

W Mathematical model *of* *Colorectal Cancer Initiation*

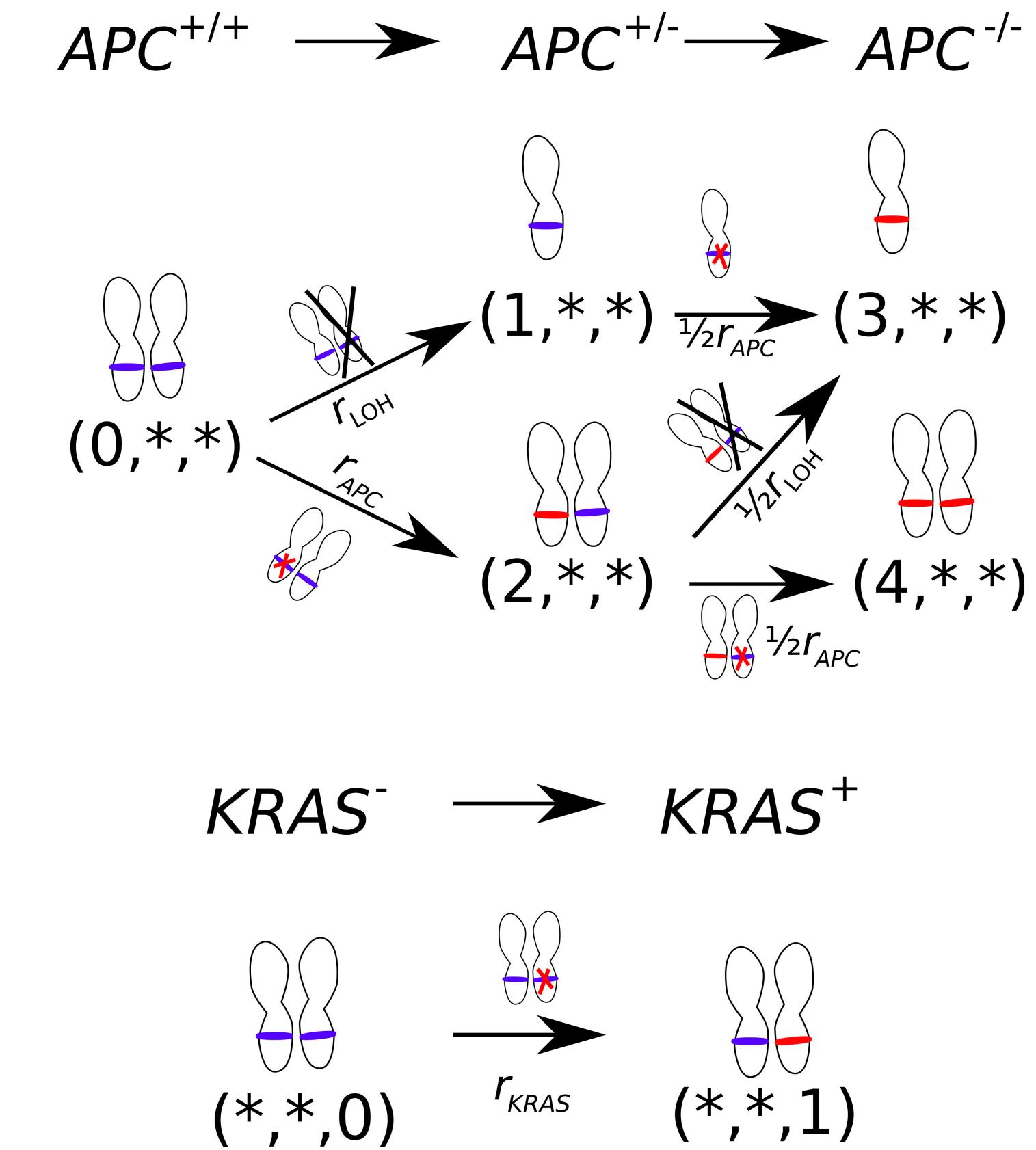
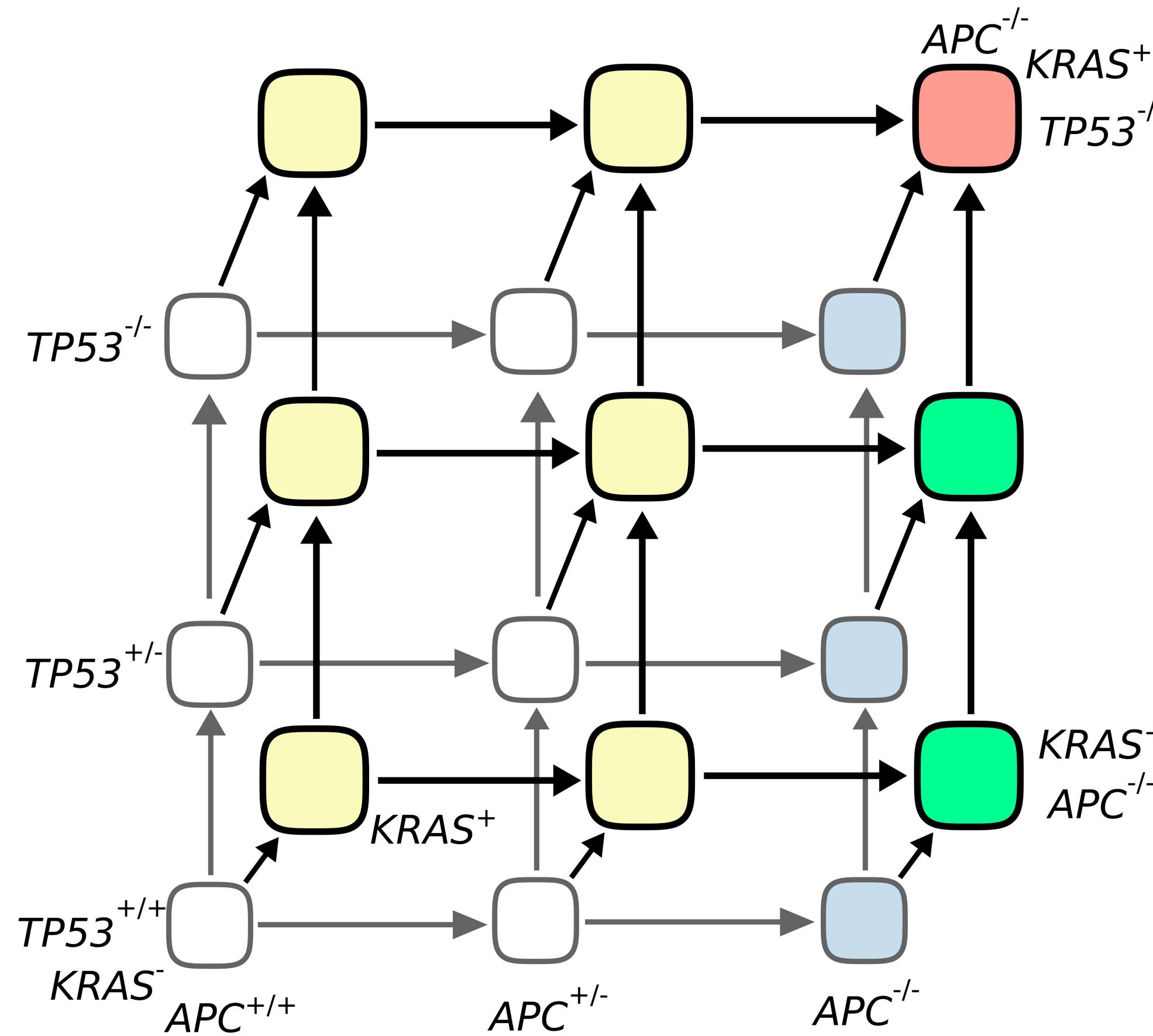
AMATH422 Project Presentation

