Lukas Köstler

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

Biological Model & Goal

The adenomatous polyposis coli (APC) gene is a cancer suppressor. Through a series of two mutations the gen gets inactivated. Afterwards, a high frequency event occurs, and the stem cell produces initiated cells that perform clonal expansion [2]. The last event is assumed to be a positional effect linked to colonic crypts. The union of all clones from the same twice mutated stem cell is called polyp. See Figure 1 where the polyp visible consists of multiple clones.

We show how to simulate the model efficiently and then evaluate different screening and intervention strategies. The results can ultimately be used to guide health policy decisions. In Germany, a colonoscopy after the age of 55 and a second colonoscopy more than ten years after the first one are paid for by health insurance. This policy is well aligned with the results from the paper [1].

Polyp Size Distribution for the Two-Stage Model

We will consider the polyp size distribution in the TSCE model conditioned on no clinical cancer, i.e. 0 malignant cells. A clone is the set of cells that originate from one initiated cell through a birth-death process.
Let $Y(u,t)$ be the number of cells of a clone at time t that was initiated at time $u \leq t$. The total number of polyp cells at time t, denoted by $Y(t)$, is then given by

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

where $u_1, \ldots, u_{M(t)}$ are the initiation event times of clones. They follow a Poisson process with rate $\rho(u) X(u)$.

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*

$$Pr[Y(t) = n | Z(t) = 0, Y(0) = 0] = \frac{\Gamma(\rho X/\alpha + n)}{\Gamma(n+1)\Gamma(\rho X/\alpha)} (1-\alpha\zeta)^{\frac{\rho X}{\alpha}} (\alpha\zeta)^n \ . \tag{2}$$

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

Proof. See Corollary 2 in [1]. □

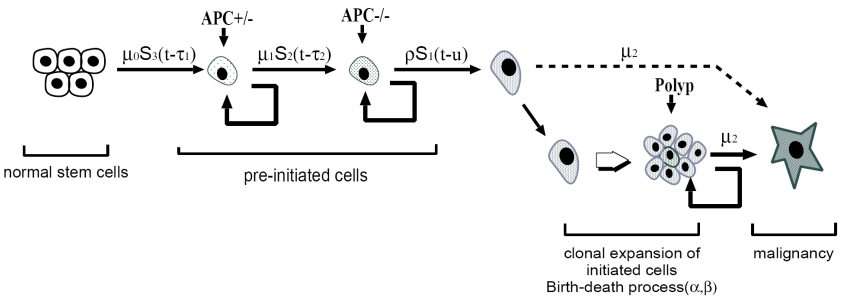


Figure 1: Schematic representation of the carcinogenesis model taken from [1]. Conditioned on no clinical cancer the following holds: Normal stem cells produce APC+/- cells with rate $\mu_0 S_3(t-\tau_1)$. Each APC-/+ cell divides asymmetrically into one APC+/- cell and one APC-/- cell with rate $\mu_1 S_2(t-\tau_2)$. Each APC-/- cell produces clones with rate $\rho S_1(t-u)$. Each clone starts with one cell which undergoes a birth-death process. The union of all clones from a single APC-/- cell is called a polyp. Each polyp is one distinct mass of cells in the colon.

Simulation of the Four-Stage Model

We will now consider the four-stage model given in Figure 1. For the four-stage model a hybrid simulation is used. The transitions from stem cells to APC+/- and then APC-/- cells are simulated directly. Afterwards, the derived size distribution (Theorem 1) is employed. The steps are:

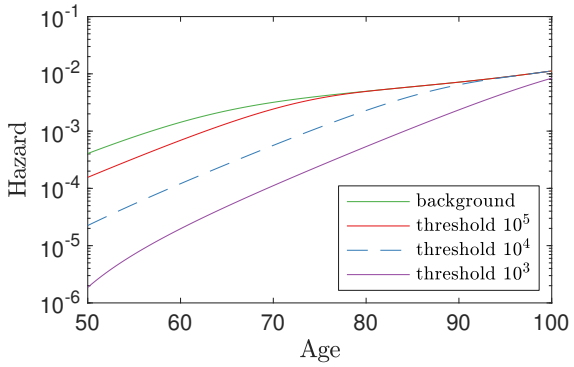
- Simulate the occurrences of APC+/- cells from a non-homogeneous Poisson process with rate $\mu_0 X S_3(t-\tau_1)$.
- For each APC+/- cell simulate the occurrences of APC-/- cells from a non-homogeneous Poisson process with rate $\mu_1 S_2(t-\tau_2)$.
- Each APC-/- cell is treated as a separate TSCE model with $X=1$, which generates one polyp. The size of the polyp is a sample from the distribution given in eqn. (2).

