Evaluation of Screening Strategies for Pre-malignant Lesions using a Biomathematical Approach

Mathematical Modelling Approaches for Cancer Mortality

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Motivation

Colorectal Cancer (CRC)

- Estimated deaths in the US in 2018: 50 630[1]
- Colonoscopies offer a method for screening and intervention

[1] National Cancer Institute. *Cancer Stat Facts: Colorectal Cancer*. 2018. URL: https://seer.cancer.gov/statfacts/html/colorect.html.

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- Colonoscopies offer a method for screening and intervention
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$\Rightarrow$ a biomathematical model can help to choose good screening strategies

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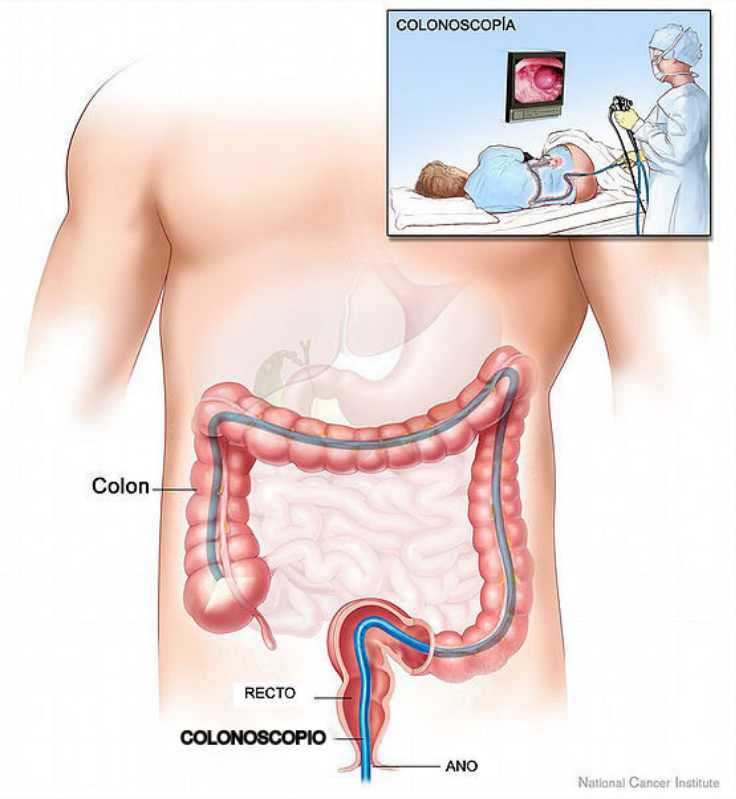
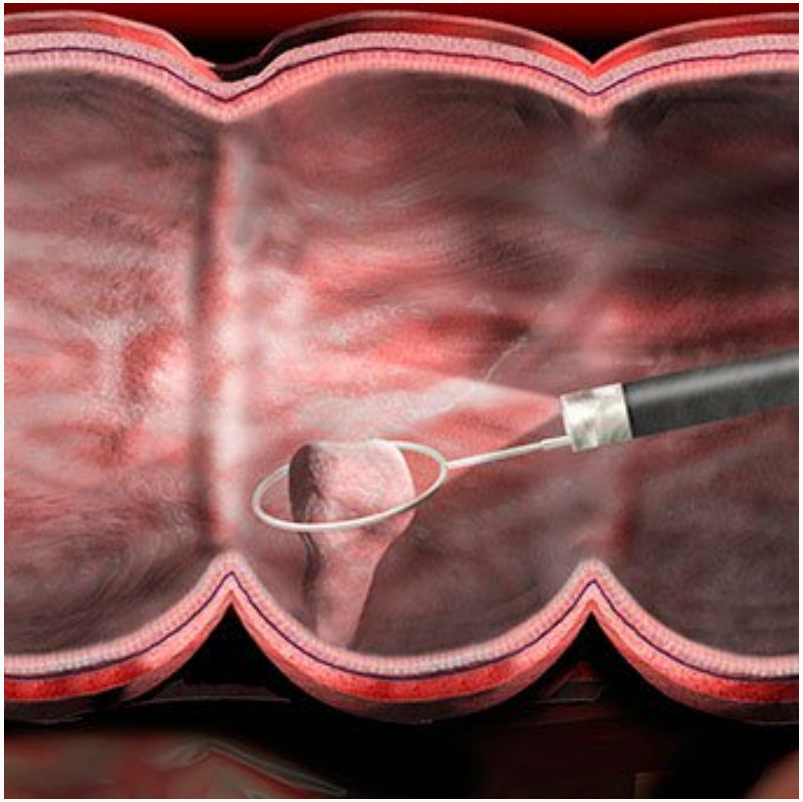


(a) Overview [2].



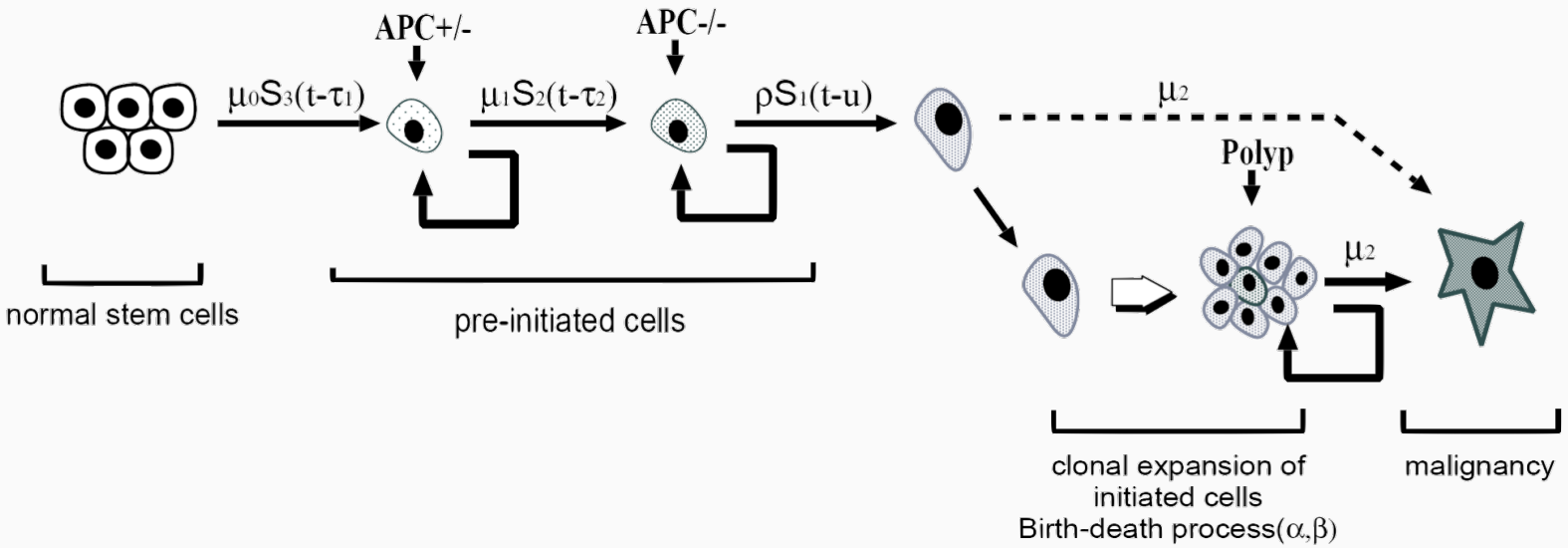
(b) Removal of polyp [6].

Figure 1: Colonoscopy: screening and intervention.

