A STUDY OF THE MATHEMATICAL MODELING OF EVOLUTION OF ADVANCED ADENOMAS, AND THE ROLE OF ASPIRIN AS A CHEMOPREVENTIVE AND DELAYING AGENT FOR COLORECTAL CANCER.

MAHAM KHALID

Applied Mathematics Department, University of Washington, Seattle, WA
mahamk@uw.edu

Abstract. Colorectal cancer (CRC) is a highly common type of cancer that often results in death. In the study of CRC prevention and treatment, long-term NSAID use, and more specifically aspirin use, has been shown to be correlated with a reduction in CRC incidence, as well as in the reduction or prevention of several other types of cancer. While the exact mechanism of this relationship is unknown, this paper follows a study to uncover one such aspect of it, namely, the effect on cellular kinetics. Through the use of mathematical models, relevant data and estimated parameters, as well as stochastic Gillespie simulations, we attempt to understand the effect that aspirin has on this type of cancer, both with regards to age during the beginning of treatment, as well as duration of treatment overall.

1. Introduction and Overview

We follow a study conducted by Yifan Wang, C. Richard Boland, Ajay Goel, Dominik Wodarz, and Natalia L Komarova [9], on the effect of aspirin on cell kinetics, and subsequently on the incidence of colorectal cancer. In the paper "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," the authors build a model based on systems of ordinary differential equations to understand the mechanism of cancer progression, and simulate it using the stochastic simulation algorithm, also known as the Gillespie simulation algorithm while varying parameters in order to visualize the effect that aspirin has on colorectal cancer incidence.

Colorectal cancer is an unfortunately common cancer type, which often requires regular screenings past the ages of around 45 or 50, and affects nearly 5% of the population in the United States [8]. Like with all cancers, early treatment and especially prevention are of utmost importance. There are several commonly used drugs that act both as treatments for other ailments, while also working as chemopreventive agents, helping reduce the risk of cancer. One such drug that has been studied more often recently is aspirin.

Aspirin is a non-steroidal anti-inflammatory drug (NSAID) often used to treat minor aches, inflammation, and on occasion, as a blood thinner. An intriguing use of this drug though, is in the prevention of cancer. Several studies have been carried out in regards to this relation between aspirin usage and cancer reduction [6], [4], and this has become a well known phenomenon. Aspirin's main mechanism of action is as a general cyclooxygenase (COX) inhibitor. COX-2 is an enzyme that acts on the hormone prostaglandin E2 (PGE2), which itself has been associated with poor prognosis of cancer. It has been expressed commonly in cancer cells [5], and has been shown to correlate to higher colorectal cancer incidence specifically [3]. Recently, NSAID's are being recommended as a primary drug for colorectal cancer prevention [1], however, the exact nature of this relation and the underlying mechanisms are still a subject of study.

Date: 7 June 2024.

In this paper, we focus on understanding and visualizing the production and incidence of advanced adenomas, and the computational modeling of the underlying mechanisms, specifically with regards to cell kinetics. While adenomas themselves are not inherently considered as malignant tumors, they can, if left untreated, develop into cancerous masses within the body. Understanding the prevention of advanced adenoma development is therefore necessary to combat the high rates of colorectal cancer. We first look at a deterministic compartmental model describing the transitions between different states, and then afterwards, incorporating the effect of inter-crypt competition and dynamics.

2. Materials and Methodology

In colorectal cancer, there are a number of cellular mutations that increase the risk of developing cancer. These include mutations in the genes KRAS, APC, TP53, TGFBR and PIK3CA, among other mutations [2]. The paper focuses on the cancer pathway that includes mutations in only the KRAS and APC genes, namely the inactivation of the APC gene, which needs two hits to be problematic, and the activation of the KRAS gene, which is also known to be a cancer causing oncogene.

