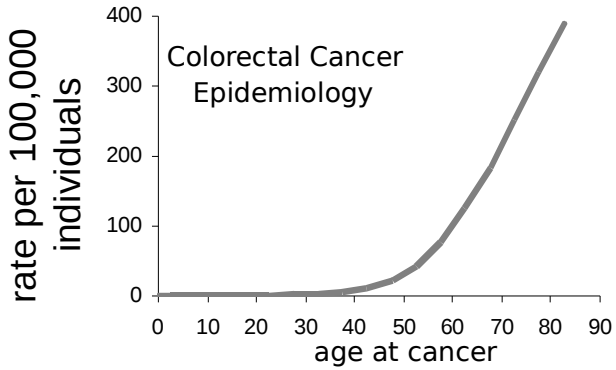
MODELING AND SIMULATION OF CELL DIVISION MODULE USING MATLAB

Problem Formulation: A fundamental question is whether human cancers may arise From relatively “normal” processes, specifically normal mutation and division rates.

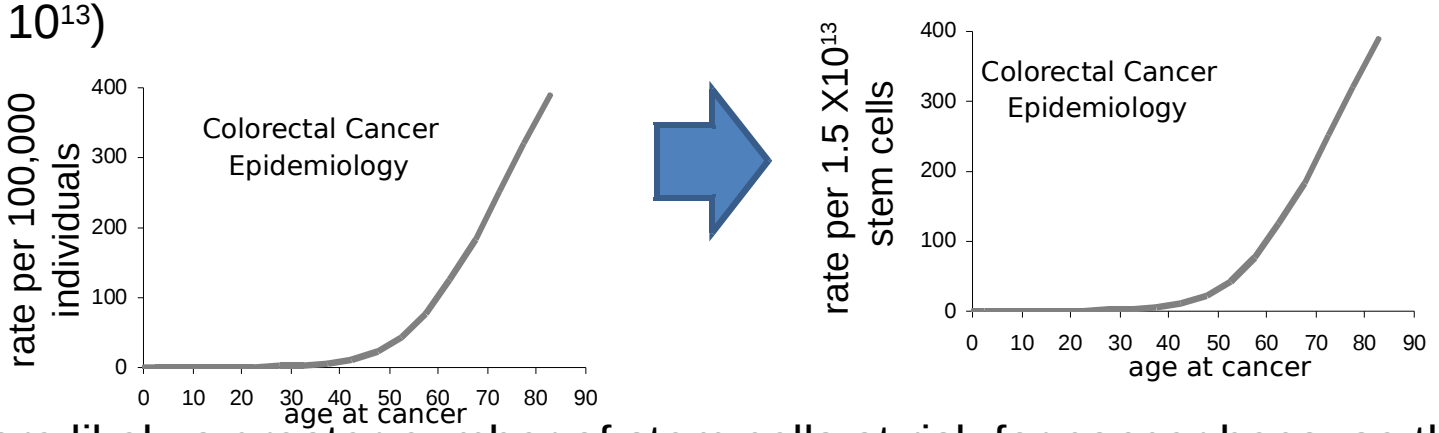
Problem Analysis: One can calculate the probability of cancer with a simple model The “answer” is provided by cancer epidemiology, or how often cancer arises in a Single cell during a lifetime:



As seen above, the incidence of colorectal cancer increases with age. Although epidemiology measures cancers in human populations, it is easy to convert this data into cell populations. A human colon contains about 15 million crypts, and each crypt has a least one long-lived stem cell lineage that may eventually transform.

Mathematical Model

Therefore the minimum number of stem cells at risk is 15,000,000 per person. For a 100,000 individual population, there are 15,000,000,000,000 stem cells at risk (1.5×10^{13})



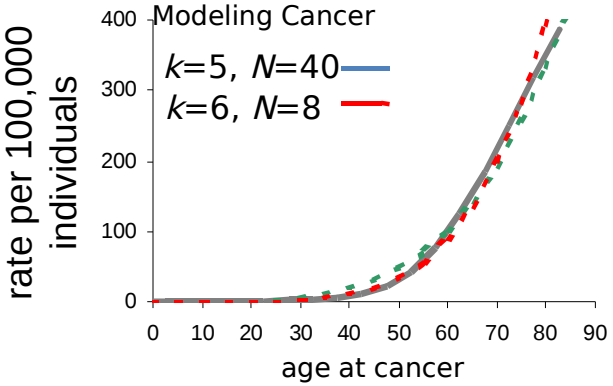
There are likely a greater number of stem cells at risk for cancer because there are likely multiple stem cells per human colon crypt. It is clear that only a small fraction of at risk stem cells transform within a lifetime (a lifetime transformation efficiency of ~3×10^{-9}).

