Analyze the resulting dynamics of a SIMCoV model

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***Abstract*—This project provides a thorough analysis of the findings from SIMCoV runs by conducting a set of experiments in which the parameters are changed to generate different dynamics of virus concentrations (called viral load) and the number of infected cells. We were able to find stability, periodic, and chaotic dynamics.We were also able to connect stability and periodic dynamics to real immunological variation scanarios.We were not able to find a real immunological variation sceario for our chaotic dyanmic dynamic. We constructed a logistic map and compared its dynamics with those of our SIMCoV time series. Our analysis attempts to tie the findings of experiments with real immunological variations among people.**

***Index Terms*—SIMCoV, dynamics, infected cells, virions, logistic map, vaccinations, boosters**

I. Introduction

SARS-CoV-2 is a complex adaptive system because of the way the virus interacts with cells in a patient's lungs. The virus is also a complex adaptive system because it is decentralized, it follows simple rules for reproducing and spreading, and it adapts to its environment. Because the virus is a complex adaptive system, it is susceptible to different dynamics which may not be intuitive. The goal of this project is to get a better understanding of possible dynamics that can occur when modeling the SARS-CoV-2 virus. By modeling the cases of stable, periodic, and chaotic dynamics, we are able to better understand the causes of these dynamics. Causes which may be other examples of complex adaptive systems. Before discussing SIMCoV, it is important to further elaborate about chaos.

Chaos is the concept of disorder and appeared randomness. With chaos comes the idea of sensitive dependence on initial conditions. According to Melanie Mitchel, sensitive dependence on initial conditions is "in which even minuscule uncertainties in measurements of initial position and momentum can result in huge errors in long-term predictions of these quantities."(Mitchell 20).Meaning that because it is impossible to have infinite precision, then it will be impossible to create perfect predictions on chaos systems. We will be bringing up the logistic map, a simple but powerful chaotic system, for understanding chaos in our modeling of the SARS-CoV-2 virus. The logistic map, in essence, is a logistic model that "is simplified by combining the effects of birth rate and death rate into one number, called R."(Mitchell 27). To model the SARS-CoV-2 virus, we will be using the SIMCoV model.

SIMCoV is a scale-able computational program that is designed to simulate a given space inside a human's lungs. The lungs are an environment that houses CD8 T cells and virion cells. The goal of the SIMCoV program is to model how infections began and how they spread inside the human lungs. SIMCoV can model the millions of cells inside the lungs and how they interact with each other though scalability, meaning it can handle large amount of workload. SIMCoV starts with initial configuration variables which determine to what/how much of an extent cells interact with each other in the human lungs. To find interesting behaviors between T cell and virion cell interactions, we changed up to three initial given parameters to find interesting behaviors.

II. Methods and Results

One component of this project was to find stability, periodicity, and chaos dynamics using the SIMCoV model. Initially SIMCoV starts out with a configuration file that contains initial parameters, which can be seen in table 1. To find each dynamic, we went through multiple parameters sets, of which many did not display any of the desired dynamics. At first we tried running simulations that only changed one parameter at a time. For example, we tried changing the number of virions at infected locations. We used values 1500, 2000, 2500, and 3000, which led to no desired dynamics. We also tried many sets of parameters which also led to no desired results. For example, one set contained virion clearance = 0.004, virion diffusion = 0.15, and t cell initial delay = 10080 which lead to no dynamics. We also tried this set again, instead using virion clearance = 0.002, virion diffusion = 0.3, and t cell initial delay = 12000. This led to a similar conclusion. Of the many sets/individual parameters changed, we recorded three sets to show stability, periodicity, and chaos. Table 1 shows each of the three sets of parameters. Each set of parameters was ran a total of three times. Figure 2 shows each dynamic found. Each graph represents a different dynamic. Each line represents the mean of three individual runs of the experiment. The shaded colored regions around each line represent the standard deviations of each individual run compared to the mean.

