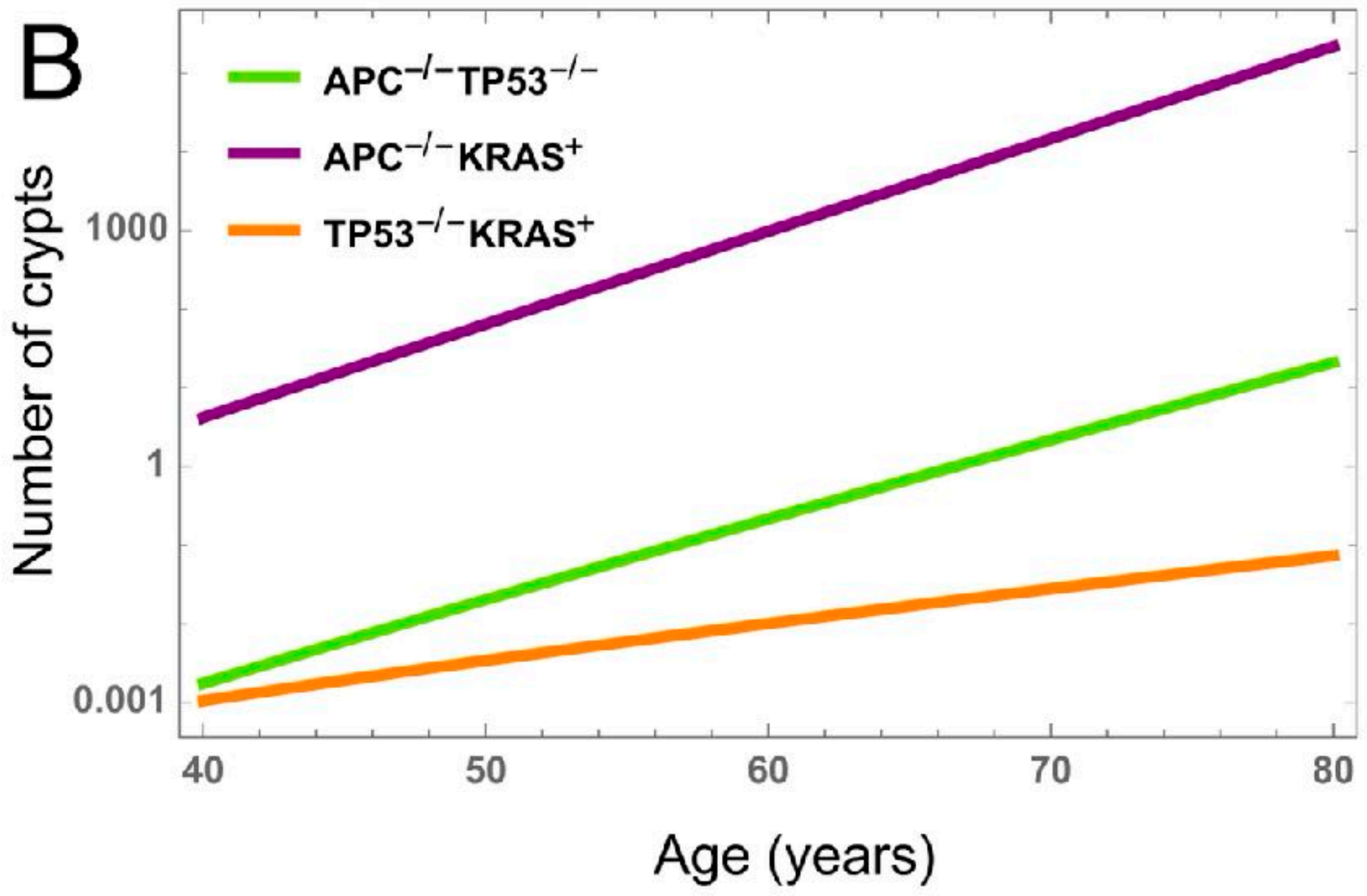
$$C_{KRAS^{+}} \approx \frac{c_2 N r_{KRAS}(e^{b_2 t} - 1)}{b_2}$$



Mathematical Model

Number of Mutated crypts

of crypts for double-mutant:



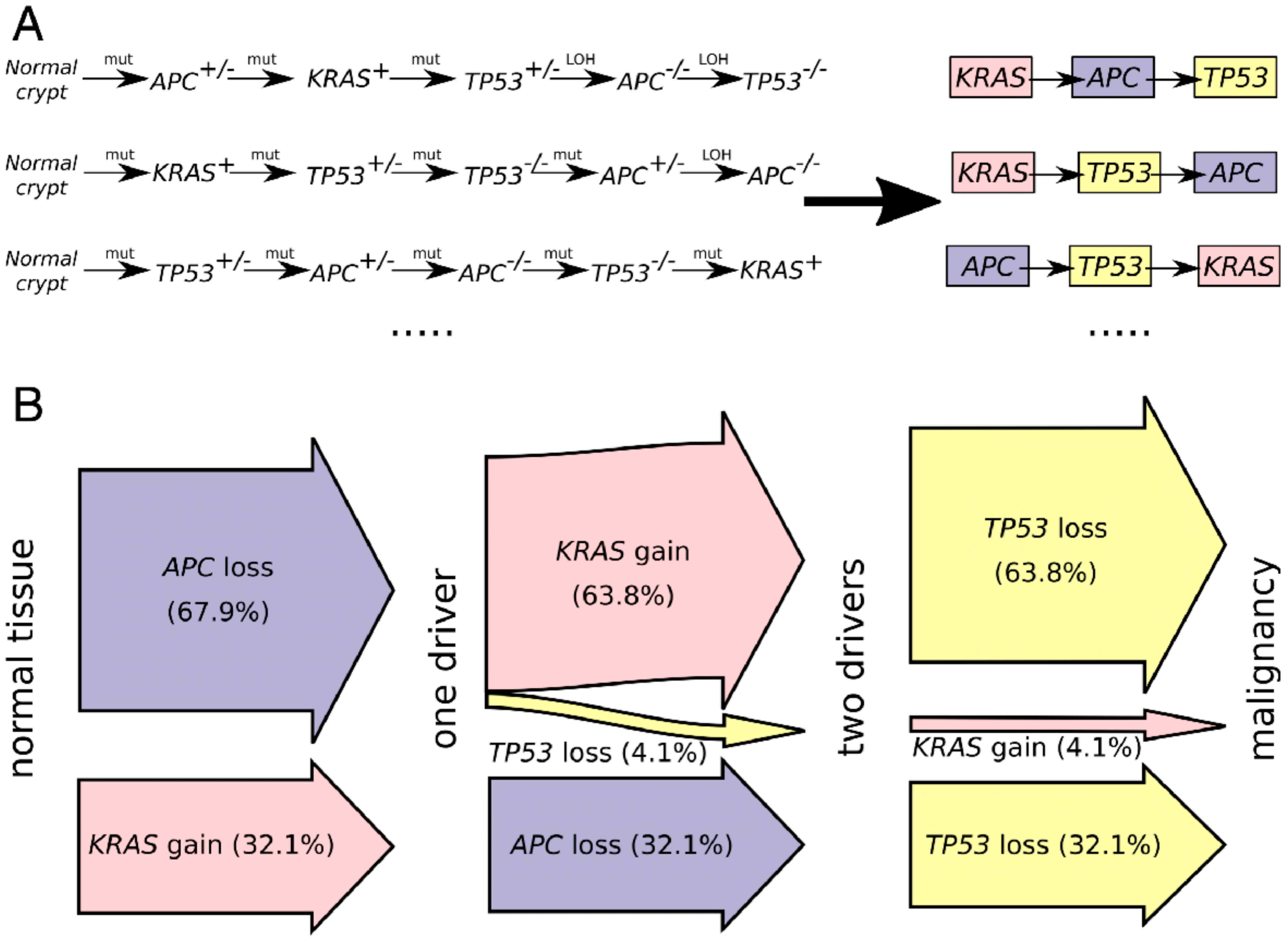
$$C_{APC^{-/-}TP53^{-/-}} \approx \frac{c_1 N r_{APC} r_{TP53} r_{LOH}^2 t^2 (e^{b_1 t} - b_1 t - 1)}{2 b_1^2}$$