Group Member

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Introduction



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Simulation of probability CRC Initiation

Tau-leaping method:

-Fixed Time Step (τ):

Advances the simulation in uniform time increments.

-Batch Event Sampling:

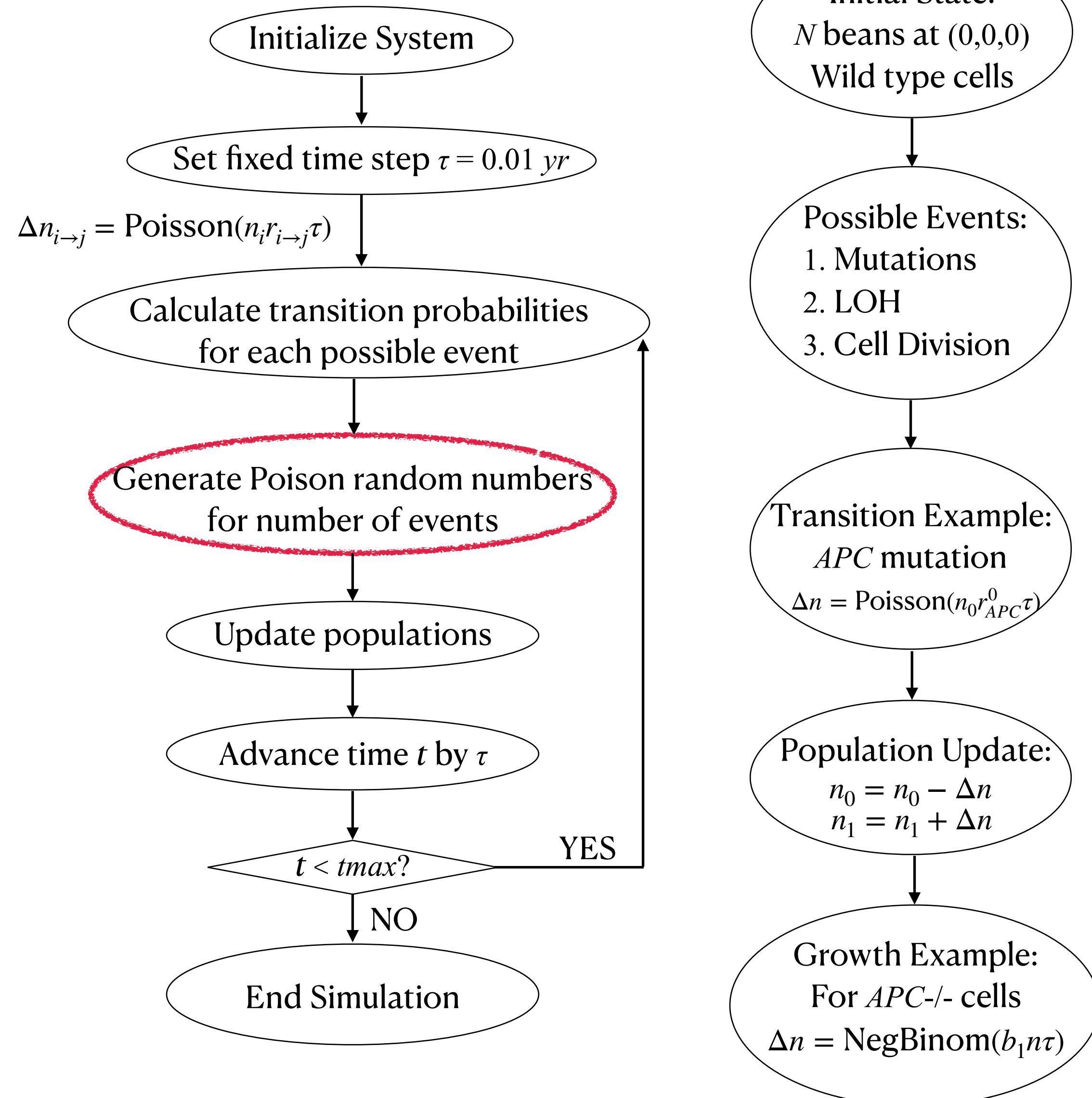
Uses *Poisson distributions* to approximate the number of events within τ .

