

Generalized mathematical model of cancer heterogeneity

Jul 10, 2020

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Motohiko Naito¹¹Ronin

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dx.doi.org/10.17504/protocols.io.bhzej73e

Motohiko Naito

ABSTRACT

The number of reports on mathematical modeling related to oncology is increasing with advances in oncology. Even though the field of oncology has developed significantly over the years, oncology-related experiments remain limited in their ability to examine cancer. To overcome this limitation, in this study, a stochastic process was incorporated into conventional cancer growth properties to obtain a generalized mathematical model of cancer growth. Further, an expression for the violation of symmetry by cancer clones that leads to cancer heterogeneity was derived by solving a stochastic differential equation. Monte Carlo simulations of the solution to the derived equation validate the theories formulated in this study. These findings are expected to provide a deeper understanding of the mechanisms of cancer growth, with Monte Carlo simulation having the potential of being a useful tool for oncologists.

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<https://www.biorxiv.org/content/10.1101/2020.05.25.115725v1.full#ref-14>

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ATTACHMENTS

[Generalized mathematical model of cancer heterogeneity.pdf](#)

DOI

dx.doi.org/10.17504/protocols.io.bhzej73e

PROTOCOL CITATION

Motohiko Naito 2020. Generalized mathematical model of cancer heterogeneity. **protocols.io**
dx.doi.org/10.17504/protocols.io.bhzej73e



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<https://doi.org/10.1101/2020.05.25.115725>

EXTERNAL LINK

<https://www.biorxiv.org/content/10.1101/2020.05.25.115725v1.full#ref-14>

KEYWORDS

cancer, heterogeneity, mathematical model

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
CREATED

Jun 27, 2020

LAST MODIFIED

Jul 10, 2020

OWNERSHIP HISTORY

Jun 27, 2020  Megan Freund

Jul 09, 2020  Motohiko Naito

PROTOCOL INTEGER ID

38662

GUIDELINES

References (Sort Version)

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2. https://www.jst.go.jp/crest/math/ja/suugakujuku/archive/text/4_Teramae.pdf (written in Japanese)
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4. https://matplotlib.org/examples/pylab_examples/barchart_demo.html

References (Detailed Protocol)

- (14) Yamazaki H, Naito M, Ghani FI, et al. characterization of cell properties of CD24 and CD26-positive human malignant mesothelioma cells. *Biochem Biophys Res Commun.* 2012; **419**(3): 529–536.
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MATERIALS TEXT

Software

- Python, matplotlib
- R Software

SAFETY WARNINGS

Refer to the Safety Data Sheet (SDS) for any hazards and safety warnings.

BEFORE STARTING

The R software was used to analyze data and simulate cancer cell growth. In addition, R was used to create all graphs except [Fig. 2\(a\)](#) and [Fig. 3\(a\)](#) (see case 'Detailed Protocol'), which were drawn using Python, matplotlib.

- 1 There's a short protocol available that contains all used codes, and a detailed version that is based on the preprint. Step 1 includes a Step case.

Short Version and Codes

Detailed Protocol

Abstract of the theory to simulate the growth of cancer cells

step case

Short Version and Codes

- 2 Number of the cancer cells at time t .

$$N(t) = n_0 e^{\lambda t} \pm e^{\lambda t} \sqrt{2n_0 \lambda} \int_0^t e^{-\lambda s} dB_s. \quad (\text{Eq. 1})$$

where, $N(0)=n_0$, λ is a parameter of the growth of cancer cells, Bs denote the brownian motion function.

- 3 In general, if appropriate experiments or the observations of cancer patients' status are performed, then the mean and variance of cancer growth are obtained. \hat{m} , \hat{v} , and \hat{t} are defined to be the actual values of mean, variance, and time, respectively.



Note that these three symbols with the hat mark are not algebraic variables but the actual experimental data obtained.

- 4 Thus, following equation are obtained:

$$n_0 = \frac{\hat{m}^2}{\hat{v} + \hat{m}}, \lambda = \frac{1}{\hat{t}} \log_e \left(\frac{\hat{v} + \hat{m}}{\hat{m}} \right)$$

In conclusion, if appropriate experiments or the observations of cancer patients' status are performed, then the number of cancer cells can be solved.

- 5 The interpretations of Eq. (1) are continued. Eq. (1) apparently consists of two equations. Thus, Eq. (1) indicates that cancer growth follows two different formulae. $N(t) = n_0 e^{\lambda t} + \gamma(t) e^{\lambda t}$, where

$$\gamma(t) = \sqrt{2n_0\lambda} \int_0^t e^{-\lambda s} dBs \text{ is defined as the Ryu pathway and}$$

$$N(t) = n_0 e^{\lambda t} - \gamma(t) e^{\lambda t} \text{ as the Ken pathway.}$$

Design of the numerical solution and Monte Carlo simulation

6



This section describes the outline of the numerical solution and simulation conducted in the preprint. The detailed programs written for these calculations are available in the next sections.