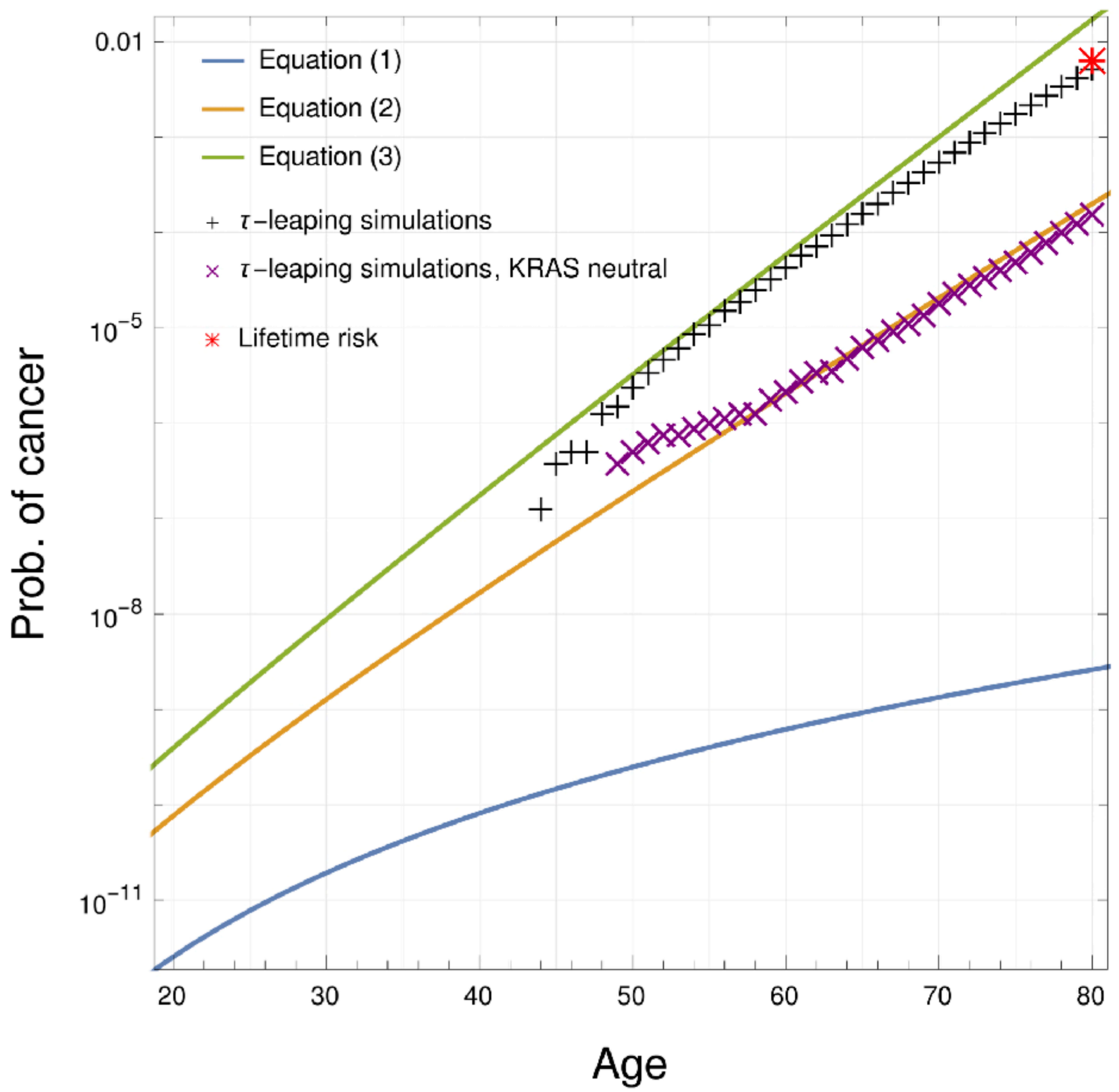
$$C_{APC^{-/-}KRAS^{+}} \approx$$

$$\frac{c N r_{APC} r_{KRAS} r_{LOH} (2 b_1 b_{12} - 3 b_{12}^2 - b_1 b_2 + 3 b_{12} b_2 - b_2^2) e^{b_{12} t}}{(b_1 - b_{12}) b_{12}^2 (b_{12} - b_2)^2}$$

$$C_{TP53^{-/-}KRAS^{+}} \approx \frac{c_2 N r_{KRAS} r_{TP53} r_{LOH} t^2 (e^{b_2 t} - 1)}{2 b_2}$$