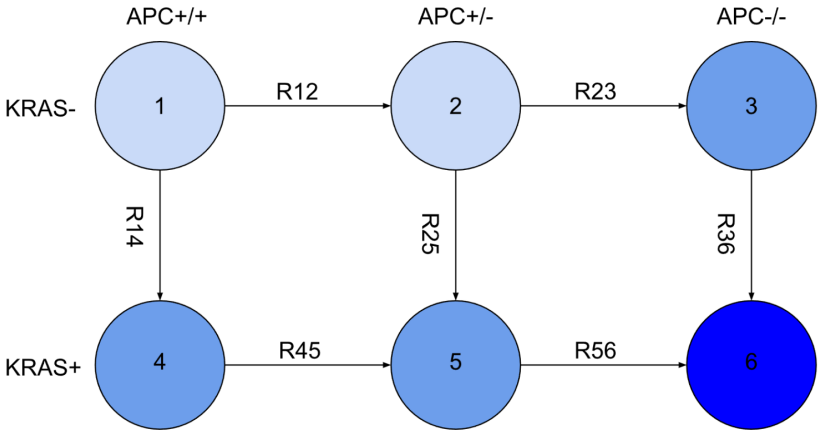

Figure 1. Compartmental model describing crypt and cell mutation transitions and subsequently crypt dynamics. Cell mutation types 1 and 2 do not cause excessive cell growth. Types 3, 4, and 5, have increased cell fission, and type 6, with both genes fully mutated, is associated with advanced adenoma incidence.

2.1. **Mathematical model.** The system of precancerous cell mutation transitions is first described via a compartmental model consisting of ordinary differential equations (Equations 1-5). These transitions can be viewed in the compartmental diagram shown in figure 1, where the R_{ij}'s describe the conversion rate from cell type i to cell type j. The cell types correspond to the types of mutations in the APC and KRAS genes. Type 1 corresponds to normal, or unmutated genes, where we have $APC^{+/+}$, and $KRAS^{-}$, while type 6 corresponds to both KRAS and APC fully mutated, and signifies the existence of an advanced adenoma that can now develop into cancer. Here, the γ_i's describe the the growth rates. This system of equations can describe not only the cell types, but also the crypt types present within the body, since crypts tend to have homogeneity with respect to driver mutations that occur within them. The initial conditions for the entire system are $n_1(0) = N_{crypt}$ an initial number of crypts of type

1, and for $i = 2, ..., 5$, we have $n_i(0) = 0$.

$$\dot{n}_1 = -(R_{12} + R_{14})n_1 \tag{1}$$
$$\dot{n}_2 = R_{12}n_1 - (R_{23} + R_{25})n_2 + \gamma_2 n_2 \tag{2}$$
$$\dot{n}_3 = R_{23}n_2 - R_{36}n_3 + \gamma_3 n_3 \tag{3}$$
$$\dot{n}_4 = R_{14}n_1 - R_{45}n_4 + \gamma_4 n_4 \tag{4}$$
$$\dot{n}_5 = R_{25}n_2 + R_{45}n_4 - R_{56}n_5 + \gamma_5 n_5 \tag{5}$$

Using the mean field approximation, we can deduce that the probability of producing a single crypt of type 6 can be described by the equation

$$\dot{P}(t) = (R_{56}n_5 + R_{36}n_6)(1 - P(t)) \tag{6}$$

For this equation, we have that $P(0) = 0$. These are fairly simple linear first order ordinary differential equations, and when outgoing rates are ignored, the system can be solved quite simply, giving us the set of solutions below,

$$n_1 = N_{crypt}$$
$$n_2 = -N_{crypt}\frac{R_{12}}{\gamma_2}$$
$$n_3 = N_{crypt}\frac{R_{12}R_{23}}{\gamma_2\gamma_3}$$
$$n_4 = -N_{crypt}\frac{R_{14}}{\gamma_4}$$
$$n_5 = N_{crypt}\left(\frac{R_{12}R_{25}}{\gamma_2\gamma_5} + \frac{R_{14}R_{45}}{\gamma_4\gamma_5}\right)$$

as well as a subsequent solution for $P(t)$ as

$$P = 1 - \exp\left(-N_{crypt}\left(-\frac{R_{1256}}{\gamma_{25}} - \frac{R_{1456}}{\gamma_{45}} - \frac{R_{1236}}{\gamma_{23}}\right)\right),$$

where $R_{ijkl} = R_{ij}R_{jk}R_{kl}$ and the corresponding $\gamma_{jk} = \gamma_j\gamma_k$. This solution shows us a clear pathway for type 6 crypts and consequently, for adenoma production. In the paper by Wang et al. [9], this equation is solution is represented slightly differently as