-Bulk Updates:

Updates all population stages (crypt genotype) simultaneously for a single τ .

-Efficient for Frequent Events:

Handles high-frequency events (crypt fission)
probabilistically in one step.



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Basic ODE Function

$P(t)$ is the possibility that at least one cancerous crypt presents in the human body by time t .

r : the rate at a gene mutation/loss happens in one crypt.

n : the number of crypts involved in that mutation/loss at time t .

$$P'(t) = \left(\frac{1}{2}r_{LOH}n_{231} + \frac{1}{2}r_{APC}n_{131} + \frac{1}{2}r_{LOH}n_{321} + \frac{1}{2}r_{TP53}n_{311} + r_{KRAS}n_{330} \right)(1 - P(t))$$

The total rate for a particular gene mutation/loss event occurs at time t .

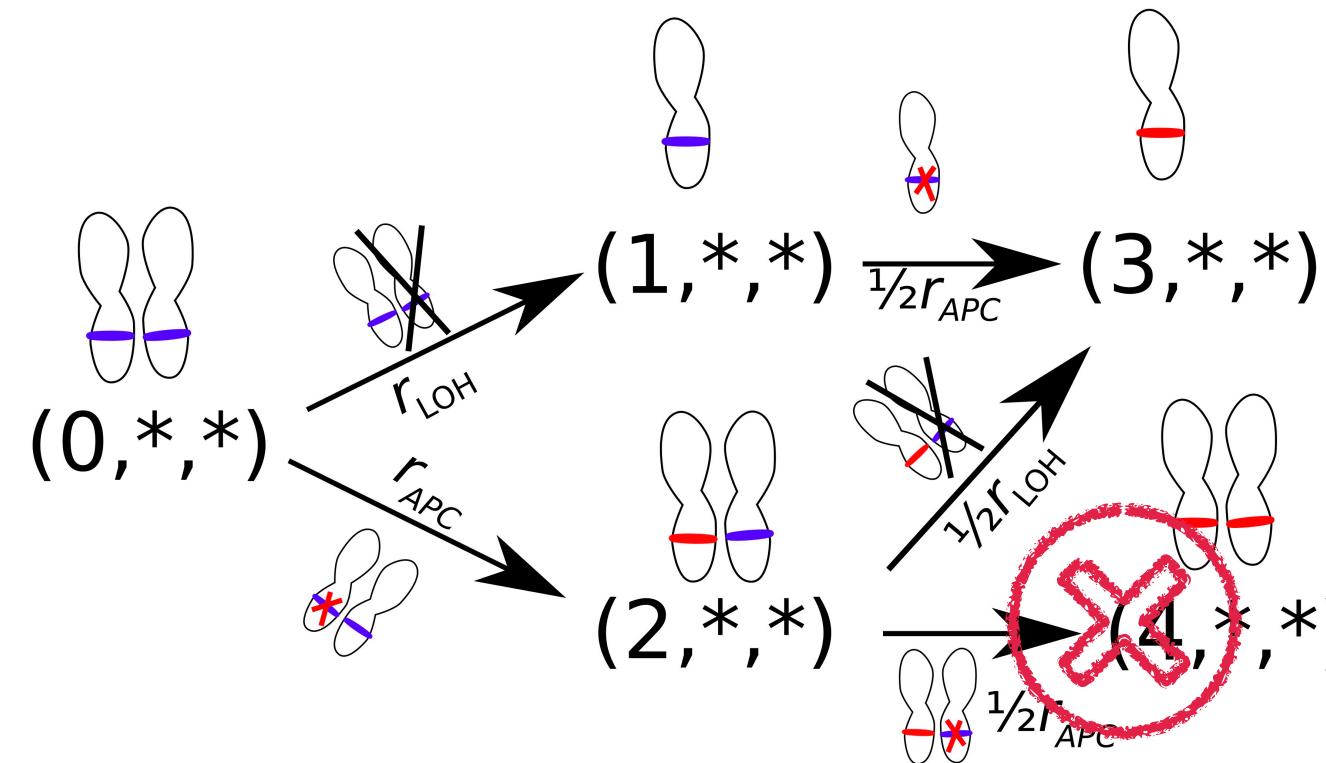
***Driver event:** All APC , $TP53$, and $KRAS$ in the crypt are mutated [crypt state:(3,3,1)].

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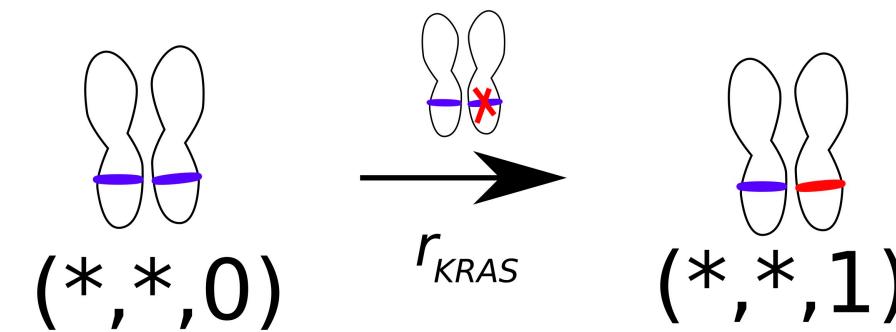
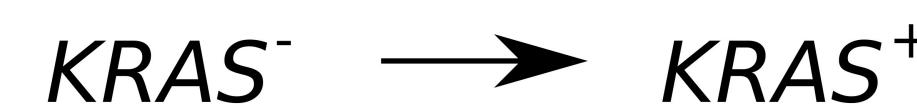
Matrix Approach: State Variables



$(APC, TP53, KRAS) \rightarrow \text{state } (x, y, z), \text{ where } x, y \in \{0,1,2,3\}, z \in \{0,1\}$



$4 \times 4 \times 2 = 32 \text{ variables}$



$$\begin{pmatrix} 10^8 \\ 0 \\ 0 \\ 0 \\ 0 \\ \vdots \end{pmatrix} \rightarrow \begin{pmatrix} (0,0,0) \\ (0,0,1) \\ (0,1,0) \\ (0,1,1) \\ (0,2,0) \\ (0,2,1) \\ \vdots \end{pmatrix}$$



We do not consider $(2,*,*) \rightarrow (4,*,*)$, which is discussed in the paper as an event that is nearly **impossible** to occur.