The numerical solution of $dN(t) = \lambda N(t)dt + \sigma dBt$ is obtained by employing the Euler-Maruyama method:

n partitions of the interval $(0, t]$ are defined as $(t_{i-1}, t_i]$, ($i = 1, 2, \dots, n$), where $\Delta t_i := t_{i+1} - t_i$. Then,

$$\Delta N_i := N_{i+1}(t) - N_i(t) = \lambda \Delta t_i + \sigma \Delta Bt_i,$$

where ΔBt_i is a random number that follows a normal distribution with $mean = 0$ and $sd = \sqrt{\Delta t_i}$.

- 7 By solving the above equation, the numerical solution for $N(t)$ is obtained: $N(t) = n_0 + \sum_i \Delta N_i$. This calculation is itself the Monte Carlo method. Based on the law of large numbers, repeating this calculation numerous times can reveal the population mean of cancer growth. This Monte Carlo calculation was repeated 100 times to simulate cancer growth; this is referred to as Monte Carlo simulations.

Code of growth simulation

- 8 First of all, because #(sentence, or number) is automatically ignored by R software as well as Python software, # is

usually used to comment to human.



Note that the code mentioned below has a random number in it. Therefore, even if you run this code with no arrangement, it is not possible to obtain the exact figures presented in this preprint.



The codes shown in Figs 2 and 3 are similar. Thus, only the code shown in Fig. 3 is presented in this manuscript (if you want the data of Fig 2, then you only exchange the value of lam, sigma, and n (appeared first time)).

If you want to re-produce the exactly same data on your PC, then you can get it to type the below code at first:

```
> set.seed (any integral, e.g. 29 )  
# code fixing the random number
```

Fig 3 code

9



Figures can be found in the case 'Detailed Protocol' or in the [preprint](#).

#Generating the function that plots the Ryu pathway of the JMM CV cell lines.

```
####  
# jmmryucv ()  
####  
jmmryucv <-function(){  
  #fixing the time and parameters  
  dt <- 0.01 # time interval  
  TT <-250 # end time. TT is 50 in some figures.  
  lam <-2.44 # growth rate: lambda, one of the parameters of this equation  
  sigma <-18.73*sqrt(dt)  
  # sigma is the coefficient of the Brownian motion function.  
  n <-188.87  
  #substituting the initial number of cancer cells, another parameter of this equation  
  #making the list of results  
  nn<-n  
  tt <- 0.0  
  #main body of this calculation  
  for(i in 1:TT){  
    #calculating the increment. The second term says that "Create the one random number that follows normal distribution  
    and multiply it by sigma."  
    dn <-(lam*n)*dt+sigma*rnorm(1)  
    n <-dn+n  
    # if variable i is integral, the latest results are added to the list nn and tt  
    if(i %% 1==0){  
      nn<-rbind(nn,n)  
      tt<-rbind(tt,i);  
    }  
  }  
  #plot the results of the calculations  
  matplot(tt,nn,type="l",ylab="Number of Cancer cells", xlab="Time",col="blue", ylim=c(0,10000))  
}
```

#Generating the function that plots the Ken pathway of JMM CV cell lines

```
####  
# jmmkencv ()  
####  
  
jmmkencv <-function(){  
  dt <- 0.01  
  TT <-250  
  lam <-2.44  
  sigma <-18.73*sqrt(dt)  
  n <-188.87  
  nn<-n  
  tt <- 0.0  
  for(i in 1:TT){  
    dn <-(lam*n)*dt-sigma*rnorm(1)  
    n <-dn+n  
    if(i %% 1==0){  
      nn<-rbind(nn,n)  
      tt<-rbind(tt,i);  
    }  
  }  
  matplot(tt,nn,type="l",ylab="Number of Cancer cells",  
  xlab="Time",col="blue",ylim=c(0,1e+05)) # 1e+05 =10,000 at R  
}
```

Generating the function that shows the two pathways in one sheet

```
####  
  
#jmmcvplot ()  
####  
  
jmmcvplot <-function(){  
  jmmkencv()  
  par(new=TRUE)  
  jmmryucv()  
}
```