$$P = 1 - \exp(-N_{crypt}(S_{25}R_{1256} + S_{45}R_{1456} + S_{25}R_{1256}).$$

Here,

$$S_{ij} = \frac{g(\gamma_i) - g(\gamma_j)}{\gamma_i - \gamma_j},$$

where

$$g(\gamma) = \frac{e^{\gamma t} - 1 - \gamma t}{\gamma^2}$$

. If one takes the limit as $\gamma_j \to \gamma_i$ and uses L'hopital's rule, while assuming $\gamma_2 = 0, \gamma_4 = \gamma_5$ the authors arrive at an expression for $S_{45} = g'(\gamma_4)$;

$$\begin{aligned}\lim_{\gamma_j \to \gamma_i}(S_{ij}) &= \frac{\frac{e^{\gamma_j t} - 1 - \gamma_j t}{\gamma_j^2} - \frac{e^{\gamma_i t} - 1 - \gamma_i t}{\gamma_i^2}}{\gamma_j - \gamma_j} \\ &= \frac{e^{\gamma_j t}(t\gamma_j t - 2) + t\gamma_j + 2}{\gamma_j^3} \\ &= g'(\gamma_j)\end{aligned}$$

Similarly, they derive $S_{25} = \frac{g(\gamma_4) - t^2/2}{\gamma_4}$, and $S_{23} = \frac{g(\gamma_3) - t^2/2}{\gamma_3}$, however, they take into account the fact that $\gamma_2 = 0$ for both of these expressions.

This system however, does not include the possibility of inter-crypt competition, which has been shown to be necessary to produce an accurate and realistic model. The system above can then be modified to include the effects of crypt competition, and can be described by

the equations below. This model incorporates the carrying capacities of the crypts, with K_A related to the carrying capacity of KRAS$^-$ crypts, and K_R for KRAS$^+$ ones. δ is also included as the crypts' death rate, which remains the same accross the last 3 crypt types.

$$\dot{n}_1 = -(R_{12} + R_{14})n_1 \tag{7}$$

$$\dot{n}_2 = R_{12}n_1 - (R_{23} + R_{25})n_2 \tag{8}$$

$$\dot{n}_3 = R_{23}n_2 - R_{36}n_3 + \gamma_3 n_3 \left(1 - \frac{n_3 + n_4 + n_5}{K_A}\right) - \delta n_3 \tag{9}$$

$$\dot{n}_4 = R_{14}n_1 - R_{45}n_4 + \gamma_4 n_4 \left(1 - \frac{n_3 + n_4 + n_5}{K_R}\right) - \delta n_4 \tag{10}$$

$$\dot{n}_5 = R_{25}n_2 + R_{45}n_4 - R_{56}n_5 + \gamma_5 n_5 \left(1 - \frac{n_3 + n_4 + n_5}{K_R}\right) - \delta n_5 \tag{11}$$

Since this is now a non-linear system, it can not be analytically solved the way the first system was. It can, however, be solved numerically. We again describe the probability of the existence of a crypt of type 6 at by equation (6). The authors of paper [9] use this system for model fitting, and find the parameters that most closely align with reality, and help in calculating the age incidence curves, both without and with the effect of addition of aspirin as a chemopreventive drug.

2.2. **Parameters and Data.** The parameters being used have been estimated by Wang et al. [9] by using previous studies, as well as using model fitting techniques in order to find best fits. The original paper describes various methods and inclusions in the fitting of the models to find parameters that closely mimic reality. These parameters are what are used for the Gillespie simulations run in order to find and view the possibility of adenoma production. Table (1) contains data related to crypt growth, transition, fission, and death dynamics, and table (2) describes the changes in rates related to different doses of aspirin used in humans.

Parameters			
R_{12}	0.000107972	K_A	1039.12
R_{14}	9.94617E-7	K_R	171.13
R_{23}	0.000127717	γ_3	0.2
R_{25}	1.59139E-6	γ_4	0.07
R_{36}	3.73976E-6	γ_5	0.07
R_{45}	0.000382222	γ_6	1.012
R_{56}	0.000452117	δ	0.05

TABLE 1. Best fit parameters found through model fitting, subsequently used for Gillespie Simulation of the system. R_{ij}'s are the crypt conversion rates, γ's the growth rates, K's the carrying capacities, and δ the death rate of cells and crypts.

The aspirin doses used in humans were estimated in a previous study by Shimura et al [7] with regards to the effect of aspirin usage in tumor xenografts in mice. The authors have estimated the equivalent doses in humans, as well as how different parameters are modified with respect to changes in aspirin dosage. The assumption relied upon here is that with the addition of aspirin, the growth and death rates within the cells' life cycles are modified as $\gamma_i \to F_r \to \gamma_i$, and $\delta \to F_d\delta$. We use the highest and lowest described doses, and summarize these parameters in the table below.