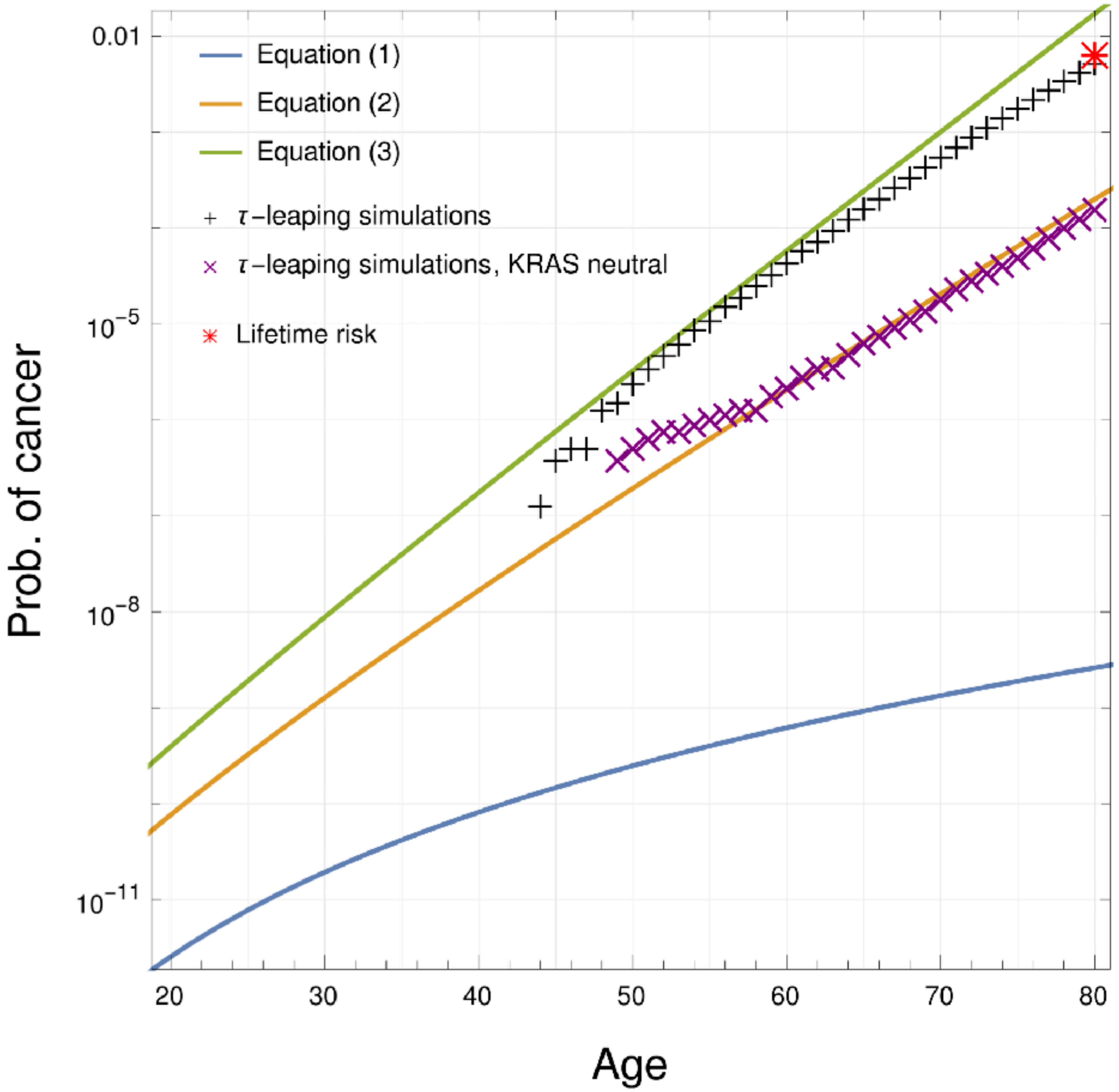
Mathematical Model





Equation (1)
Equation (2)
Equation (3)
τ−leaping simulations
τ−leaping simulations, KRAS neutral
Lifetime risk
0.01
10^{-5}
10^{-8}
10^{-11}
20
30
40
50
60
70
80
Prob. of cancer
Age

Innovation



Equation (3)

$$P(t) \approx cNr_{APC}r_{TP53}r_{KRAS}r_{LOH}^2$$

$$\left(\frac{1}{b_{12}^3(b_{12}-b_1)}+\frac{1}{b_{12}^3(b_{12}-b_2)}+\frac{1}{b_{12}^2(b_{12}-b_2)^2}\right) te^{b_{12}t}$$

Explore the corresponding change in long-term cancer risk in response to change of *b (growth advantage)* **of different genes.**

Innovation

$$\begin{pmatrix} a_{1,1} & a_{1,2} & a_{1,3} & a_{1,4} & \cdots & a_{1,20} \\ a_{2,1} & a_{2,2} & a_{2,3} & a_{2,4} & \cdots & a_{2,20} \\ a_{3,1} & a_{3,2} & a_{3,3} & a_{3,4} & \cdots & a_{3,20} \\ a_{2,1} & a_{2,2} & a_{2,3} & a_{2,4} & \cdots & a_{2,20} \\ \vdots & \vdots & \vdots & \vdots & \cdots & \vdots \\ a_{20,1} & a_{20,2} & a_{20,3} & a_{20,4} & \cdots & a_{20,20} \end{pmatrix}^N$$