Stability dynamics can be seen in figure 2a. By increasing the number of virions produced by expressing cells, in each time step, we were able to show stability dynamics. We changed virion production from what was originally 1.1 to 2.0. Using this parameter change we noticed that Infected cells and viral load follow a similar shape after day one through the entire simulation.Using original configurations we saw that

once number of virions peaks at around 8 days, a sharp decline in virions and infected cells occurred. However, this does not happen in this scenario. While virion and infected cells peak at highest value at 8 days, they do not decline rapidly. Instead, they decrease with very flat lowered slopes to each line.

The next dynamic that we were able to observe through set two, plotted in 2b, was periodicity. We were able to find periodic dynamics in the number of infected cells when we increased the number of virions produced from expressing cells, decreased fraction of virion drop counts, and increased the number of T cells generated. We increased Virion production from 1.1 to 3, decreased virion clearance from 0.004 to 0.0004, and increased T cell generation rate from 105000 to 1050000. Looking at figure 2b, from days zero through eight we see similar paths for viral load and infected cells like results from the default configurations and from the stability dynamics experiment (2a). The data, however, changes after around day eight. The range of days eight through ten we see a nonlinear decline in infected cells. It is interesting that from day ten through the rest of the experiment, infected cells appear to experience periodic behavior. The periodic line has amplitudes ranging around 1e4 cells, with a period roughly about two to three days.The periodicity behavior from the infected cells arises from both incubation and expressing cells. Figure 1 shows that both incubating and expressing cells have crests and troughs around the same says. Since total infected cells = incubating cells + expressing cells, it makes sense that infected cells also has crests and troughs on similar days. Looking at viral load, after around day eight on figure 2b, we don't see any periodic dynamics until around day sixteen. After day sixteen we noticed that there is periodic behavior alongside viral load's nonlinear decrease. What's also interesting to note in figure 2b is that while there is a periodic trend in viral load, notice that as time(days) increases after day 10, data from each of the 3 experiments starts to deviate away from the mean plot more and more. While this may seem like chaotic behavior at first, we are still confident to classify figure 2b more as periodic due to the standard deviations still following a similar periodic amplitude and period as the mean plot.

Lastly, using the parameters of set three we observe chaotic dynamics, which can be seen in figure 2c. To find our data for chaotic dynamics we had to change many values in the SIMCoV configuration file. Virion production was increased to 3, virion clearance decreased to 0.0004, chemokine production decreased in half to 0.5, minimum chemokine concentration decreased to 1e-8, and T cell generation rate increased to 1050000. Looking at figure 2c, after day twenty, chaotic dynamics are formed within both infected cells and viral load. While it appears that all values after day twenty range within 1e3 count, no visible trend of periods were observed. Another sign of chaotic behavior is more prominent when looking at the standard deviations from each of the 3 experiments. In figure 3c there is no trend of increasing standard deviation as time increases, unlike what was found in figure 2b. The time steps in which standard deviation increases or decreases appears to be random, giving insight that this set of parameters creates chaotic behavior.

TABLE I
DEFAULT PARAMETERS AND CHANGES FOR 3 SETS OF SIMCOV.

SimCov Parameters (NC = no change)			
Default parameters	Set 1 stable	Set 2 periodic	Set 3 chaotic
dim = 15000 15000 1	NC	NC	NC
whole-lung-dim = 48000 40000 20000	NC	NC	NC
timesteps = 33120	NC	NC	NC
infection-coords = uniform:1	NC	NC	NC
initial-infection = 1000	NC	NC	NC
incubation-period = 480	NC	NC	NC
apoptosis-period = 180	NC	NC	NC
expressing-period = 900	NC	NC	NC
infectivity = 0.001	NC	NC	NC
infectivity-multiplier = 1.0	NC	NC	NC
virion-production = 1.1	**2.0**	**3.0**	**3.0**
virion-production-multiplier = 1.0	NC	NC	NC
virion-clearance = 0.004	NC	**0.0004**	**0.0004**
virion-diffusion = 0.15	NC	NC	NC
chemokine-production = 1.0	NC	NC	**0.5**
chemokine-decay = 0.01	NC	NC	NC
chemokine-diffusion = 1.0	NC	NC	**0.5**
min-chemokine = 1e-6	NC	NC	**1e-8**
antibody-factor = 1	NC	NC	**4**
antibody-period = 5760	NC	NC	NC
tcell-generation-rate = 105000	NC	**1050000**	**1050000**
tcell-initial-delay = 10080	NC	NC	NC
tcell-vascular-period = 5760	NC	NC	NC
tcell-tissue-period = 1440	NC	NC	NC
tcell-binding-period = 10	NC	NC	**100**
max-binding-prob = 1	NC	NC	NC
tcells-follow-gradient = false	NC	NC	NC
seed = 29	NC	NC	NC
sample-period = 1440	NC	NC	NC
sample-resolution = 1	NC	NC	NC
max-block-dim = 10	NC	NC	NC