Original dose in mice (mg/kg)	**Equivalent dose in humans(pills per week)**	**Multiplicative factor (F_r) for division rate**	**Multiplicative factor (F_d) for death rate**
15	1.8	0.9	1.5
100	12.2	0.5	2.0

TABLE 2. Parameter modifications based on low (first row) and high (second row) doses of aspirin.

Other important inclusions and assumptions made within the paper are that we assume that wild type crypts with no mutations, or crypts with only one APC gene mutation do not proliferate, i.e., $\gamma_1 = \gamma_2$. We also assume $\gamma_4 = \gamma_5$, and that relative cell fitness of a cell of type j can be described in terms of probability and cell death and division rates, as

$$F_j = \frac{r_j d_1}{r_1 d_j} = \frac{Pr(j)}{1 - Pr(j)}$$

for cells of type 2 ($APC^{+/-}$), 3($APC^{-/-}$) and 4($KRAS^{+}$). The relative fitnesses of cells of the types mentioned are

Cell type	Relative fitness value
$APC^{+/-}$	1.6
$APC^{-/-}$	3.76
$KRAS^{+}$	3.54

TABLE 3. Relative fitness values

2.3. **Model Simulation.** In order to incorporate stochasticity in our simulations, we adapted the Fortran and Mathematica code for the Gillespie Algorithm provided along with [9], and implemented both in Python. The general functionality of the code remains the same as in the originally provided code, while some modifications were made. Namely, due to issues with computation speed in python as compared to Fortran, we only run 10,000 simulations, instead of the 500,000 that were run by the authors of the paper. We, however, found that 10,000 simulations were enough to achieve similar behavior. While the code does work for both calculating cancer incidence curves and viewing the evolutionary pathways to cancer, we choose to view only cancer incidence curves, as they provide a clear visual description of the focus of this paper, which is the effect of aspirin on the possibility of cancer.

We test for two different doses of aspirin, as well as modified lengths of treatment schedules, ranging from 10 years of treatment with aspirin, to 20 years. The parameters used for all simulations and code were calculated in the original paper through best fit curves with relation to real world data sourced from several previous papers and studies. The models used to fit the data come majorly from equations 6-11.

The Mersenne Twister algorithm was used to initialize random states which were used in order to calculate times at each run through the simulation. Simulations were stopped and final values recorded each time the total time (signifying age) reached 80 years, or if we reached a specific number of type 6 crypts, which we describe as the detection size. For the current simulations presented in this paper, we fixed $N_6 = 100$, and so stopped each time 100 crypts consisting of complete mutations within the KRAS and APC genes were produced. Several intermediate parameters are calculated within the simulation, which are then used in order to modify the number of crypts of each type. All values are recorded, however, only crypts of type 6 are plotted. We also incorporate the effect of intercrypt dynamics as well as intracrypt dynamics by modifying F_d and F_r as described in table (2).

3. Computational Results

Through the Gillespie algorithm, we were able to visualize the effect of aspirin modifying cell kinetics. We used the parameters in table (1), and modified our code so that we could see

the effect of high versus low aspirin doses, along with age during the start of treatment, and varying treatment times for each of the cases. The relevant incidence curves for low and high doses of aspirin can be viewed in figures (2) and (3) respectively.