Biological Model

Colorectal Cancer Model

- Luebeck & Moolgavkar propose a 4 stage MSCE model [5]
- APC gene is a cancer suppressor
- Two mutations and one positional effect lead to clonal expansion



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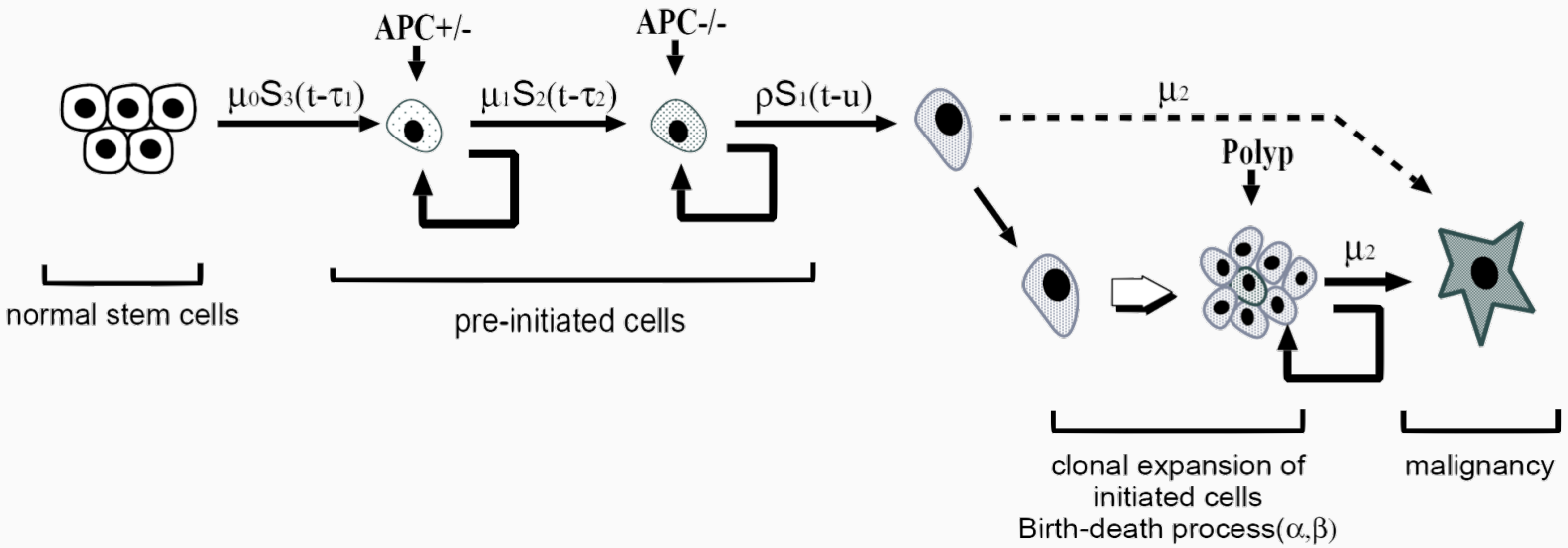

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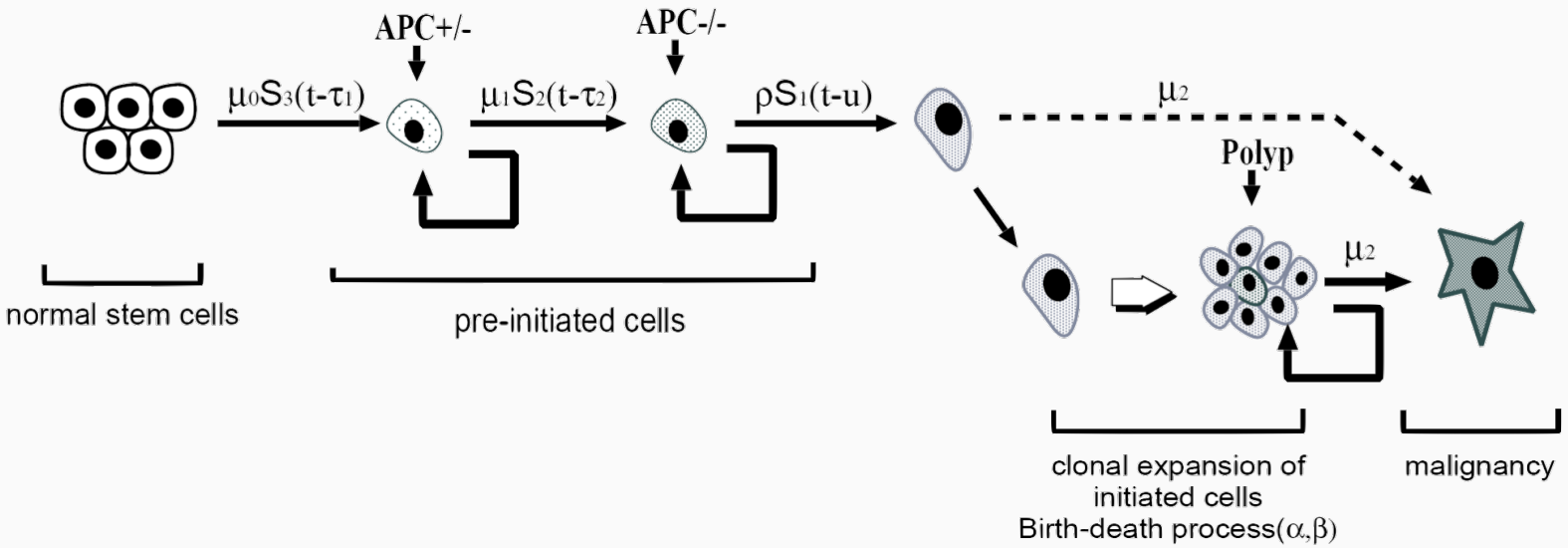

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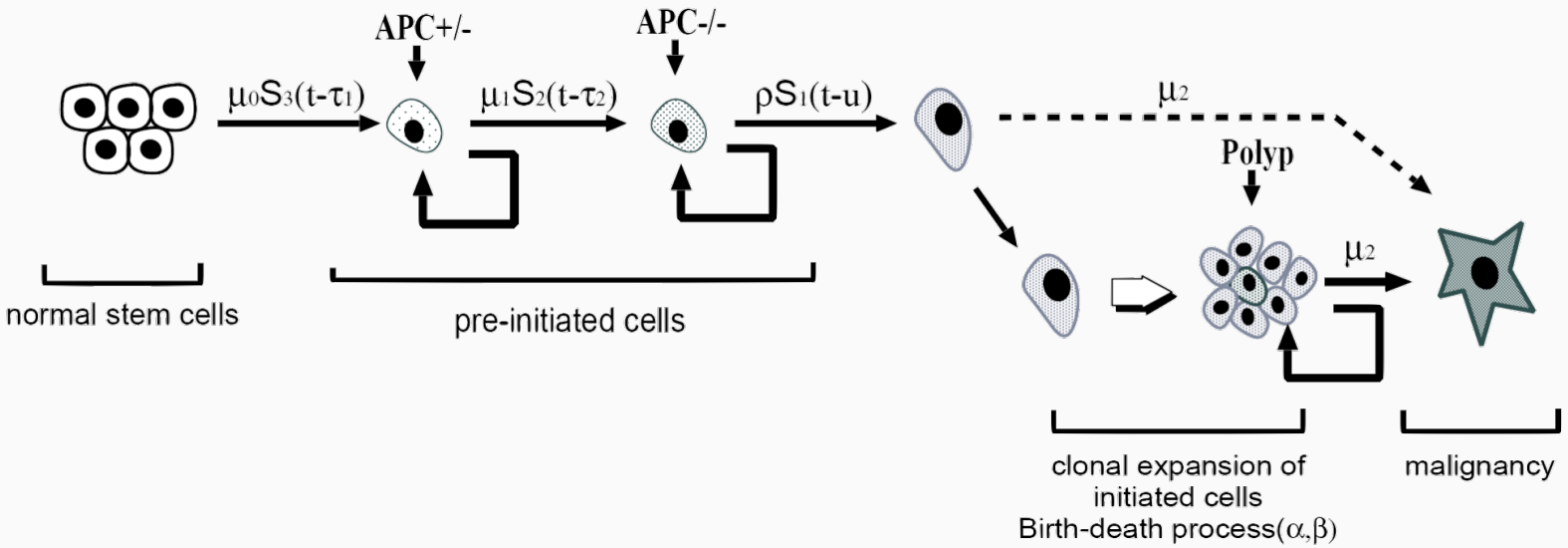

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Mathematical Model

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- At screening we only consider individuals without malignant cells
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- Need to evaluate hazard/survival function after screening and different possible interventions, e.g. (in)complete removal of polyps

$\Rightarrow$ Different screening strategies can be compared against each other

Mathematical Model

TSCE Model

Definitions

Clone All pre-malignant cells that are produced through a birth-death process from one initiated cell. Size $Y(u, t)$, initiation time u.