Calculation codes of the JMM sh-CD24 cell lines, which is basically the same as that of the JMM CV cell lines.

```
####  
# jmmsd24ryu()  
####  
  
jmmsd24ryu <-function(){  
  dt <- 0.01  
  TT <-250  
  lam <-2.33  
  sigma <-21.11*sqrt(dt)  
  n <-134.22  
  nn<-n  
  tt <- 0.0  
  for(i in 1:TT){  
    dn <-(lam*n)*dt-sigma*rnorm(1)  
    n <-dn+n  
    if(i %% 1==0){  
      nn<-rbind(nn,n)  
    }  
  }  
}
```

```

tt<-rbind(tt,i);
}
}
matplot(tt,nn,type="l",ylab="Number of Cancer cells",
xlab="Time",col="red",ylim=c(0,1e+05))
}

###
# jmmsd24ken()
###

jmmsd24ken <-function(){
dt <- 0.01
TT <-250
lam <-2.33
sigma <-21.11*sqrt(dt)
n <-134.22
nn<-n
tt <- 0.0
for(i in 1:TT){
dn <-(lam*n)*dt+sigma*rnorm(1)
n <-dn+n
if(i %% 1==0){
nn<-rbind(nn,n)
tt<-rbind(tt,i);
}
}
matplot(tt,nn,type="l",ylab="Number of Cancer cells",
xlab="Time",col="red",ylim=c(0,1e+05))
}

###
# jmmsd24plot()
###

jmmcd24plot <-function(){
jmmsd24ken()
par(new=TRUE)
jmmsd24ryu()
}

```

Calculation codes of the JMM sh-CD26 cell lines

```

###
# jmmsd26ryu()
###

jmmcd26ryu <-function(){
dt <- 0.01
TT <-250
lam <-2.75
sigma <-9.74*sqrt(dt)
n <-17.69
nn<-n
tt <- 0.0
for(i in 1:TT){
dn <-(lam*n)*dt+sigma*rnorm(1)
n <-dn+n
if(i %% 1==0){

```

```

nn<-rbind(nn,n)
tt<-rbind(tt,i);
}
}
matplot(tt,nn,type="l",ylab="Number of Cancer cells", xlab="Time",col="black",ylim=c(0,1e+05))
}

###
# jmmsd26ken()
###
jmmcd26ken <-function(){
dt <- 0.01
TT <-250
lam <-2.75
sigma <-9.74*sqrt(dt)
n <-17.69
nn<-n
tt <- 0.0
for(i in 1:TT){
dn <-(lam*n)*dt-sigma*rnorm(1)
n <-dn+n
if(i %% 1==0){
nn<-rbind(nn,n)
tt<-rbind(tt,i);
}
}
matplot(tt,nn,type="l",ylab="Number of Cancer cells",
xlab="Time",col="black",ylim=c(0,1e+05))
}

###
# jmmsd26plot()
###

jmmcd26plot <-function(){
jmmcd26ken()
par(new=TRUE)
jmmcd26ryu()
}

# Codes of Monte Carlo simulations. These codes generate the plot x times that calculates the above programming.

###
# jmmcvgraph (x)
#Generating the function that draws jmmcvplot () x times in one sheet.
###
jmmcvgraph<-function(x){
if(x<=0){
print("Please enter one or more.")
}else{
for(i in 1:x){
if(i>1){
par(new=TRUE)
jmmcvplot ()
}else{
if(i==1){
jmmcvplot ()
}
}
}
}
}

```

```

}
}
}
}

###
# jmmcd24graph (x)

###
jmmcd24graph<-function(x){
  if(x<=0){
    print("Please enter one or more.")
  }else{
    for(i in 1:x){
      if(i>1){
        par(new=TRUE)
        jmmcd24plot ()
      }else{
        if(i==1){
          jmmcd24plot ()
        }
      }
    }
  }
}

###
# jmmcd26graph (x)

###
jmmcd26graph<-function(x){
  if(x<=0){
    print("Please enter one or more.")
  }else{
    for(i in 1:x){
      if(i>1){
        par(new=TRUE)
        jmmcd26plot ()
      }else{
        if(i==1){
          jmmcd26plot ()
        }
      }
    }
  }
}

```

Fig 4 code

```

10 # Simulation code of  $n_0 = 1$  and  $\lambda = 2.5$ 
###
# ryu pathway
##

ryu <-function(){
  dt <-0.01
  TT <-250
  lam <-2.5