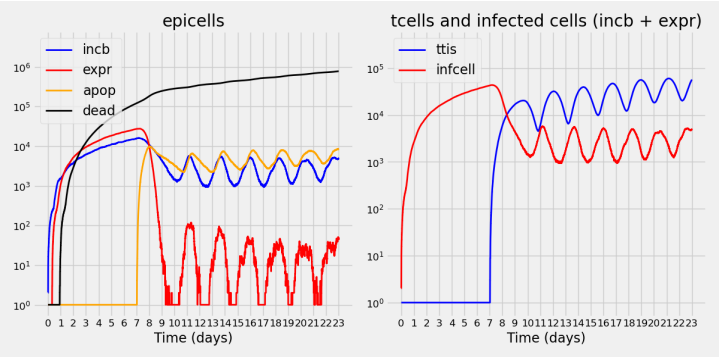

Fig. 1. SIMCoV simulation from set 2; (left panel) shows the dynamics of epithelial cell state, and (right panel) shows infected cells and T cell dynamics.

Figure 3 is the output of four time series events from the logistic map. The logistic map is a simplified nonlinear dynamic model showing how deterministic chaos may arise over a period of time [2]. It is typically used to demonstrate population growth of a species within an environment over time. The logistic map incorporates two parameters, R and x, into a relatively simple mathematical equation [1, 3]

$$x_{t+1} = Rx_t(1 - x_t).$$

R represents the reproductive rate of a population, combining both the birth and death rates of the population into a single value, usually over the interval [0, 4] in order to bound the