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$Z(t)$ Indicator for clinical cancer, i.e. at least one malignant cell. $Z(t) \in \{0, 1\}$.

Clone: Conditional Size Distribution

$$P^*\left[Y(u,t)=n\right]=Pr\left[Y(u,t)=n|Z(u,t)=0,\ Y(u,u)=1\right]$$

$$=\begin{cases}\dfrac{\xi\left(\alpha+p\right)\left(\alpha+q\right)\left(qe^{-p(t-u)}-pe^{-q(t-u)}\right)}{q\left(\alpha+p\right)e^{-p(t-u)}-p\left(\alpha+q\right)e^{-q(t-u)}}, & n=0\\ \left(1-P^*\left[Y(u,t)=0\right]\right)\left(1-\alpha\zeta\right)\left(\alpha\zeta\right)^{n-1}, & n\geq 1\end{cases}$$

$$\xi=\frac{e^{-p(t-u)}-e^{-q(t-u)}}{\left(q+\alpha\right)e^{-p(t-u)}-\left(p+\alpha\right)e^{-q(t-u)}}$$

$$\begin{Bmatrix}p\\q\end{Bmatrix}=\frac{1}{2}\left(-\alpha+\beta+\mu\begin{Bmatrix}-\\+\end{Bmatrix}\sqrt{\left(\alpha+\beta+\mu\right)^2-4\alpha\beta}\right)$$

From Clones to Polyps

The size of a polyp is the sum over the sizes of its clones:

$$Y(t) = \sum_{j=1}^{M(t)} Y\left(u_j, t\right) \tag{1}$$

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Remark: The derivations are valid for any positive X. For this presentation we consider the case of a single $APC-/-$ progenitor cell, i.e. $X \equiv 1$.

Conditional Polyp Size Distribution

Theorem (1)

For $n \geq 0$, and $Z(t)$ the indicator for clinical cancer at time t, the size distribution for the number of polyp cells at time t conditioned on no clinical cancer is given by

$$Pr[Y(t) = n | Z(t) = 0, Y(0) = 0] = \frac{\Gamma(\rho X/\alpha + n)}{\Gamma(n+1)\Gamma(\rho X/\alpha)} (1 - \alpha\zeta)^{\frac{\rho X}{\alpha}} (\alpha\zeta)^n \ .$$

This is the negative binomial distribution with parameters $r = \rho X/\alpha$ and success probability $p = 1 - \alpha\zeta$.

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Remark I: Because the size distribution follows a known, parametric distribution, generating samples, evaluating the PMF, etc. is computationally cheap.
Remark II: This is Theorem 1 and Corollary 1 & 2 in [4].

Mathematical Model

MSCE Model

Goals

- Generalize the results for the TSCE model (Theorem 1) to the MSCE model

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- It should be possible to efficiently sample from the resulting distribution

Definitions

Let $X(t)$ be the number of normal cells, $Y_1(t), \ldots, Y_{k-2}(t)$ be the number of cells in pre-initiation stages, $Y_{k-1}(t)$ be the total number of polyp cells and $Y_k(t)$ be the indicator for clinical cancer.

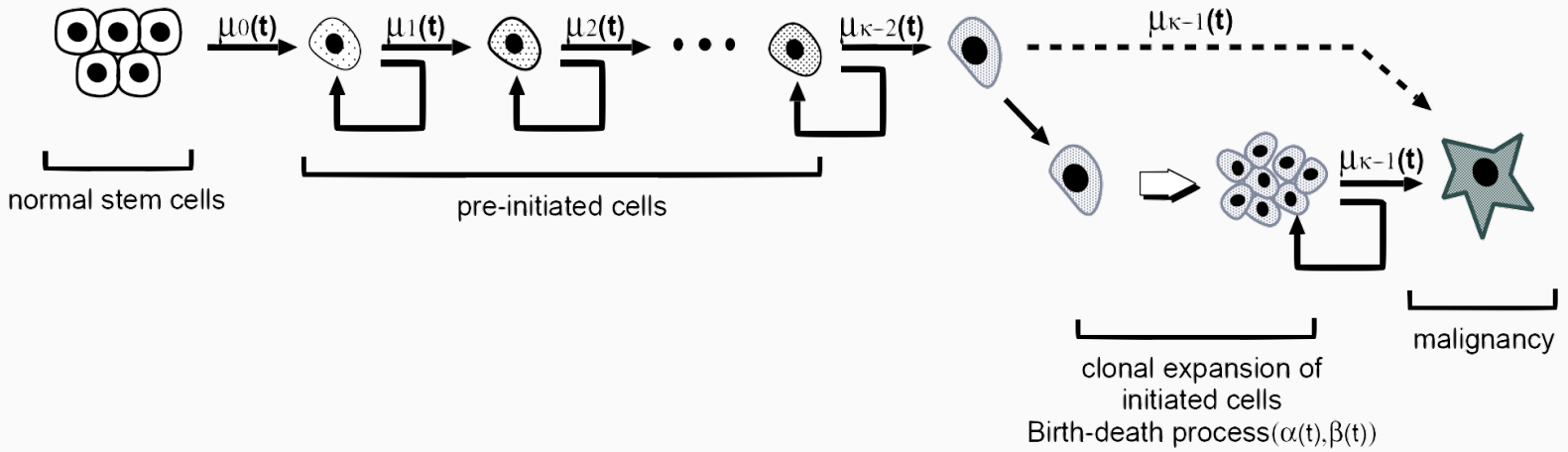

Figure 3: Schematic representation of the MSCE model [4].

Conditional Size Distribution I

Theorem (2)
Let $\phi^*(y; u, t)$ be the PGF of the size of a clone born at $u \leq t$. Let $\Psi^*(y_1, \ldots, y_{k-2}, y; t)$ be the joint PGF of the number of cells in each stage, conditioned on no clinical cancer at t, then

$$\Psi^*(1, \ldots, 1, y; t) =$$

$$\exp\Big[\int_0^t \mu_0(u_1) X(u_1) S_{k-1}(t-u_1) \Big(\exp\Big[\int_{u_1}^t \mu_1(u_2) S_{k-2}(t-u_2) \Big(\ldots$$

$$\Big(\exp\Big[\int_{u_{k-2}}^t \mu_{k-2}(u_{k-1}) S_{k-2}(t-u_{k-1}) (\phi^*(y; u_{k-1}, t) - 1)\, \mathrm{d}u_{k-1}\Big] - 1\Big) \ldots$$

$$-1\Big)\mathrm{d}u_2\Big] - 1\Big)\mathrm{d}u_1\Big]$$

Conditional Size Distribution II

Theorem 2 shows that the MSCE model conditioned on no clinical cancer at time t is equivalent to an unconditional MSCE model with rates

$$\begin{aligned}
&\mu_0(u_1)\, S_{k-1}(t-u_1)\, X(u_1) \ , \\
&\mu_1(u_2)\, S_{k-2}(t-u_2) \ , \\
&\qquad \vdots \\
&\mu_{k-2}(u_{k-1})\, S_1(t-u_{k-1}) \ .
\end{aligned}$$

$S_{k-1}(t-u)$ is the survival function of $k-1$ stage MSCE model starting with one cell in the first pre-initiation stage at time u, i.e.