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Matrix Approach: Transition Matrix

$$\begin{pmatrix} a_{1,1} & a_{1,2} & \color{red}{r_{LOH}} & a_{1,4} & \cdots & a_{1,20} \\ a_{2,1} & a_{2,2} & a_{2,3} & a_{2,4} & \cdots & a_{2,20} \\ a_{3,1} & a_{3,2} & a_{3,3} & a_{3,4} & \cdots & a_{3,20} \\ a_{2,1} & a_{2,2} & a_{2,3} & a_{2,4} & \cdots & a_{2,20} \\ \vdots & \vdots & \vdots & \vdots & \cdots & \vdots \\ a_{32,1} & a_{32,2} & a_{32,3} & a_{32,4} & \cdots & a_{32,32} \end{pmatrix} \cdot \begin{pmatrix} 10^8 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \text{ or } \begin{pmatrix} (0,0,0) \\ (0,0,1) \\ (0,1,0) \\ (0,1,1) \\ (0,2,0) \\ (0,2,1) \\ \vdots \end{pmatrix}$$

Setup Example:

From State	To State	Transition Rate
(0, 0, 0)	(0, 1, 0)	r_{LOH}
(0, 0, 0)	(0, 2, 0)	r_{TP53}
...

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Matrix Approach: Growth Rate Matrix

$$\begin{pmatrix} b_{1,1} & 0 & 0 & \cdots & 0 & 0 \\ 0 & b_{2,2} & 0 & \cdots & 0 & 0 \\ 0 & 0 & b_{3,3} & \cdots & 0 & 0 \\ 0 & 0 & 0 & \cdots & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & 0 & 0 & b_{32,32} \end{pmatrix} \cdot \begin{pmatrix} 10^8 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \text{ or } \begin{pmatrix} (0,0,0) \\ (0,0,1) \\ (0,1,0) \\ (0,1,1) \\ (0,2,0) \\ (0,2,1) \\ \vdots \end{pmatrix}$$

$b_{i,i}$ represents the growth rate for state i .

$(APC, TP53, KRAS) \rightarrow \text{state } (x, y, z)$,

where $x, y \in \{0,1,2,3\}$, $z \in \{0,1\}$

Source of Growth Rates:

1. **b_{APC}**

APC gene mutation leads to complete functional loss ($APC \geq 3$).

2. **b_{KARS}**

$KRAS$ gene undergoes an activating mutation ($KRAS = 1$).

3. **b_{BOTH}**

Both APC and $KRAS$ mutations occur simultaneously.

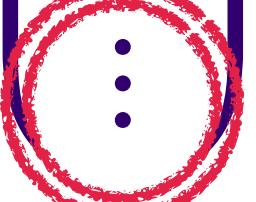
$APC \geq 3$ ($x \geq 3$) AND $KRAS = 1$ ($z \geq 3$)

* $TP53$ has no growth advantage.

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Matrix Approach:

$$\begin{pmatrix}
 b_{1,1} & 0 & 0 & \cdots & 0 & 0 \\
 0 & b_{2,2} & 0 & \cdots & 0 & 0 \\
 0 & 0 & b_{3,3} & \cdots & 0 & 0 \\
 0 & 0 & 0 & 0 & \cdots & 0 \\
 \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
 0 & 0 & 0 & 0 & 0 & b_{32,32}
 \end{pmatrix}
 \begin{pmatrix}
 a_{1,1} & a_{1,2} & a_{1,3} & a_{1,4} & \cdots & a_{1,20} \\
 a_{2,1} & a_{2,2} & a_{2,3} & a_{2,4} & \cdots & a_{2,20} \\
 a_{3,1} & a_{3,2} & a_{3,3} & a_{3,4} & \cdots & a_{3,20} \\
 a_{2,1} & a_{2,2} & a_{2,3} & a_{2,4} & \cdots & a_{2,20} \\
 \vdots & \vdots & \vdots & \vdots & \cdots & \vdots \\
 a_{32,1} & a_{32,2} & a_{32,3} & a_{32,4} & \cdots & a_{32,32}
 \end{pmatrix}
 \overset{\textcolor{red}{N}}{=}
 \begin{pmatrix}
 10^8 \\
 0 \\
 0 \\
 0 \\
 \vdots \\
 0
 \end{pmatrix}
 \quad
 \begin{array}{l}
 \text{Growth Rate Matrix} \\
 \text{Transition Matrix} \\
 \text{32 states} \\
 \text{32 states at age } \textcolor{red}{N}
 \end{array}$$



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Matrix Result Comparison

sets is set to $b_1 = 10^{-11}$. Division rates set to vantage: division of $KRAS^+$ crypts is faster than $APC^{-/-}KRAS^+$. These genotypes have a higher probability of double-mutant than assuming that APC and $KRAS$ mutations act additively and direction of mutation with confidence. In scenarios, we will see that mutations is not the main driver of CRC.