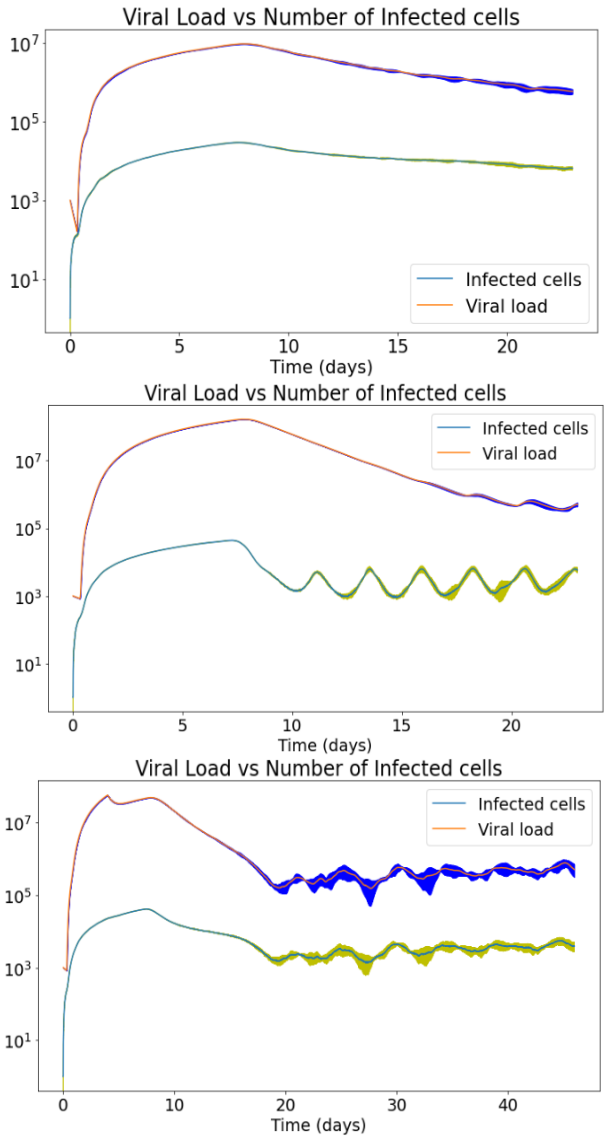

Fig. 2. Time series of viral load and infected cells; (top, Set 1) stability, (middle, Set 2) periodicity, (bottom, Set 3) chaos. Lines represent the mean of 3 sets, shaded area is the standard deviation.

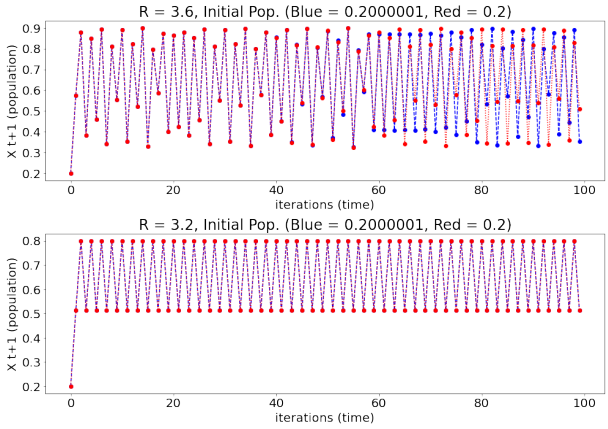

Fig. 3. Logistic Map time series; (top) chaotic, (bottom) periodic.

TABLE II
ENTROPY FOR LOGISTIC MAP DATA POINTS AND TIME SERIES
(H = SHANNON ENTROPY, MI = MUTUAL INFORMATION, TE = TRANSFER ENTROPY)
* 1 → N, ** (N + 1) → 100, WHERE N = 50 IS POINT OF DIVERGENCE

R = 3.6
Initial pop. = 0.2000001 H_Binned(col_0) = 2.4464 bits* H_Binned(col_0) = 2.3219 bits** MI_Binned(col_0 → col_1) = 2.4464 bits* MI_Binned(col_0 → col_1) = 1.9219 bits** TE_Binned(col_0 → col_1) = 0.4444 bits
Initial pop. = 0.2 H_Binned(col_1) = 2.4464 bits* H_Binned(col_1) = 2.4464 bits** MI_Binned(col_1 → col_0) = 2.4464 bits* MI_Binned(col_0 → col_1) = 1.9219 bits** TE_Binned(col_1 → col_0) = 0.4444 bits
R = 3.2
Initial pop. = 0.2000001 H_Binned(col_0) = 0.7219 bits* H_Binned(col_0) = 0.7219 bits** MI_Binned(col_0 → col_1) = 0.7219 bits* MI_Binned(col_0 → col_1) = 0.7219 bits** TE_Binned(col_0 → col_1) = 0.0000 bits
Initial pop. = 0.2 H_Binned(col_1) = 0.7219 bits* H_Binned(col_0) = 0.7219 bits** MI_Binned(col_1 → col_0) = 0.7219 bits* MI_Binned(col_0 → col_1) = 0.7219 bits** TE_Binned(col_1 → col_0) = 0.0000 bits

output between [0, 1]. The second parameter, x, represents a ratio of the current population to the maximal carrying capacity of that population and is limited to the interval [0, 1]. In essence, the logistic map is a nonlinear mathematical equation of deterministic chaos, used to plot the growth of populations over time within a particular environment.