The above procedure gives the quadruple $\{X, N_2^-, N_3^-, N_4^-\}$, where N_2^- is the number of APC+/- cells, N_3^- is the number of APC-/- cells and N_4^- is the number of polyp cells, all before the screening at $t=\sigma$.

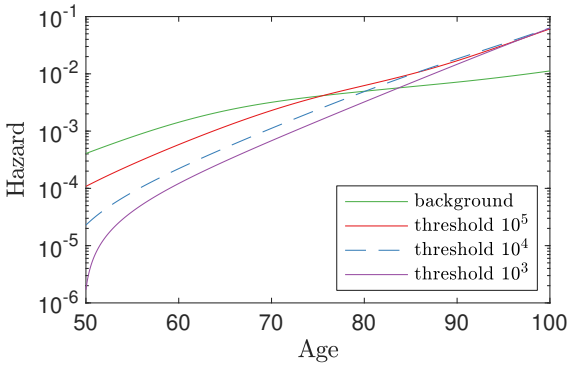
The above procedure is repeated e.g. $N = 10\,000$ times to generate a population. During screening a polyp is detected if its size exceeds a threshold. Different intervention strategies, e.g. complete removal of detected polyps including their APC-/- cells, are employed and the post screening data is $A_i = \{X, N_{2i}^+, N_{3i}^+, N_{4i}^+\}$. The survival and hazard functions for $t > \sigma$ are given by:

$$
\begin{aligned}
S(t-\sigma|A_i) &= S_4(t-\sigma)^X \; S_3(t-\sigma)^{N_{2i}^+} \; S_2(t-\sigma)^{N_{3i}^+} \; S_1(t-\sigma)^{N_{4i}^+} \\
h(t-\sigma|A_i) &= X h_4(t-\sigma) + N_{2i}^+ h_3(t-\sigma) + N_{3i}^+ h_2(t-\sigma) + N_{1i}^+ h_4(t-\sigma) \\
S(t-\sigma) &\approx \frac{1}{N}\sum_{i=1}^{N} S(t-\sigma|A_i) \\
h(t-\sigma) &\approx \frac{\sum_i S(t-\sigma|A_i)\, h(t-\sigma|A_i)}{\sum_i S(t-\sigma|A_i)}
\end{aligned}
$$

$S_k,\ k=1,2,3,4$ are the survival functions for the k-stage MSCE model.



(a) Post-screen hazard for negative screening groups.



(b) Post-screen hazard for positive screening groups with incomplete intervention, i.e. removal of detected polyps, but without removal of APC-/- cells.

Figure 2: Simulation results for $N = 10\,000$ and screening at $\sigma = 50$. Post-screen intervention reduces the risk for positive groups to approximately the same level as the risk for negative groups.

References

[1] Jihyoun Jeon et al. "Evaluation of screening strategies for pre-malignant lesions using a biomathematical approach". In: *Mathematical biosciences* 213.1 (2008), pp. 56–70.

[2] E Georg Luebeck and Suresh H Moolgavkar. "Multistage carcinogenesis and the incidence of colorectal cancer". In: *Proceedings of the National Academy of Sciences* 99.23 (2002), pp. 15095–15100.

Auxiliary Formulas

$$
\begin{Bmatrix} p \\ q \end{Bmatrix} = \frac{1}{2}\Big(-\alpha + \beta + \mu \begin{Bmatrix} - \\ + \end{Bmatrix} \sqrt{(\alpha+\beta+\mu)^2 - 4\alpha\beta} \Big) \qquad \zeta = \frac{e^{-pt} - e^{-qt}}{(q+\alpha)\, e^{-pt} - (p+\alpha)\, e^{-qt}}
$$