Intuition: The probability that a single cell within an individual transforms likely depend on a number of parameters. Transformation is more likely with greater numbers of cells at risk, greater numbers of divisions, higher mutation rates, and fewer numbers of required drivers (selective) mutations. The relative contributions of these risk factors towards transformation can be formally related in the derived equation.

Parameters: 1) k number of required driver mutations
2) m number of crypts per colon
3) N number of stem cells per crypt
4) u mutation rate
5) d divisions since birth

$$p = 1 - (1 - (1 - (1 - u)^d)^k)^{Nm}$$

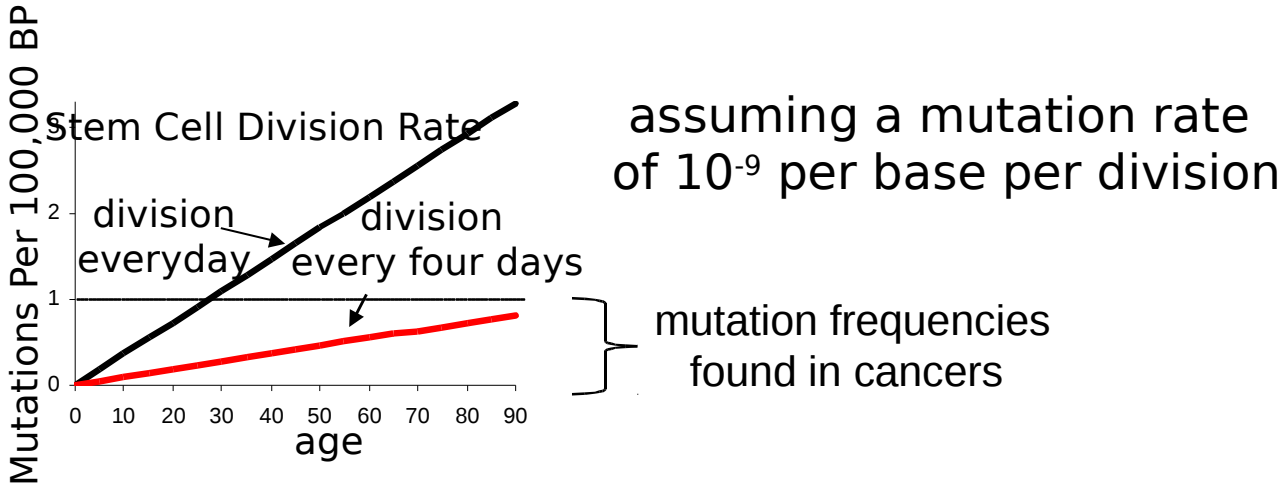
p is the probability that a single stem cell within an individual will transform after d divisions. The question is whether this equation can match the epidemiology of cancer with reasonable or "normal" values for the mutation rate, cell division rate, numbers of stem cells, and numbers of driver mutations. As illustrated below, the equation can yield an cancer/age incidence curve similar to human colorectal cancer epidemiology with reasonable parameter values:



m (number of crypts per colon) = 15,000,000
u (mutation rate) = ~ 1 X 10^{-6} per gene per division
d (divisions) = once every 4 days

The equation demonstrates that colorectal cancers can arise within a lifetime with relatively normal division and mutation rates. Recent cancer genome sequencing projects allow an independent test of this conclusion because the actual numbers of somatic mutations per cancer genome are measured.

Although cancers are thought to have “genomic instability”, the actual number of somatic mutations detected by cancer genome sequencing projects is generally < 1 per 100,000 bases (in DNA mismatch repair proficient cancers). By contrast, the difference between any two unrelated “normal” individuals is about 100-fold greater and ~100 SNPs per 100,000 bases. This relatively low frequency of somatic mutations is consistent with relatively normal mutation and division rates.



Implementation

```
% probability equation used for calculatng cancer
% p=1-(1-(1-(1-u)^2)^d)^(N*m);
% Parameter description :-
% muh denotes mutation_rate
% N denotes stem_cell_per_crypt
% m denote no_of_crypts
% d denotes division since birth
% k denote rate_limiting_mutation
% ++++++++++++++++++++++++++++++++++++++++++ %
for j=1:2
   muh=3.00E-06;
   N=input('enter crypt_stem cell per crypt');
   m=1.50E+07;
   k=input('enter value of limiting_rate mutation');
   d=[0 456.5 912.5 1368.5 1825 2281.25 2737.5 3193.75 3650 4106.25
4562.5 5018.75 5475 5931.25 6387.5 6843.75 7300 7756.25 8212.5 ];
   prob=zeros(1,19);
   t=k;
   l=N;
```

```
for i=1:19
   prob(i)=1-(1-(1-(1-muh)^d(i))^t)^(l*m);

end
% person's age array with increment of five %
   age=0:5:90;
if(j==1)
   plot(age,prob,'r');
   legend('N1=8');
   xlabel('Person age');
   ylabel('Rates per 100,000 individual');
   grid on
   hold on
end
if(j==2)
    plot(age,prob,'g--');
    grid on
end

end
hold off
```