Inspired by Leslie Matrix

Innovation

$$\begin{pmatrix} a_{1,1} & a_{1,2} & a_{1,3} & a_{1,4} & \cdots & a_{1,20} \\ a_{2,1} & a_{2,2} & a_{2,3} & a_{2,4} & \cdots & a_{2,20} \\ a_{3,1} & a_{3,2} & a_{3,3} & a_{3,4} & \cdots & a_{3,20} \\ a_{2,1} & a_{2,2} & a_{2,3} & a_{2,4} & \cdots & a_{2,20} \\ \vdots & \vdots & \vdots & \vdots & \cdots & \vdots \\ a_{20,1} & a_{20,2} & a_{20,3} & a_{20,4} & \cdots & a_{20,20} \end{pmatrix}^N \begin{pmatrix} 10^8 \\ 0 \\ 0 \\ 0 \\ \vdots \\ 0 \end{pmatrix} = \begin{pmatrix} \vdots \\ \vdots \\ \vdots \\ \vdots \\ \vdots \\ \vdots \end{pmatrix}$$

$\uparrow$ *Inspired by Leslie Matrix*

$\uparrow$ ***20 states***

$\uparrow$ ***20 states at age N***

Innovation

$$\left(\begin{pmatrix} b_{1,1} & 0 & 0 & \cdots & 0 & 0 \\ 0 & b_{2,2} & 0 & \cdots & 0 & 0 \\ 0 & 0 & b_{3,3} & \cdots & 0 & 0 \\ 0 & 0 & 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & 0 & 0 & b_{20,20} \end{pmatrix} \begin{pmatrix} a_{1,1} & a_{1,2} & a_{1,3} & a_{1,4} & \cdots & a_{1,20} \\ a_{2,1} & a_{2,2} & a_{2,3} & a_{2,4} & \cdots & a_{2,20} \\ a_{3,1} & a_{3,2} & a_{3,3} & a_{3,4} & \cdots & a_{3,20} \\ a_{2,1} & a_{2,2} & a_{2,3} & a_{2,4} & \cdots & a_{2,20} \\ \vdots & \vdots & \vdots & \vdots & \cdots & \vdots \\ a_{20,1} & a_{20,2} & a_{20,3} & a_{20,4} & \cdots & a_{20,20} \end{pmatrix}\right)^N \begin{pmatrix} 10^8 \\ 0 \\ 0 \\ 0 \\ \vdots \\ 0 \end{pmatrix} = \begin{pmatrix} \vdots \\ \vdots \\ \vdots \\ \vdots \\ \vdots \\ \vdots \end{pmatrix}$$

Growth Rate

Inspired by Leslie Matrix

20 states

20 states at age N

Innovation

$$\left(\underset{\text{Growth Rate}}{\begin{pmatrix} b_{1,1} & 0 & 0 & \cdots & 0 & 0 \\ 0 & b_{2,2} & 0 & \cdots & 0 & 0 \\ 0 & 0 & b_{3,3} & \cdots & 0 & 0 \\ 0 & 0 & 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & 0 & 0 & b_{20,20} \end{pmatrix}} \underset{\text{Inspired by Leslie Matrix}}{\begin{pmatrix} a_{1,1} & a_{1,2} & a_{1,3} & a_{1,4} & \cdots & a_{1,20} \\ a_{2,1} & a_{2,2} & a_{2,3} & a_{2,4} & \cdots & a_{2,20} \\ a_{3,1} & a_{3,2} & a_{3,3} & a_{3,4} & \cdots & a_{3,20} \\ a_{2,1} & a_{2,2} & a_{2,3} & a_{2,4} & \cdots & a_{2,20} \\ \vdots & \vdots & \vdots & \vdots & \cdots & \vdots \\ a_{20,1} & a_{20,2} & a_{20,3} & a_{20,4} & \cdots & a_{20,20} \end{pmatrix}}\right)^{80} \underset{\text{20 states}}{\begin{pmatrix} 10^8 \\ 0 \\ 0 \\ 0 \\ \vdots \\ 0 \end{pmatrix}} = \begin{pmatrix} \vdots \\ \vdots \\ \vdots \\ \vdots \\ \vdots \\ \vdots \end{pmatrix}$$

20 states at age 80

Next Plan

1. Working on recreating Plot 2
2. Innovation Part. I
3. Writing our project paper

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Many thanks!

Group Member

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