```



```

sigma <-sqrt(lam*1*2)*sqrt(dt)
n <-1
nn<-n
tt <- 0.0
for(i in 1:TT){
dn <-(lam*n)*dt+sigma*rnorm(1)
n <-dn+n
if(i %% 1==0){
nn<-rbind(nn,n)
tt<-rbind(tt,i);
}
}
matplot(tt,nn,type="l",ylab="Number of Cancer cells", xlab="Time",col="black", ylim=c(0,750))
}

##
#ken pathway
##

ken <-function(){
dt <-0.01
TT <-250
lam <-2.5
sigma <-sqrt(lam*1*2)*sqrt(dt)
n <-1
nn<-n
tt <- 0.0
for(i in 1:TT){
dn <-(lam*n)*dt-sigma*rnorm(1)
n <-dn+n
if(i %% 1==0){
nn<-rbind(nn,n)
tt<-rbind(tt,i);
}
}
matplot(tt,nn,type="l",ylab="Number of Cancer cells", xlab="Time",col="red", ylim=c(0,750))
}

##
# Simulation code of growing cancer clones
##
#Ryu code of the JMM CV cell lines
jmmngryucv <-function(){
dt <- 0.01
TT <-250
lam <-2.44
sigma <-18.73*sqrt(dt)
n <-188.87

nn<-n
tt <- 0.0
for(i in 1:TT){
dn <- sigma*rnorm(1)
n <-dn+n
if(i %% 1==0){
nn<-rbind(nn,n)
tt<-rbind(tt,i);
}
}
}

```

```

}
matplot(tt,nn,type="l",ylab="Number of Growing clones", xlab="Time", col="black", ylim=c(0,250))
}

#Ken code of the JMM CV cell lines
jmmngkencv <-function(){
dt <- 0.01
TT <-250
lam <-2.44
sigma <-18.73*sqrt(dt)
n <-188.87
nn<-n
tt <- 0.0
for(i in 1:TT){
dn <- -sigma*rnorm(1)
n <-dn+n
if(i %% 1==0){
nn<-rbind(nn,n)
tt<-rbind(tt,i);
}
}
matplot(tt,nn,type="l",ylab="Number of Growing clones", xlab="Time", col="red", ylim=c(0,250))

}

# JMM sh-cd26 simulations

# Ryu code

jmmcd26ngryu <-function(){
dt <- 0.01
TT <-250
lam <-2.75
sigma <-9.74*sqrt(dt)
n <-17.69
nn<-n
tt <- 0.0
for(i in 1:TT){
dn <-sigma*rnorm(1)
n <-dn+n
if(i %% 1==0){
nn<-rbind(nn,n)
tt<-rbind(tt,i);
}
}
matplot(tt,nn,type="l",ylab="Number of Growing Cancer cells", xlab="Time", col="black", ylim=c(-10,30))
par(new=TRUE)
matplot(tt, 0*tt, type="l", lty=6, ylab="Number of Growing Cancer cells", xlab="Time", col="blue", ylim=c(-10,30))
}

#Ken code
jmmcd26ngken <-function(){
dt <- 0.01
TT <-250
lam <-2.75
sigma <-9.74*sqrt(dt)
n <-17.69
nn<-n

```

```

tt <- 0.0
for(i in 1:TT){
  dn <- sigma*rnorm(1)
  n <- dn+n
  if(i %% 1==0){
    nn<-rbind(nn,n)
    tt<-rbind(tt,i);
  }
}
matplot(tt,nn,type="l",ylab="Number of Growing Cancer cells", xlab="Time", col="red", ylim=c(-10,30))
par(new=TRUE)
matplot(tt, 0*tt, type="l", lty=6, ylab="Number of Growing Cancer cells", xlab="Time", col="red", ylim=c(-10,30))
}

# Plotting the growing clones of the JMM sh-CD26 cell line
jmmcd26ngplt <- function(){
  jmmcd26ngken()
  par(new=TRUE)
  jmmcd26ngryu()
}

```

Fig 2(a) and Fig 3(a) code

```

11 #Note: This graph is written by Python, matplotlib
import numpy as np
import matplotlib.pyplot as plt
JMMcvm = (1., 8.93, 23.46, 79.63)
JMMcvsd = (0., 0.15, 2.79, 57.90)
JMMsh24m = (1., 7.37, 13.47, 29.18)
JMMsh24sd = (0., 0.28, 0.43, 18.91)
JMMsh26m = (1., 4.40, 10.44, 24.04)
JMMsh26sd = (0., 0.87, 2.29, 4.57)
#the above six results are same as those listed in Table 1
n_groups = 4
fig, ax = plt.subplots()
index = np.arange(n_groups)
bar_width = 0.3
# Drawing the bar graph
JMMcvBar = plt.bar(index, JMMcvm, bar_width,
alpha=opacity,
color='blue',
yerr=JMMcvsd,
error_kw=error_config)
JMMsh24Bar = plt.bar(index + bar_width, JMMsd24m, bar_width,
alpha=opacity,
color='red',
yerr=JMMsh24sd,
error_kw=error_config)
JMMsh26Bar = plt.bar(index + 2*bar_width, JMMsh26m, bar_width,
alpha=opacity,
color='black',
yerr=JMMsh26sd,
error_kw=error_config)
plt.xlabel('Time')
plt.ylabel('Number of cancer cells')
plt.xticks(index + 2*bar_width / 3, ('Day1', 'Day4', 'Day7', 'Day10'))
plt.tight_layout()
plt.show()

```