In our experiment, the top time series (Figure 3) demonstrates a chaotic environment where it is impossible to predict the current population at any given time after the point of divergence. This is in contrast to the bottom time series (Figure 3) which demonstrates a more predictable periodic population growth over time. The key factor here is based on a concept termed sensitive dependence on initial conditions. In deterministic nonlinear systems such as the logistic map, small perturbations of the initial conditions may have dramatic changes in the outcomes of later states [4]. This is clearly evident in our time series as we move R from 3.2, demonstrating a periodic behavior, to 3.6, demonstrating a chaotic behavior. The initial x value also shows initial condition dependency. Looking at the chaotic behavior in the top section of Figure 3, we see that both red and blue outcomes are identical until approximately 50 iterations on the graph. At this point divergence of the two plots occur and continue as diverted from then on. This divergence point is also dependent upon the initial conditions. As both initial populations become closer and closer, the divergence point is pushed further and further out in time.

Table II is the result of analyzing our logistic map data using the JIDT [7] tool for calculations of Shannon entropy (H), mutual information (MI), and transfer entropy (TE). Shannon's

entropy is the average amount of information that is present in a random variable[8]. It is typically described as the amount of "surprise", "uncertainty", or "information" that is captured by its probability of occurrence and is calculated as

$$H(X) = -\sum_{x \in X} p(x) log p(x).$$

Mutual Information describes the amount of mutual dependence between two variables [9]. It describes the amount of information one can obtain (in nats or bits) about one variable by observing the other variable [9]. Transfer entropy describes the amount of information one may obtain about the future of variable Y by knowing the history of variable X, given the past history of Y [10]. For the purposes of our experiment, we calculated four separate time series using the logistic map, using R and x values as described in the table for 100 iterations. These were then binned into groups of 10 and passed into the JIDT calculator. The parameters for JIDT included a calculator type "Binned", using "All Paired", and a base property of 10.

Our results for entropy of the chaotic group (R = 3.6) showed similar values (2.4464 bits) for both the 0.2 and 0.2000001 series prior to the point of divergence. Following divergence, the entropy reduced for the 0.2000001 series (2.3219 bits), while remained constant for the 0.2 series (2.4464 bits). The periodic group (R = 3.2) remained constant (0.7219 bits) for all series and data points. Mutual information was similar to entropy for the chaotic group as it was identical between the 0.2 and 0.2000001 series prior to divergence (2.4464 bits). However, it still remained identical between the two series following divergence (1.9219 bits). Mutual information in the periodic group, again remained constant for (0.7219 bits) for all series and data points. We attempted to identify two arbitrary groups of transfer entropy, one that had a statistically significant non-zero transfer entropy, and one that was non-significant transfer entropy that is indistinguishable from 0. We were unsuccessful in our attempts. If we were successful, the former example would indicate that if TE(X→Y) = some significant non-zero value, then we could conclude that X has some influence over Y. The opposite would hold true for the latter example.

Our logistic map data demonstrates both a chaotic as well as a periodic series. We believe this is very similar to two of our SimCov series of similar descriptions. In the logistic map we had an R value that incorporates both the birth and death rates of a population. This is similar to the increased viral production and reduced viral clearance of our chaotic series, leading to a recurrent fluctuation of viral load to host defense and a stable chaotic environment. Similarly, we had a periodic series in the logistic map with a lower R value than that of the chaotic series. The SimCov periodic module was similar to increased and maintained T-cell activity that would reduce the viral reproduction rate. Periodicity and chaotic behaviors are both demonstrated in our figures 2 and figures 3.

A set of real-word time series was chosen from the country-by-country data on global COVID-19 vaccinations. They relied on figures that are verifiable based on public official sources. This data-set was filtered to just include United States. The population estimates were based on one of the revisions of the United Nations World Population Prospects, according to the source. Fig. 4 shows cumulative vaccinations and boosters on a log scale. It seems to attain a stable dynamic post September of 2021. Fig. 5 shows daily vaccinations and boosters. The time series seems to draw a chaotic pattern. Both time series were cleaned up to remove null values and it is ensured that there is data for all days represented. For the purpose of identifying dynamics, we used daily vaccinations and daily boosters time series, as can be noted in Fig.5. Entropy, mutual information and transfer entropy are calculated using customized python scripts that used PyInform and SciPy modules. To accommodate binning continuous values, PyInform bins the time series, forcing the values into discrete states. It must be noted that this method can sometimes introduce bias. It was observed that without some kind of guiding principle it is difficult to decide precisely on a specific binning approach. The time series is binned into 10 equal sized bins prior to entropy, mutual information and transfer entropy calculations. To contrast approaches and values, JIDT Auto Analyse calculator was used. The estimator selected was 'binning' with base value of 10. The estimator makes equal-sized bins for shannon entropy, but also uses maximum entropy binning for mutual information and transfer entropy calculations. The base values used in both cases was 10. Binned data was fed into JIDT. It must be noted that JIDT is sensitive to binning, and misses subtleties in data.