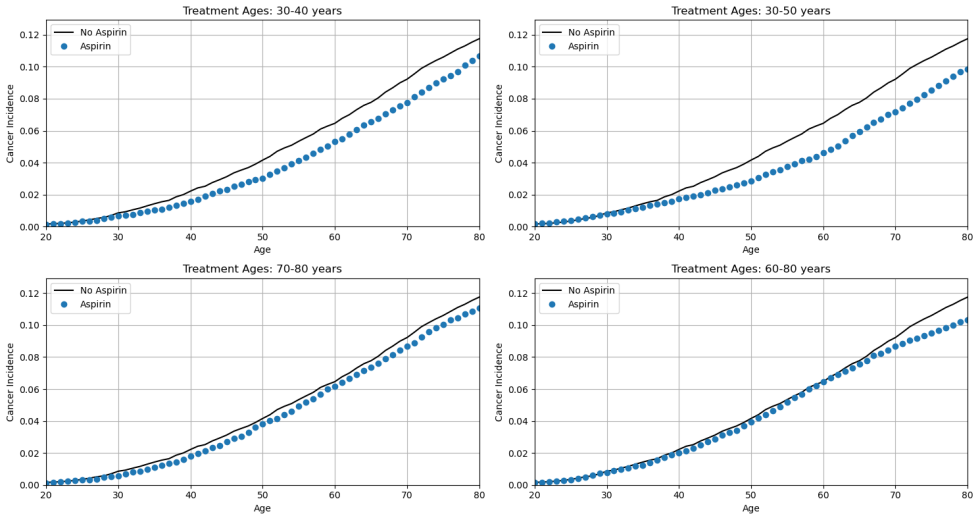

FIGURE 2. Age incidence curves for advanced adenoma with **low dose** treatments with aspirin. From top, going left to right, we treat from ages 30-40, 30-50, 70-80, and 60-80. Dotted line is with aspirin treatment for the specified amount of time, while the black solid line is without any treatment regimens.

For low dose treatments, such as with only an average of 1.8 pills, or around 585mg per week, we can easily see that, while aspirin does have an effect on cancer and adenoma incidence, it does not seem to be extremely large. There is a clear difference in the reduction of adenoma possibility with longer treatments however, as we can see easily in the cases of 20 year long treatments versus 10 year long treatment regimens. We can also see the benefit of starting treatment earlier in life, and notice how much higher adenoma age incidence is when treatment is started later in life.

We also look at the effect of long term high dose treatments, which correspond to an average of 12.2 aspirin pills per week, or 3,965 mg of aspirin. It is evident through the model used and the parameters applied and modified, that cancer incidence is clearly reduced with long term use of higher doses. When the dosage period is changed from 10 to 20 years, we notice nearly a two-fold reduction compared with treatment for 10 years only. It is interesting to notice, however, that even with starting high dose treatment later in life, cancer incidence at the age of 80 years, which is when we end the simulations, is quite similar. This goes to show that even if one starts treatment later, the benefits can still majorly be seen.

4. Conclusions and future directions

Despite a lack of understanding of aspirin's effect on cancer incidence, through this study, and through the modification and fitting of cellular kinetic parameters, we can see that there may indeed be a correlation between the action of aspirin and the growth and death rates of cancer cells. This was visualized clearly through the use of stochastic simulations on the results of deterministic systems of ordinary differential equations, describing the transition of cancer cell types between different states.

In the interest of time, we were unfortunately unable to fit the model parameters ourselves and visualize the changes, which constituted a large, and very important part of this study. However, with the wide availability of data, and with the availability of the parameters used within this model, we can see that the results are clearly reproducible.

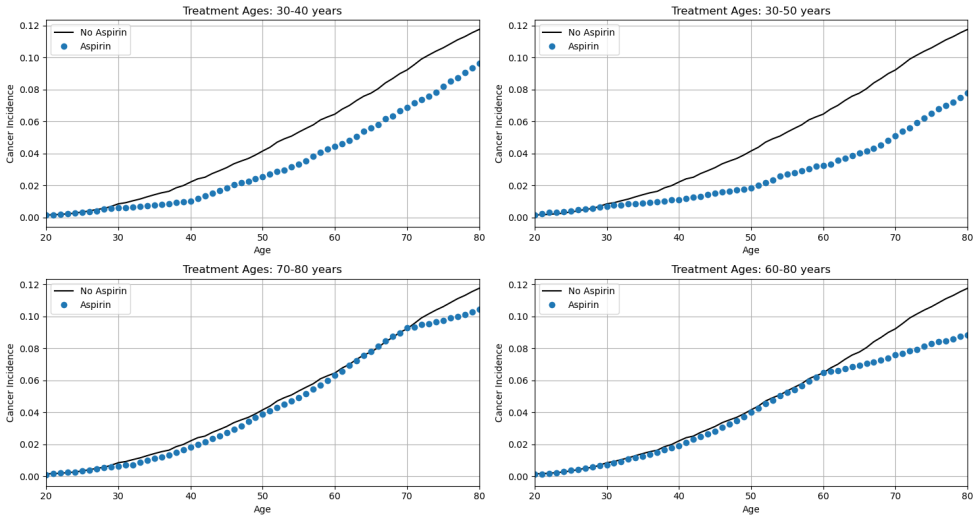

FIGURE 3. Age incidence curves for advanced adenoma with **high dose** treatments with aspirin. From top, going left to right, we treat from ages 30-40, 30-50, 70-80, and 60-80. Dotted line is with aspirin treatment for the specified amount of time, while the black solid line is without any treatment regimens.