output

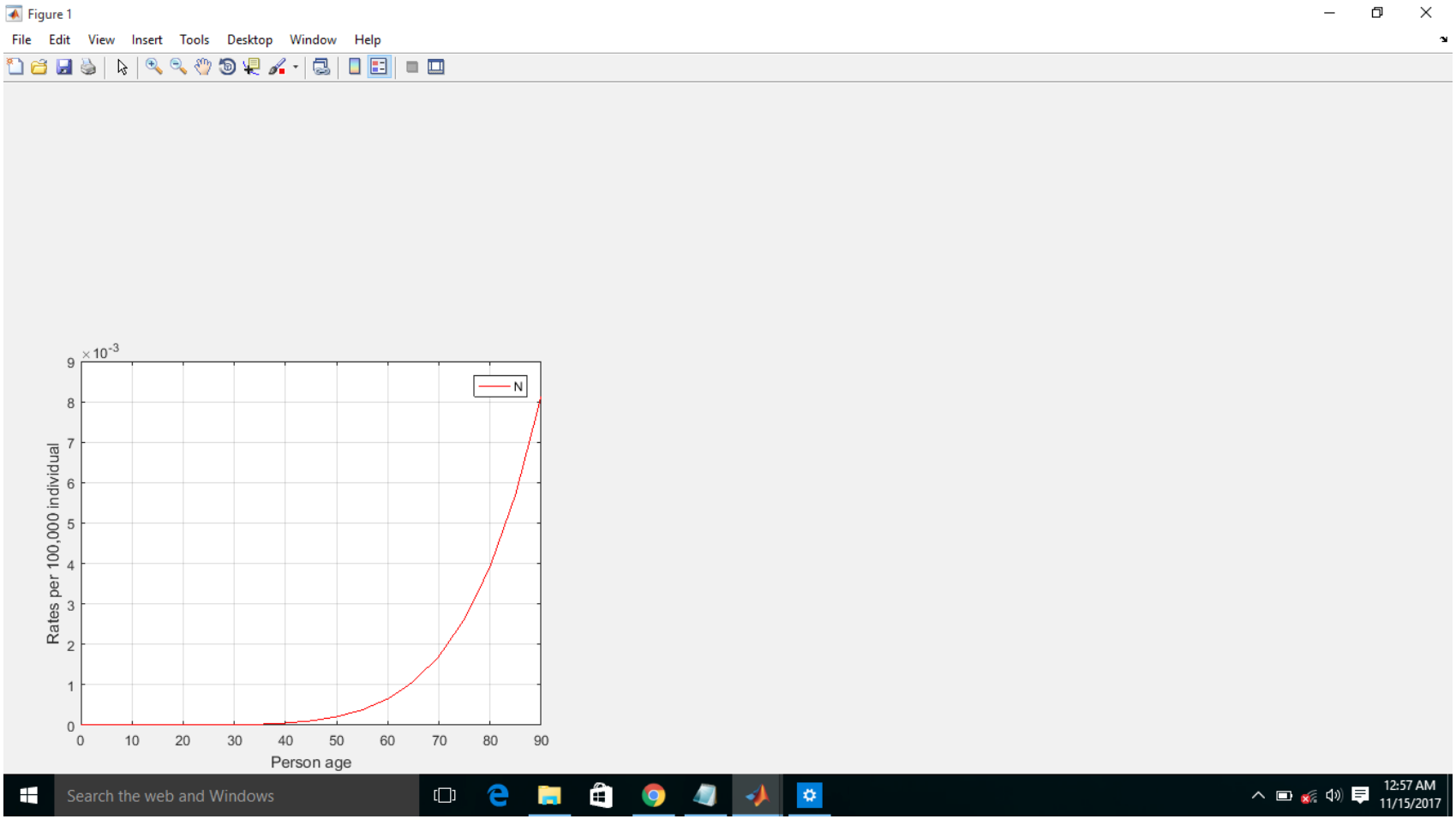


Figure 1
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Rates per 100,000 individual
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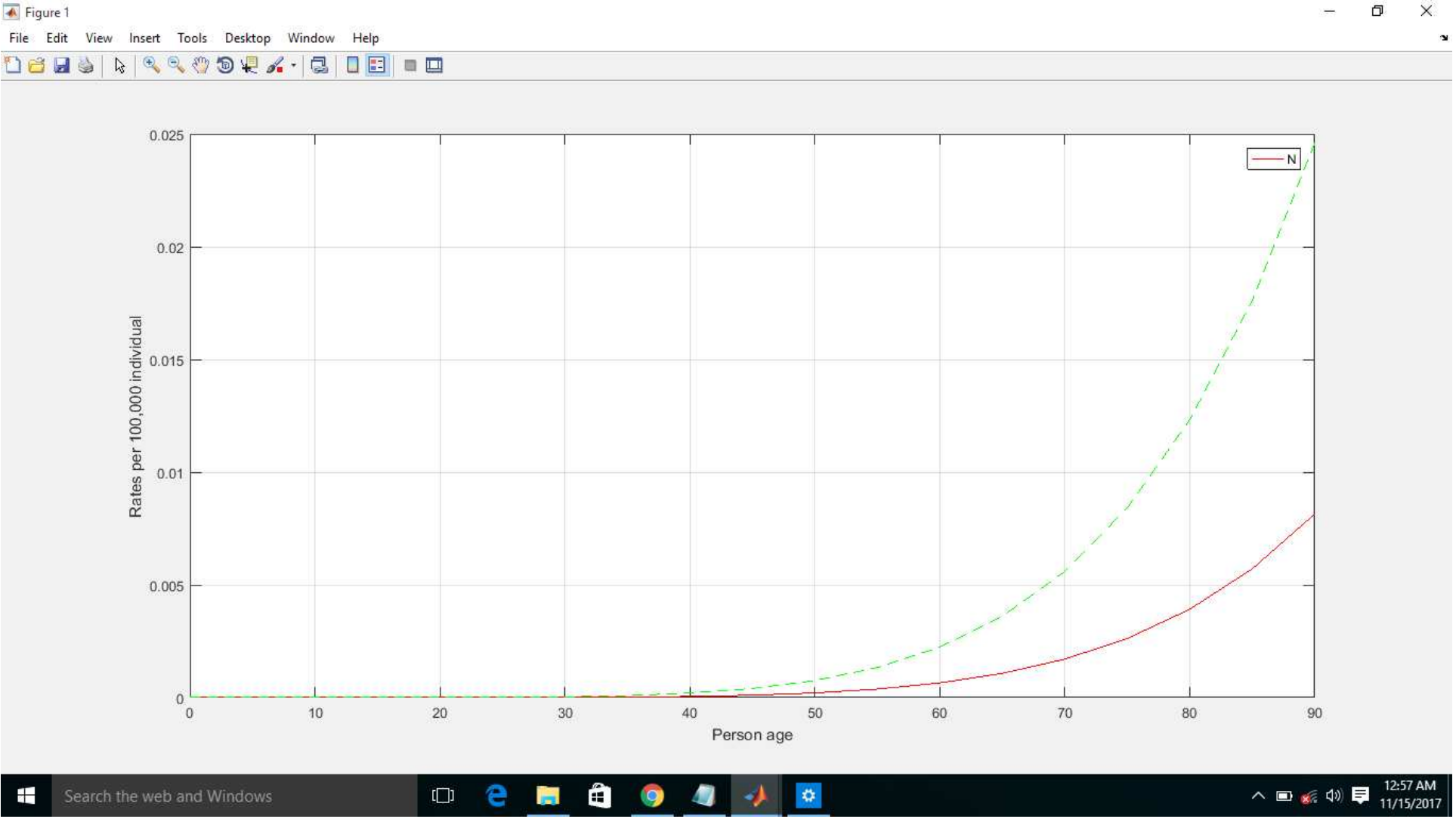
Figure 1
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Rates per 100,000 individual
0 10 20 30 40 50 60 70 80 90
Person age
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11/15/2017

Conclusions

1)The equation $p = 1 - (1 - (1 - (1 - u)^d)^k)^{Nm}$ illustrates that cancers can arise at rates matching human cancer epidemiology with relatively normal mutation and Division rates.

2) How small variations in the parameters can predict the relatively risks seen with greater height, germline APC mutations, aspirin use, and ulcerative colitis. Although this equation does not encompass all of the Complexity of cancer (especially changes that occur during aging and with mutation)

3) Model serve as a “beginners” guide to demonstrate how different biological Cancer features may be related.