$$X(u) = 0, \ Y_1(u) = 1, Y_2(u) = 0, \ldots Y_k(u) = 0 \ .$$

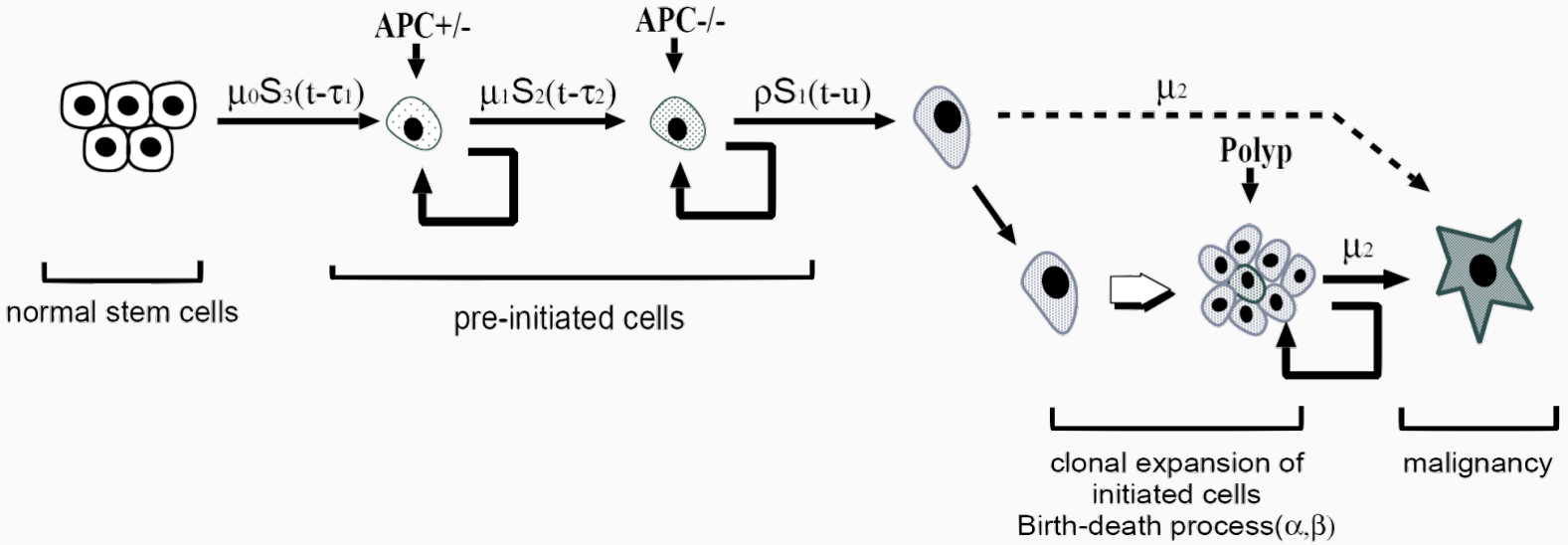

Figure 4: Schematic representation of the carcinogenesis model [4].

Simulation

Steps

- By Theorem 2 we know that we have to simulate a k-stage (4 for the example) MSCE model with modified rates
- We simulate non-homogeneous Poisson processes up to the last pre-initiation stage and then use Theorem 1

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  - Draw samples from negative binomial distribution
  - Simulate screening/intervention
  - Calculate hazard functions after screening

Survival Functions I

The formulas for the survival functions are:

$$S_k(t) = exp\Big[\int_0^t \mu_0\Big(\exp\Big[\int_{u_1}^t \mu_1\Big(\dots$$

$$\Big(\exp\Big[\int_{u_{k-3}}^t \mu_{k-3}\left(S_2\left(t-u_{k-2}\right)-1\right)\mathrm{d}u_{k-2}\Big]-1\Big)\cdots-1\Big)\mathrm{d}u_2\Big]-1\Big)\mathrm{d}u_1\Big]$$

$$S_2(t) = \left(\frac{q-p}{qe^{-pt}-pe^{-qt}}\right)^{\mu_{k-2}/\alpha}$$

$$S_1(t) = 1+\frac{1}{\alpha}\frac{pq\left(e^{-pt}-e^{-qt}\right)}{qe^{-pt}-pe^{-qt}}$$

Survival Functions II

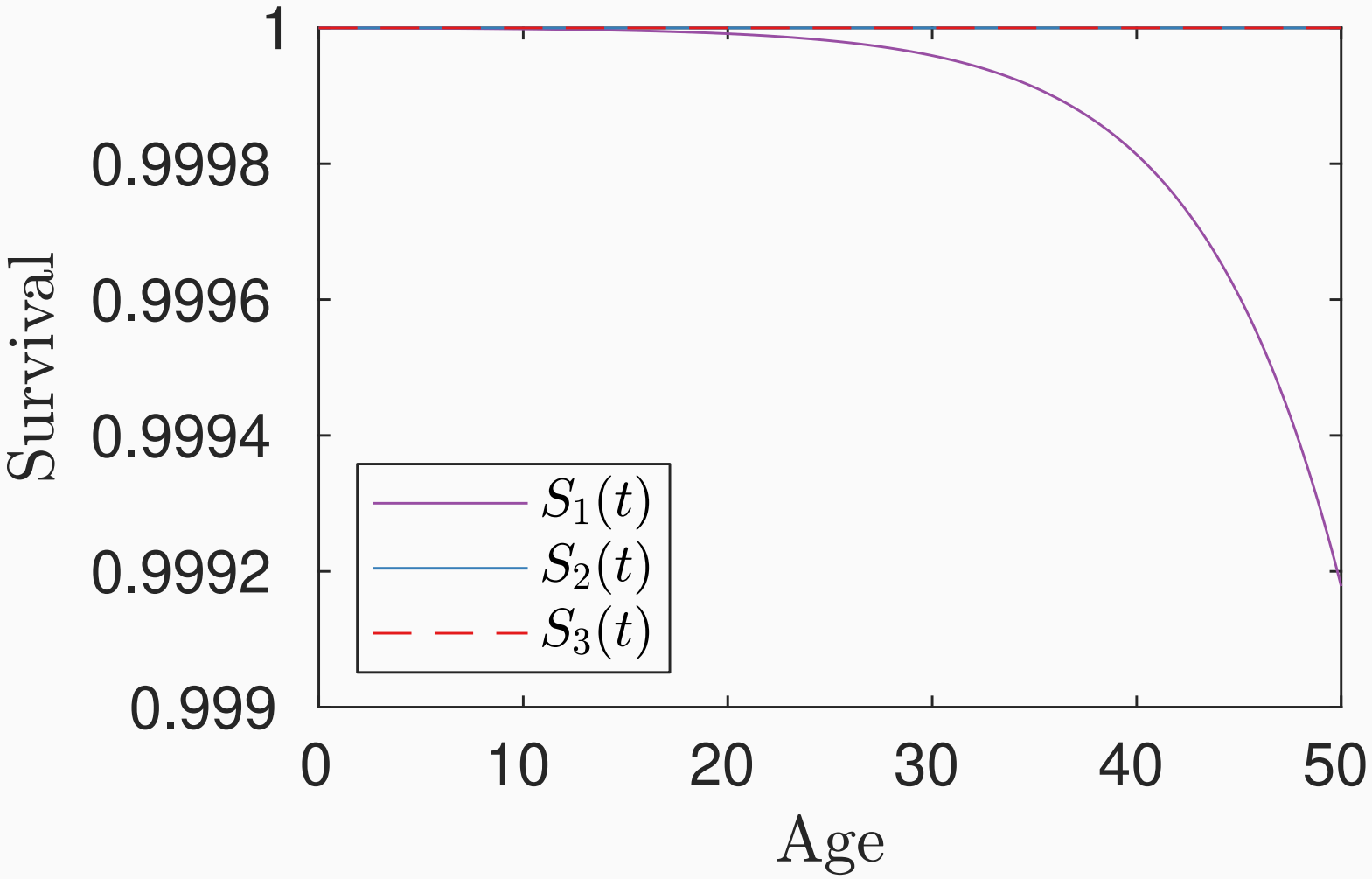

Figure 5: Survival functions for $0 \leq t \leq 50$.