We are interested in how has collected all data from approximately 15% of the population (APC, TP53, KRAS) in adenocarcinoma. Comparing CRC cancer risk, we will compare our

simulations and

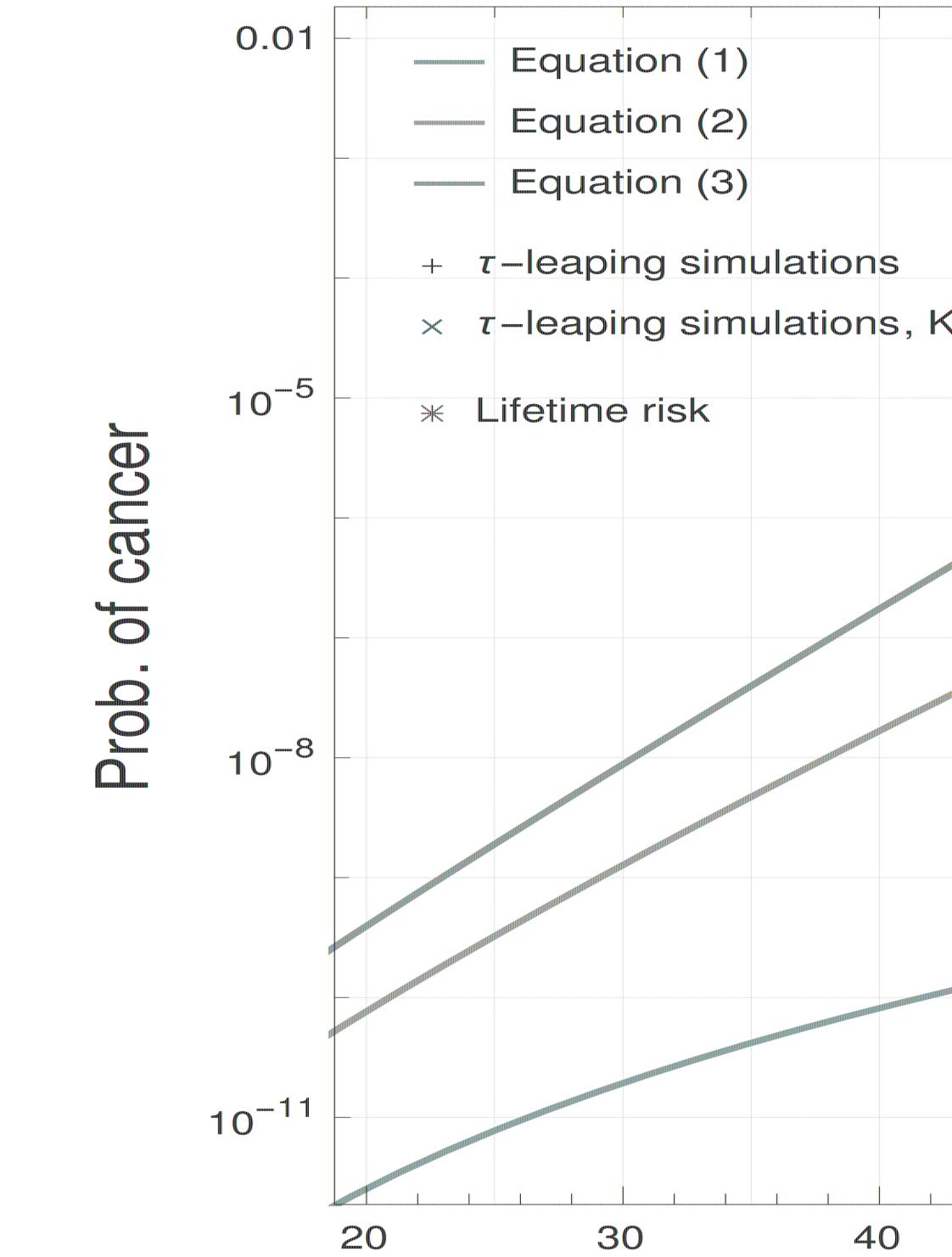
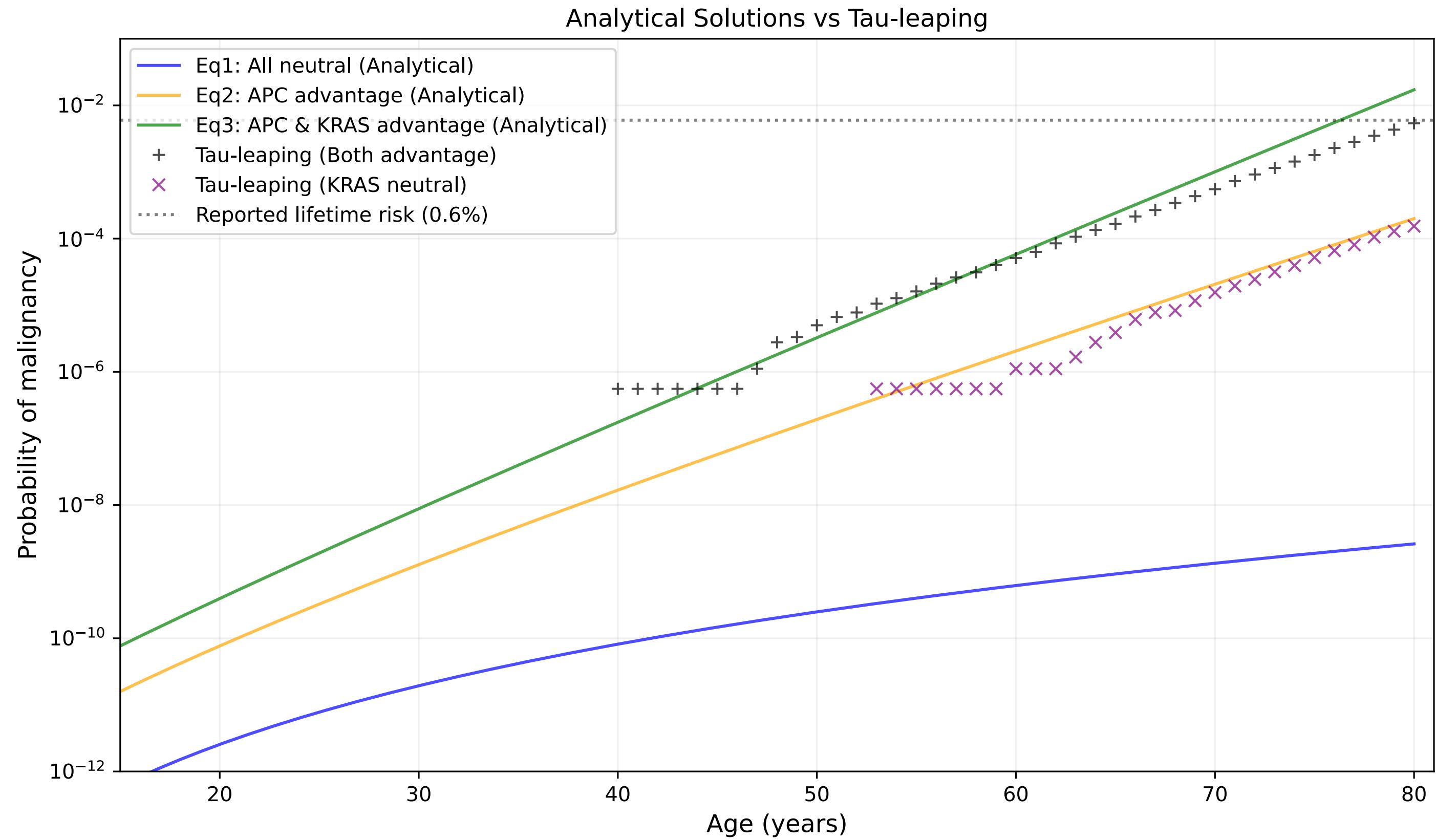