The paper studied showed the importance of incorporating crypt competition within the mechanism of cancer growth. This assumes that all mutated crypts are close to one another. Since cancer may not all be growing in one localized area, in further research and projects, one could instead study how inter-crypt dynamics of crypts sufficiently spaced away change both naturally and in response to treatment, and whether or not this will modify the carrying capacity or the equations describing the growth and proliferation of each type of cell. Some other further directions of research could be to incorporate the mechanism of action on hormones such as PGE2 which are both associated with increase in cancer likelihood, as well as affected by aspirin. We can then use computational modeling to understand the effect of aspirin on not just gene mutations, but the overall mechanism of the growth and incidence of cancer.

REFERENCES

[1] Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.s. preventive services task force recommendation statement. *Annals of Internal Medicine*, 164(12):836–845, 2016. PMID: 27064677.

[2] T. Armaghany, J. D. Wilson, Q. Chu, and G. Mills. Genetic alterations in colorectal cancer. *Gastrointestinal cancer research: GCR*, 5(1):19, 2012.

[3] M. D. Castellone, H. Teramoto, B. O. Williams, K. M. Druey, and J. S. Gutkind. Prostaglandin e¡sub¿2¡/sub¿ promotes colon cancer cell growth through a g¡sub¿s¡/sub¿-axin-β-catenin signaling axis. *Science*, 310(5753):1504–1510, 2005.

[4] P. J. Lochhead and A. T. Chan. Aspirin and the prevention of colorectal cancer. *NSAIDs and Aspirin: Recent Advances and Implications for Clinical Management*, pages 219–240, 2016.

[5] D. Pu, L. Yin, L. Huang, C. Qin, Y. Zhou, Q. Wu, Y. Li, Q. Zhou, and L. Li. Cyclooxygenase-2 inhibitor: A potential combination strategy with immunotherapy in cancer. *Frontiers in Oncology*, 11, 2021.

[6] R. S. Sandler, S. Halabi, J. A. Baron, S. Budinger, E. Paskett, R. Keresztes, N. Petrelli, J. M. Pipas, D. D. Karp, C. L. Loprinzi, et al. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. *New England Journal of Medicine*, 348(10):883–890, 2003.

[7] T. Shimura, S. Toden, N. L. Komarova, C. Boland, D. Wodarz, and A. Goel. A comprehensive in vivo and mathematic modeling-based kinetic characterization for aspirin-induced chemoprevention in colorectal cancer. *Carcinogenesis*, 41(6):751–760, 01 2020.

[8] R. L. Siegel, K. D. Miller, A. Goding Sauer, S. A. Fedewa, L. F. Butterly, J. C. Anderson, A. Cercek, R. A. Smith, and A. Jemal. Colorectal cancer statistics, 2020. *CA: a cancer journal for clinicians*, 70(3):145–164, 2020.

[9] Y. Wang, C. R. Boland, A. Goel, D. Wodarz, and N. L. Komarova. 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, apr 2022.