Survival Functions III

- Multiple evaluations at $t_1 < t_2$: $\int^{t_2} = \int^{t_1} + \int_{t_1}^{t_2}$
- When useful use $\log S_k$, $S_k - 1$, $log1p$ and $exp1m$
- Use cheap but accurate approximation to S_3

Survival Functions III

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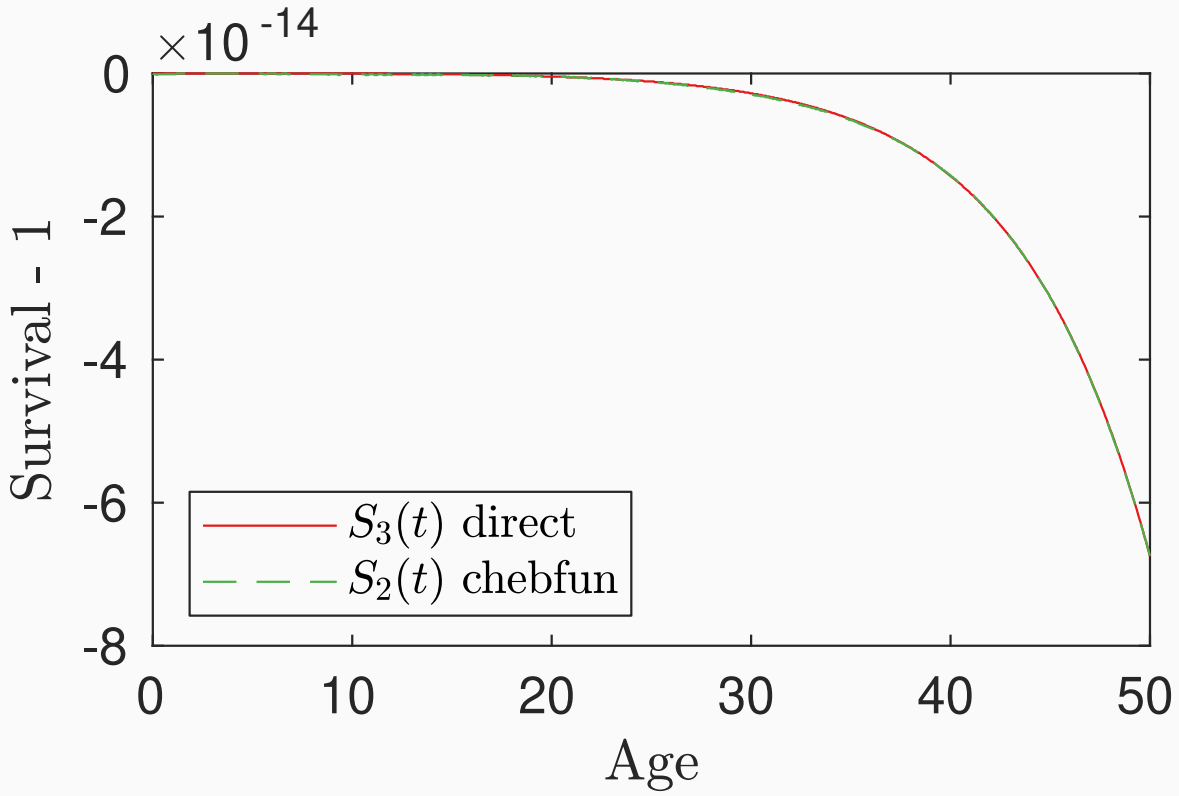
$\Rightarrow$ Chebyshev polynomials using chebfun[1] toolbox

[1] T. A Driscoll, N. Hale, and L. N. Trefethen. *Chebfun Guide*. Pafnuty Publications, 2014. URL: `http://www.chebfun.org/docs/guide/`

Survival Functions IV



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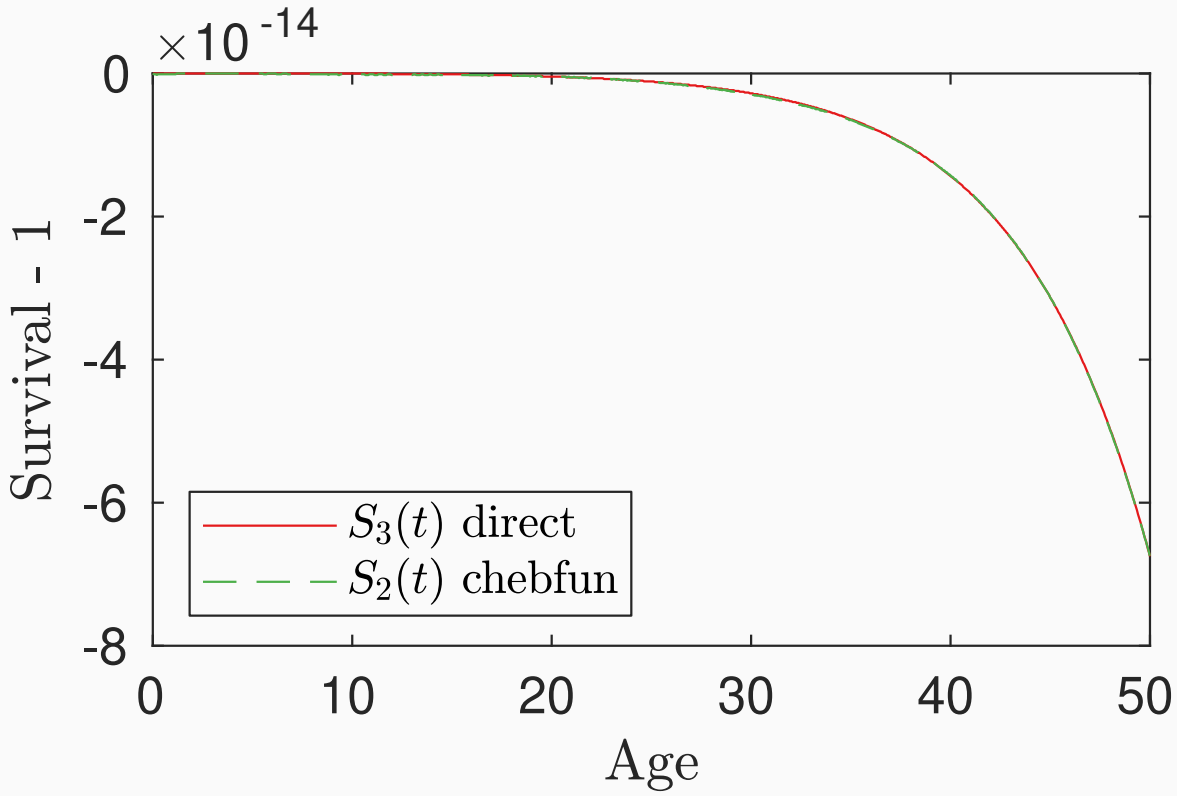

- Maximum Error $2.2\,10^{-16} = eps\,(1)$, i.e. accurate to machine precision
- Evaluation takes $O\left(10^{-4}\right)$ s for the direct method and $O\left(10^{-7}\right)$ s for the approximation

Non-homogeneous Poisson Process & Negative Binomial Distribution

Non-homogeneous Poisson Process

- Standard Problem
- One possible method: Thinning, i.e. rejection sampling
- Simulate a homogeneous Poisson process with rate $\lambda_\infty \geq ||\lambda(t)||_\infty$ and accept each occurrence t_j with probability

$$\frac{\lambda(t_j)}{\lambda_\infty}.$$

Negative Binomial distribution

- Standard Problem
- Use MATLAB's built in methods

Intervention Methods I

- Perform simulation for $i = 1, \ldots, N = 10^4$ individuals/samples
- Before screening/intervention at time σ^-

Number healthy cells	X
Number APC+/- cells	N_2^-
Number APC-/- cells	N_3^-
Polyp size set	$\mathcal{N}_4^-$
Number polyp cells	$N_4^- = \left\lvert \mathcal{N}_4^- \right\rvert$

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Number polyp cells	$N_4^- = \left\lvert \mathcal{N}_4^- \right\rvert$

- After screening/intervention $A_i = \left\{X, N_{2i}^+, N_{3i}^+, N_{4i}^+\right\}$

Intervention Methods II

Method	Description	Example
Complete	Remove all polyps above threshold and associated APC-/- cells.	$\mathcal{N}_4^+ = \{5000\}$
Incomplete	Remove all polyps above threshold and leave APC-/- progenitor cells.	$\mathcal{N}_4^+ = \{5000, 0\}$
Realistic	Decrease polyp size to 10% of threshold and leave APC-/- cells.	$\mathcal{N}_4^+ = \{5000, 1000\}$