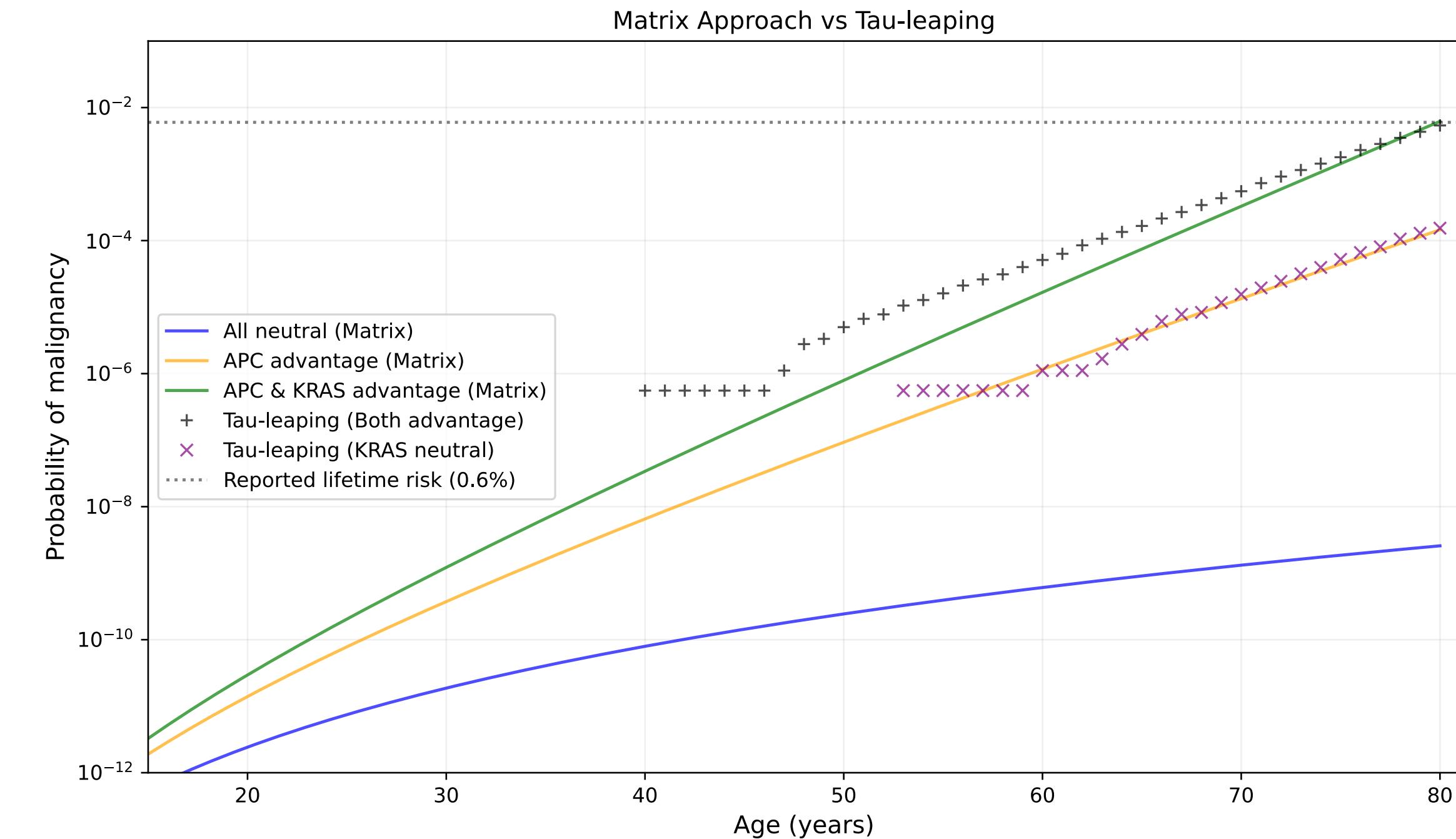
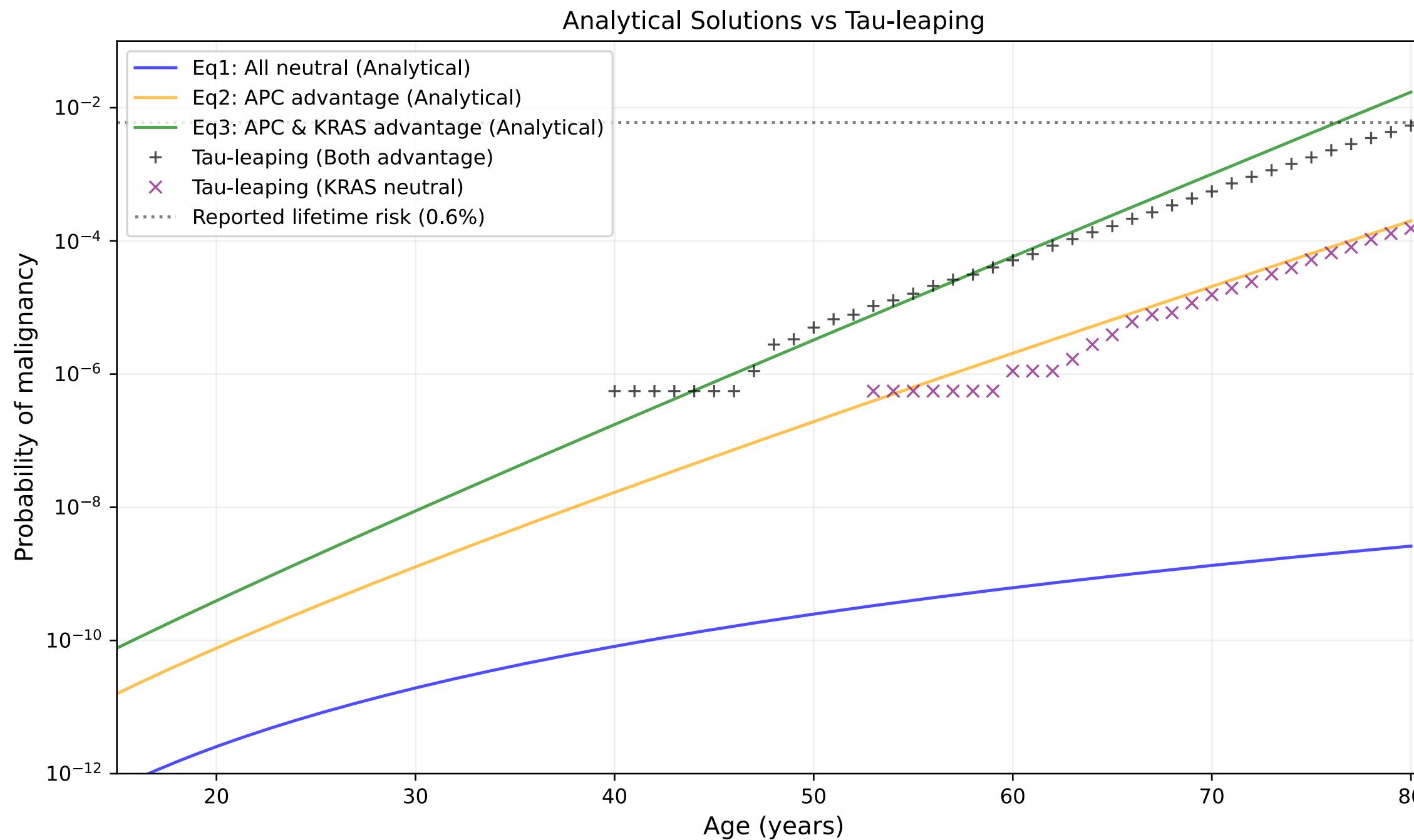
Figure in paper