X and Y represent daily vaccinations and daily boosters respectively. The mutual information between the both is 1.356 bits. The transfer entropy (X→Y) is 0.2719 bits. This means that the history of the X (daily vaccinations) has 0.2719 bits of additional information for predicting the next value of Y (daily boosters). Since the transfer entropy is non-zero, we concluded that daily vaccinations influence daily booster shots in some way. It must be remembered that TE should not be negative. To see if the TE is actually significant, we compared it with the entropy of Y. The shannon entropy of Y is 1.356 bits. This proves the transfer entropy to be significant. The transfer entropy (Y→X) is 0.0742 bits. This means that the history of the Y (daily boosters) has 0.0742 bits of additional information for predicting the next value of X (daily vaccinations). The shannon entropy of X is 2.3219 bits which shows the transfer entropy might not be significant compared to marginal entropy of X (daily vaccinations). So the daily boosters do not tell us a great deal more about daily vaccinations.

III. Discussion

Based on figure 2a parameters, it would suggest that SARS-CoV-2 variants with larger amounts of virion production would cause the virus to infect a person's lungs for longer periods of time. According to Samuel Lebourgeois, "The emergence of new SARS-CoV-2 variants, with several data suggesting higher viral loads and/or better resistance to seroneutralisation... especially as the Alpha variant provides higher viral loads

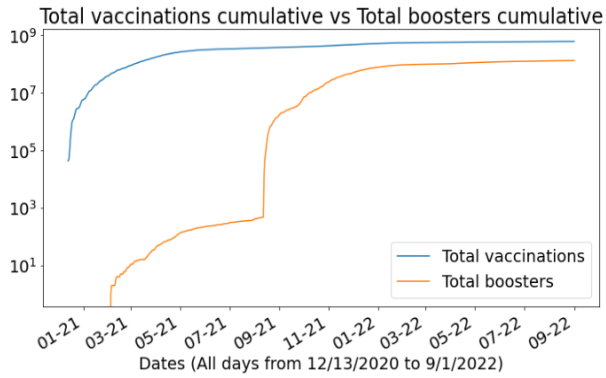

Fig. 4. Time Series of Cumulative Total Vaccinations and Total Boosters

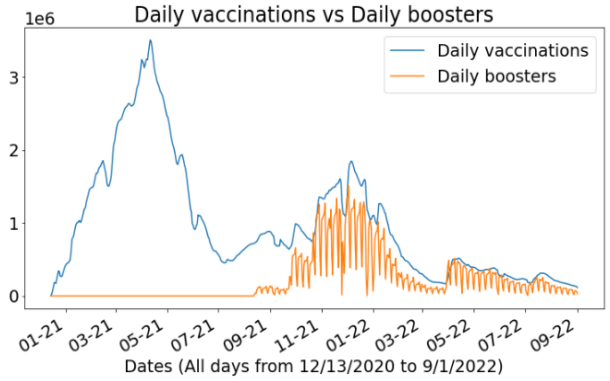

Fig. 5. Time Series of Daily Vaccinations and Daily Boosters

and higher death rates than the historical strains".Lebourgeois article on viral production suggests that a increase in viral production in newer SARS-CoV-2 variants leads to a increase in deaths. Our data follows this observation. When we increased the virion production to 2, in figure 2a, the number of infected cells and viral load stayed way above 0 even after day 20. Whereas using the default SIMCoV parameter viral load of 1.1, both infected cells and viral load was near 0 by day 20.