Table 1: Intervention Methods. For the example: $N_3^- = 2$, $\mathcal{N}_4^- = \{5000, 20000\}$ and the threshold is 10^4. $N_3^+ = \left|\mathcal{N}_4^+\right|$

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After screening

- Separate $N = 10^4$ samples into groups, e.g. negative screen with threshold 10^3, positive screen with threshold 10^4
- For each group, the average survival and hazard functions are:

$$S\left(t-\sigma|A_i\right) = S_4\left(t-\sigma\right)^X \; S_3\left(t-\sigma\right)^{N_{2i}^+} \; S_2\left(t-\sigma\right)^{N_{3i}^+} \; S_1\left(t-\sigma\right)^{N_{4i}^+}$$

$$\begin{aligned} h\left(t-\sigma|A_i\right) = {} & Xh_4\left(t-\sigma\right) + N_{2i}^+ h_3\left(t-\sigma\right) \\ & + N_{3i}^+ h_2\left(t-\sigma\right) + N_{1i}^+ h_4\left(t-\sigma\right) \end{aligned}$$

$$S\left(t-\sigma\right) \approx \frac{1}{N}\sum_{i=1}^{N} S\left(t-\sigma|A_i\right)$$

$$h\left(t-\sigma\right) \approx \frac{\sum_j S\left(t-\sigma|A_i\right) h\left(t-\sigma|A_i\right)}{\sum_j S\left(t-\sigma|A_i\right)}$$

Parameters

The paper [4] uses the following parameters for the simulation:

$$
\begin{aligned}
\alpha &= 9 \\
X &= 10^8 \\
p &= -1.519930 \times 10^{-1} \\
q &= 3.893446 \times 10^{-6} \\
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Estimated from SEER data: white males (1973-2000) [5].

Results

APC-/- progenitor cells

Num. APC-/- cells	Count	Percent
0	7893	78.93 %
1	1886	18.86 %
2	204	2.04 %
3	16	0.16 %
4	1	0.01 %

Table 2: Distribution of the number of APC-/- progenitor cells for $N = 10'000$ at age $\sigma = 50$ years.

Polyp size distribution

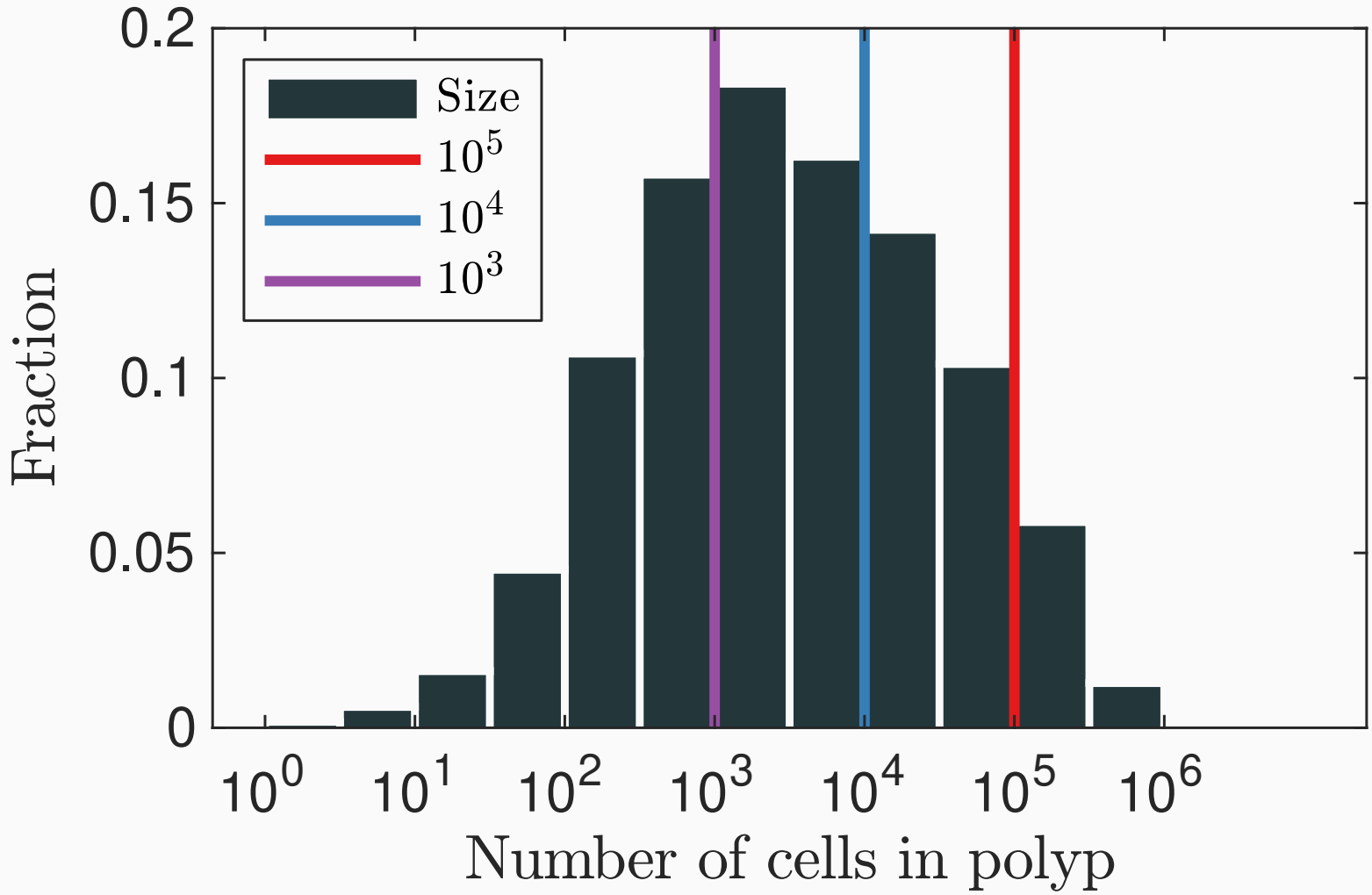

Figure 6: Size distribution of polyps at age $\sigma = 50$ years for $N = 10'000$. Note that one individual might have multiple polyps.