Analytical Method

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Matrix Result Comparison

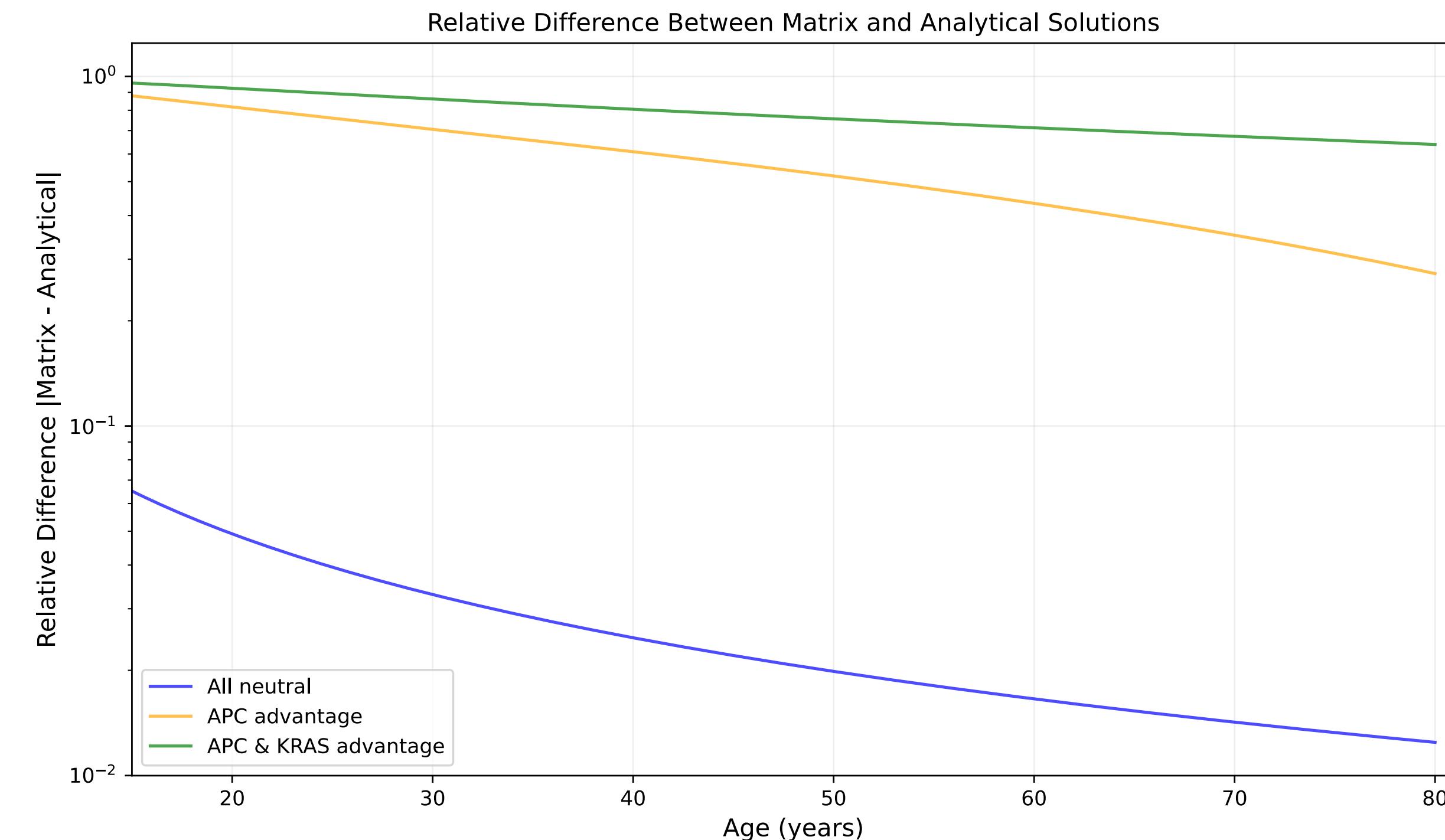
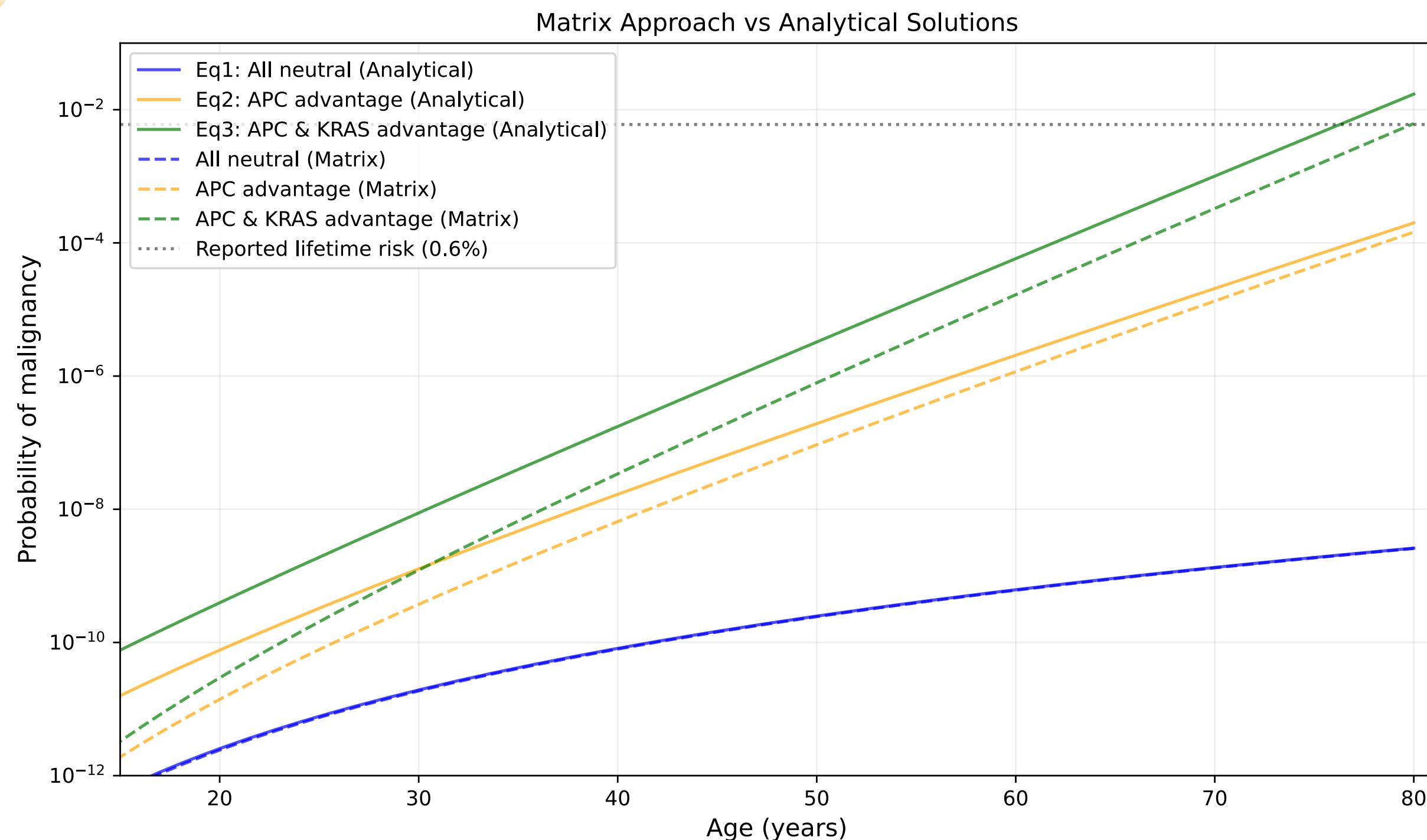


Analytical Method

Matrix Method

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Matrix Result Comparison



Analytical Method v.s. Matrix Method

Relative Error

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Future Work

1. Analyze the reasons behind the differences between the two methods.
2. Conduct a matrix analysis to check for any hidden properties.
3. Attempt to implement our own *tau-leaping* simulation in Python.

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Many thanks!

Good luck on finals :)

Group Member

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