Appendix

Gillespie Algorithm Adaptation in Python. The general structure of the code is given here, with values for each of the parameters listed in table 1. In the interest of space, since parameters are initialized several times, we replace the initial values with `<initial parameters>`, or `<modified parameters>`. The full code can be viewed on github (https://github.com/maham-khalid1/Gillespie-sim)

```
rng = np.random.Generator(np.random.MT19937()) #using MT19937 64-bit floats
xran = rng.random()
iran = int(1e+6 * xran)
np.random.seed(iran)

<initial parameters>

iruns = 0
aspirin = False
xtime = 0.0

pathcount = 0
patharr = np.zeros(1000000, dtype=int)

results = []
paths = []

def ran0():
    return np.random.rand()

while True:
    iruns +=1
    if iruns >= 10000:
        break
    t = 0
    n1 = Ncrypt * np.exp(-(R12 + R14) * t)
    n2 = (Ncrypt * R12 * (np.exp(-(R23 + R25) * t) -
            np.exp(-(R12 + R14) * t))) / (R12 + R14 - R23 - R25)
    n3 = 0
    n4 = 0
    n5 = 0
    n6 = 0

    <initial R12, R14, R23, R25, R36, R45, R56, k1,
             k2, gamma3, gamma4, gamma5, gamma6, d, Ncrypt>

    aspirin = False
    xtime = 0.

    pathcount = 0
    patharr[:] = 0

    while True:
        # ASPIRIN
        if xtime >= 30 and not aspirin:
            aspirin = True
            gamma3 *= 0.9
            gamma4 *= 0.9
```

```
    gamma6 *= 0.9
    d *= 1.5
    <initial R12, R14, R23, R25, R36, R45, R56>

if xtime >= 50:
    <modified R12, R14, R23, R25, R36, R45, R56>
    gamma3 = 0.2
    gamma4 = 0.07
    gamma5 = 0.07
    gamma6 = 1.012
    d = 0.05
    Ncrypt = 1e7

sss = n3 + n4 + n5

g1 = abs(gamma3 * n3 * (1 - sss / k1))
gg1 = gamma3 * n3 * (1 - sss / k1)
g2 = d * n3
g3 = R23 * n2
g4 = R36 * n3
g5 = abs(gamma4 * n4 * (1 - sss / k2))
gg5 = gamma4 * n4 * (1 - sss / k2)
g6 = d * n4
g7 = R14 * n1
g8 = R45 * n4
g9 = abs(gamma5 * n5 * (1 - sss / k2))
gg9 = gamma5 * n5 * (1 - sss / k2)
g10 = d * n5
g11 = R25 * n2
g12 = R56 * n5
g13 = gamma6 * n6
g14 = d * n6

ss = g1 + g2 + g3 + g4 + g5 + g6 +
          g7 + g8 + g9 + g10 + g11 + g12 + g13 + g14
if ss == 0:
    break

aa = g1 / ss
bb = g2 / ss
cc = g3 / ss
dd = g4 / ss
ee = g5 / ss
ff = g6 / ss
gg = g7 / ss
hh = g8 / ss
ii = g9 / ss
jj = g10 / ss
kk = g11 / ss
ll = g12 / ss
mm = g13 / ss
nn = g14 / ss

xran = ran0()
```

```
if xran < aa:
    if gg1 > 0:
        n3 += 1
    elif gg1 < 0:
        n3 -= 1
elif xran < aa + bb:
    n3 -= 1
elif xran < aa + bb + cc:
    n3 += 1
elif xran < aa + bb + cc + dd:
    n3 -= 1
    n6 += 1
    pathcount += 1
    patharr[pathcount] = 1
elif xran < aa + bb + cc + dd + ee:
    if gg5 > 0:
        n4 += 1
    elif gg5 < 0:
        n4 -= 1
elif xran < aa + bb + cc + dd + ee + ff:
    n4 -= 1
elif xran < aa + bb + cc + dd + ee + ff + gg:
    n4 += 1
elif xran < aa + bb + cc + dd + ee + ff + gg + hh:
    n4 -= 1
    n5 += 1
elif xran < aa + bb + cc + dd + ee + ff + gg + hh + ii:
    if gg9 > 0:
        n5 += 1
    elif gg9 < 0:
        n5 -= 1
elif xran < aa + bb + cc + dd + ee + ff + gg + hh + ii + jj:
    n5 -= 1
elif xran < aa + bb + cc + dd + ee + ff + gg + hh + ii + jj + kk:
    n5 += 1
elif xran < aa + bb + cc + dd + ee +
            ff + gg + hh + ii + jj + kk + ll:
    n5 -= 1
    n6 += 1
    pathcount += 1
    patharr[pathcount] = 0
elif xran < aa + bb + cc + dd + ee +
            ff + gg + hh + ii + jj + kk + ll + mm:
    n6 += 1
elif xran < aa + bb + cc + dd + ee +
            ff + gg + hh + ii + jj + kk + ll + mm + nn:
    n6 -= 1
if n6 >= 100: #1e2:
    results.append([xtime, n1, n2, n3, n4, n5])
    paths.append(patharr[:pathcount].tolist())
    break

if xtime >= 80 and n6 < 100: #1e2:
```

```
    break

xran = ran0()
xtime += -np.log(xran) / ss

t = xtime
n1 = Ncrypt * np.exp(-(R12 + R14) * t)
n2 = (Ncrypt * R12 * (np.exp(-(R23 + R25) * t) -
        np.exp(-(R12 + R14) * t))) / (R12 + R14 - R23 - R25)
```