Negative Groups

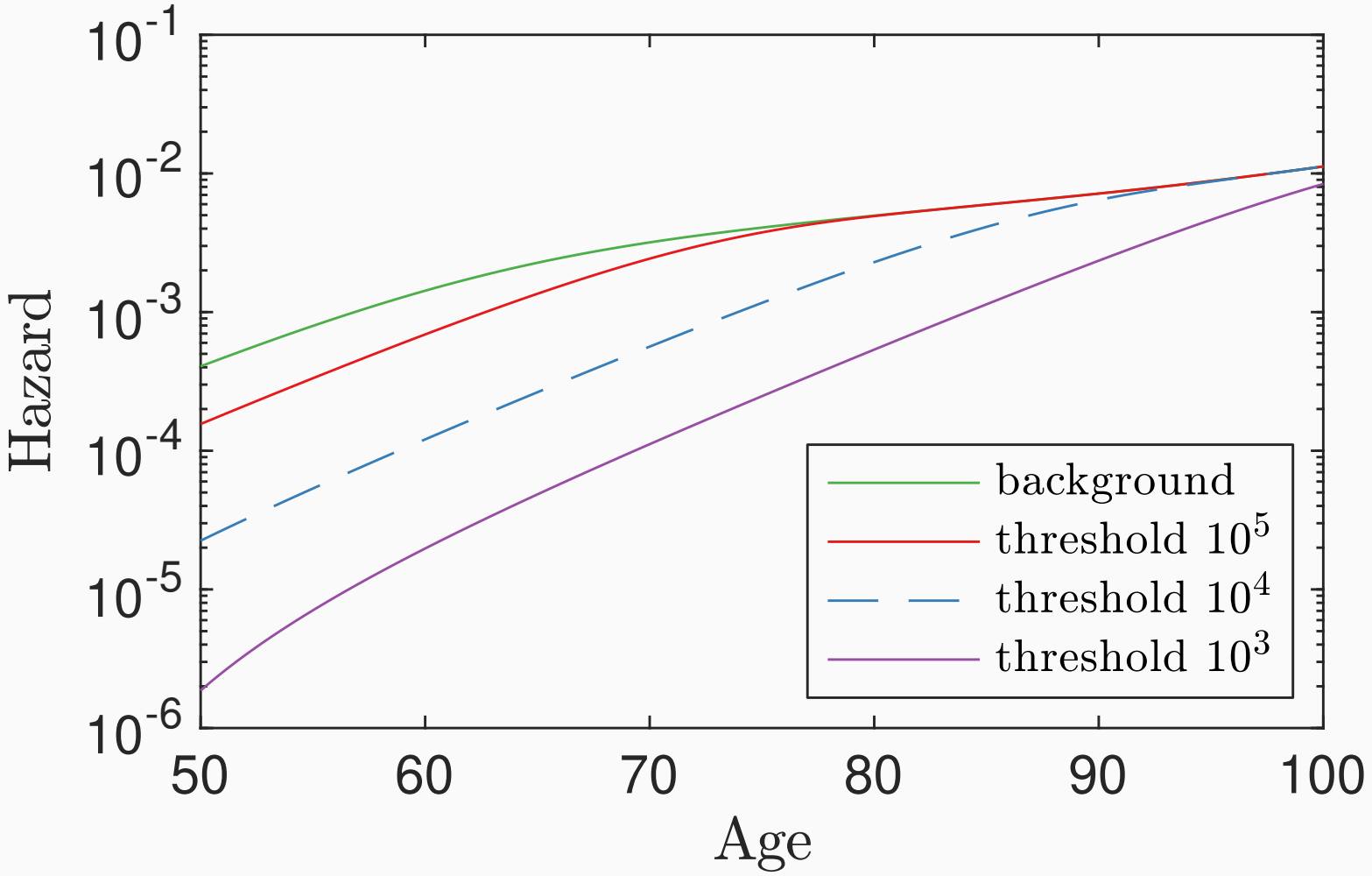

Figure 7: Hazard after screening at age $\sigma = 50$ for negative screening groups. Sample size $N = 10'000$.

Negative vs. Positive Group

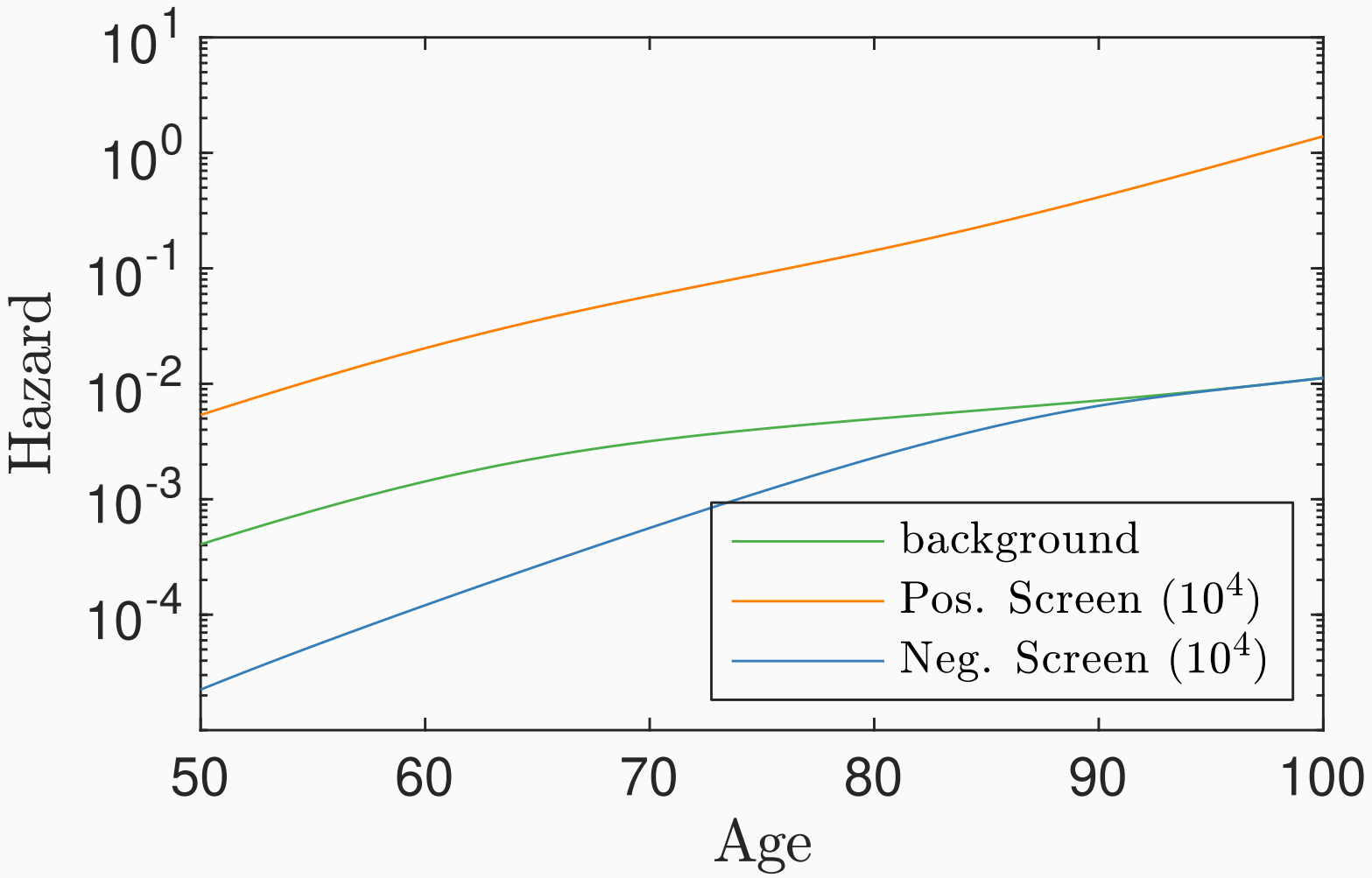

Figure 8: Hazard after screening at age $\sigma = 50$. $N = 10'000$.

Positive Groups with complete Intervention

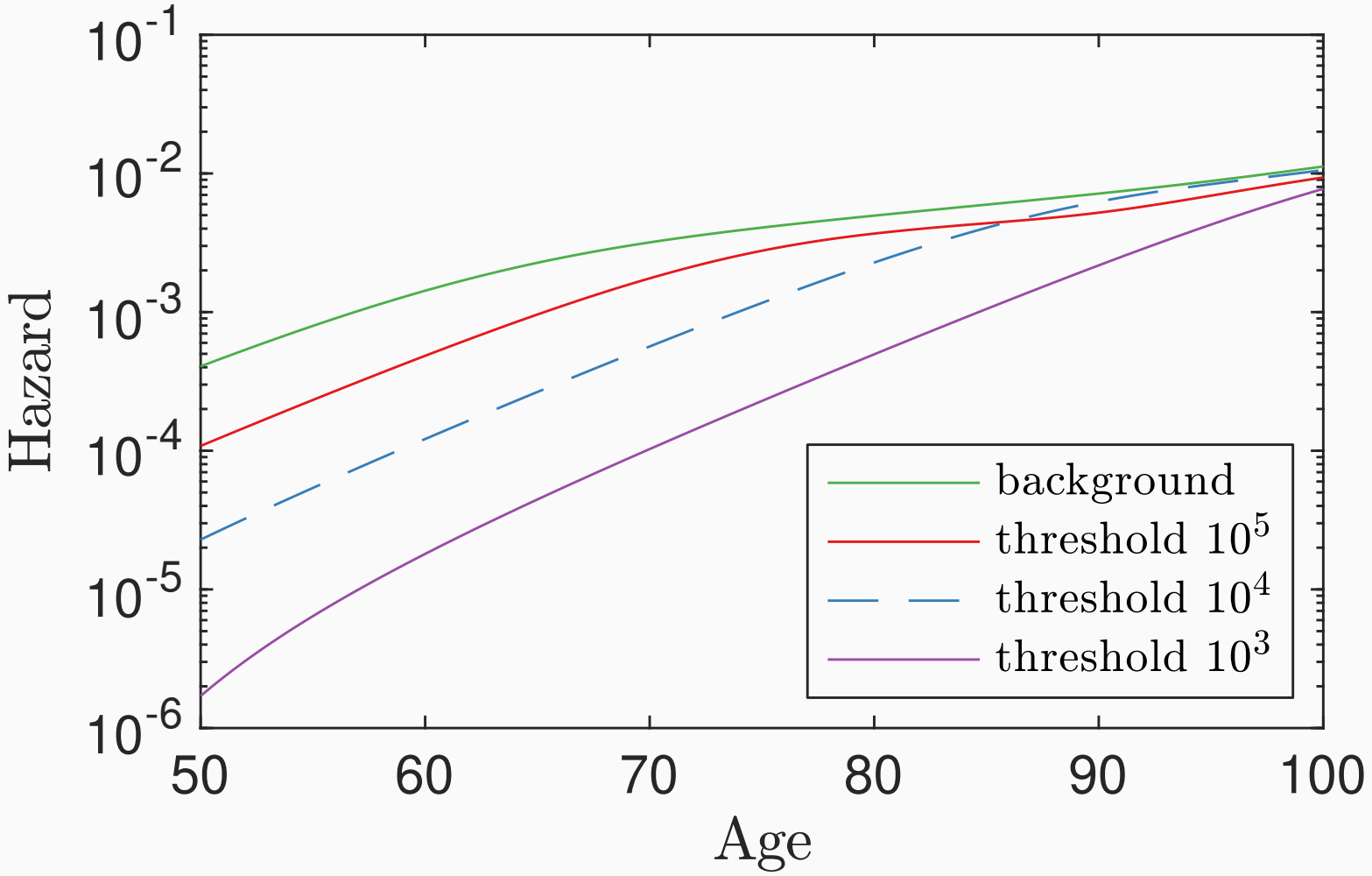

Figure 9: Hazard after screening at age $\sigma = 50$ with complete intervention. $N = 10'000$.

Positive Groups with incomplete Intervention

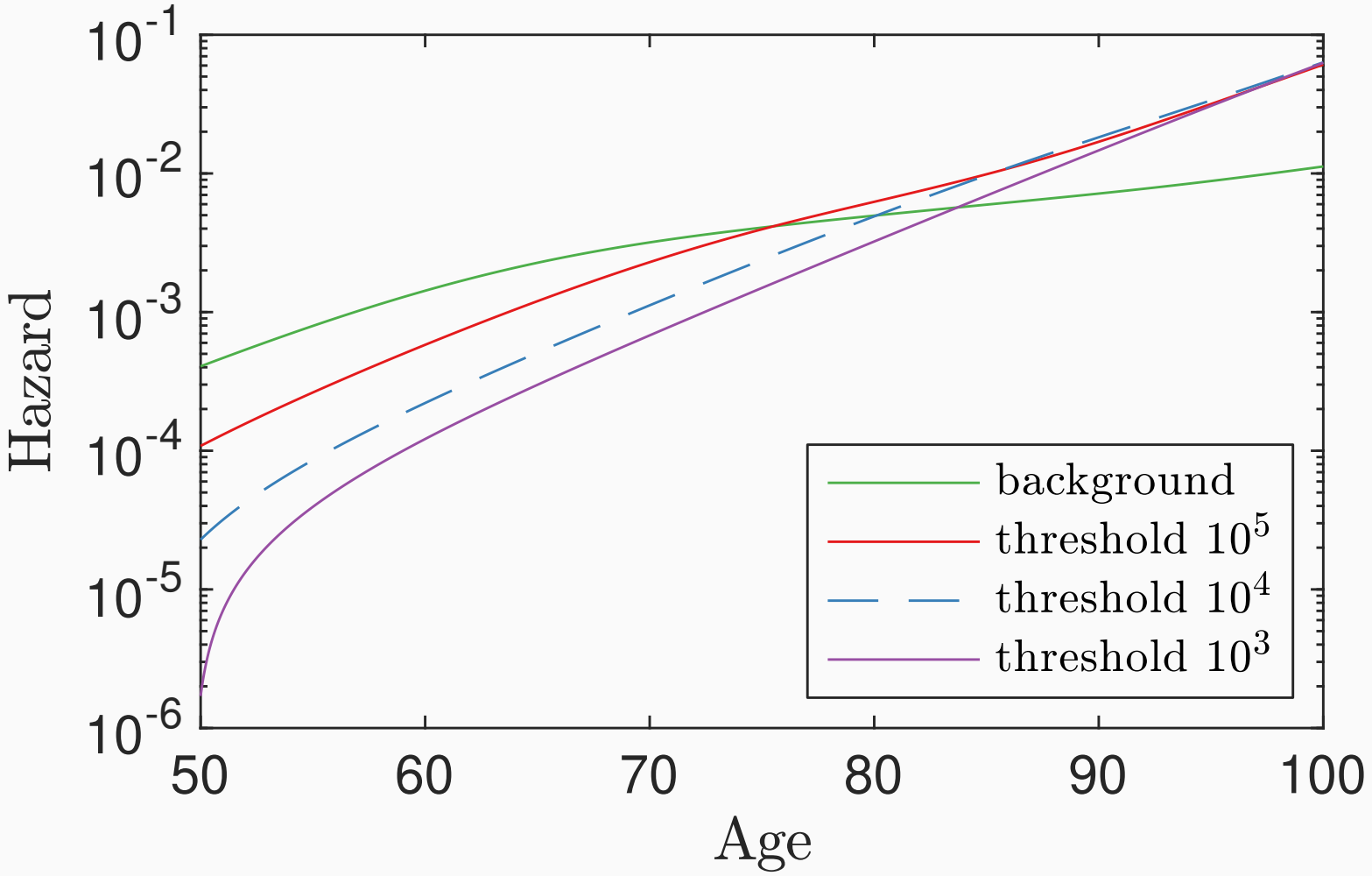

Figure 10: Hazard after screening at age $\sigma = 50$ with incomplete intervention. $N = 10'000$.

Lifetime CRC Risk

Table 3: Lifetime colorectal cancer (CRC) risk at 80 years for different scenarios. Screening at $\sigma = 50$ years. Sample size $N = 10'000$.

Scenario	Threshold	Lifetime Risk
Background		6.57 %

Lifetime CRC Risk

Table 3: Lifetime colorectal cancer (CRC) risk at 80 years for different scenarios. Screening at $\sigma = 50$ years. Sample size $N = 10'000$.

Scenario	Threshold	Lifetime Risk
Background		6.57 %
Neg. Screen	10^5	4.99 %
Neg. Screen	10^4	1.25 %
Neg. Screen	10^3	0.11 %

Lifetime CRC Risk

Table 3: Lifetime colorectal cancer (CRC) risk at 80 years for different scenarios. Screening at $\sigma = 50$ years. Sample size $N = 10'000$.

Scenario	Threshold	Lifetime Risk
Background		6.57 %
Neg. Screen	10^5	4.99 %
Neg. Screen	10^4	1.25 %
Neg. Screen	10^3	0.11 %
Pos. Screen	10^5	99.72 %
Pos. Screen	10^4	75.22 %
Pos. Screen	10^3	44.79 %

Lifetime CRC Risk

Table 3: Lifetime colorectal cancer (CRC) risk at 80 years for different scenarios. Screening at $\sigma = 50$ years. Sample size $N = 10'000$.

Scenario	Threshold	Lifetime Risk
Background		6.57 %
Neg. Screen	10^5	4.99 %
Neg. Screen	10^4	1.25 %
Neg. Screen	10^3	0.11 %
Pos. Screen	10^5	99.72 %
Pos. Screen	10^4	75.22 %
Pos. Screen	10^3	44.79 %
Realistic Intervention	$10^4 \rightarrow 10^3$	5.36 %
Complete Intervention	$10^4 \rightarrow 0$	1.27 %

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