Increasing the parameter "t cell generation rate" can be viewed as running a experiment using the lungs of a younger person.In Jörg J. Goronzy's article *Aging and T-cell diversity*" Homeostatic control mechanisms are very effective to maintain a large and diverse subset of naïve CD4 T cells for many years up to the 8th decade of life, but eventually and abruptly fail at about the age of 75 years... It is, therefore, clear that age has a major impact on the composition of the T-cell compartment". The younger a person is, the higher amount of t cells, with diversity, can be created by a given person's body. In our experiment, visualized using figure 2c, we also increase virion production and virion clearance , which in real world examples can be viewed as a stronger Covid variant infecting a younger person. Our data suggest that with a SARS-CoV-2 variant this strong inside a younger person would lead to a long term ongoing battle between the immune system and the virus. Both this example variant and the persons strong immune system would cause a long-term tug of war battle, where between two to three days,the approximate period of the periodic plot, the immune system would start winning, killing off infected cells. Only to be then followed up with the variant re-generating back infected cells. While a real-world example of a strong SARS-CoV-2 variant and a strong young immune system may not be as periodic as our data, it is still interesting to find a set of parameters which creates periodic behaviors that may suggest a possible scenario in the real-world.

Despite adding parameters to create chaos dynamics for figure 2c, virion production, virion clearance, and t cell generation rate remain the same from values in the periodic experiment. These kept values may explain why infected cells and viral load seem to end, on day twenty, roughly around the same value as from the periodic experiment. Because of the large changing of paramaters, compared to the default SIMCoV configurations, it is hard to find a reflecting immunological variation among people in real life which reflects our example of chaos. The reason being is that the many parameter changes as a whole are too specific to be backed by outside evidence. We would need a resource that conducted research on how SARS-CoV-2 was impacted in the case of enhanced virion traits, chemokine weakening, increased antibodies, and stronger t cells. Despite this specific example of chaos, it is still worth mentioning why chaos occurred in this first place with this set of parameters.

What creates the chaotic behavior in figure 2c was changing parameters to very small values. Going back to Melanie Mitchell's quote on chaos, they write "even minuscule uncertainties in measurements of initial position and momentum can result in huge errors in long-term predictions of these quantities."(Mitchell 20). Mitchell means to say that the values we use in some systems, if small enough, will create errors large enough to change the output of data completely. We see a similar occurrence in our results from the eight parameter changes in figure 2c. Because of the many parameter changes that use small values, we believe chaos occurs due to the issue of extreme sensitivity.We used values 0.0004 for virion clearance, dividing chemokine production and diffusion in half, and changing minimum chemokine concentration from 1e-6 to 1e-8. While each of the three runs for set three have the same starting initial conditions, the values are small and sensitive enough to generate different outcomes when ran by the SIMCoV model.

IV. Contributions

Ben worked on writing the Introduction, Methods part 1 and Results. Ben also helped run multiple experiments in SIMCoV to try and find dynamics of interest for part 1 of the project.

Michael worked on logistic map and binning code, obtained SimCov data for the periodic and chaotic sets, and worked on analyzing the logistic map data.

Siva worked on the Abstract, Discussion and Methods in the report. Siva also worked on H, MI, TE calculations and on another set of real-world time series. All of us ran multiple experiments using SIMCoV varying parameters.

Student Jason Stewert, while not a group member of the project, helped Ben understand how to run the starting configuration of SIMCoV.

V. Appendix

Listing 1. Python code for binning data.

```
import pandas as pd

df = pd.read_table(
    "file location", header=None,
        sep='\t')
df = df.iloc[:, a].copy()# a = column to bin
binned = pd.cut(df, 10, include_lowest=True,
    ordered=True)
print(binned.value_counts().to_list())
binned_count = binned.value_counts()
print(binned_count)
for i in binned_count:
    print(i)
```

Listing 2. Python code for logistic map.

```
import numpy as np
import matplotlib.pyplot as plt
import pandas as pd
from pylab import rcParams

def lm(x0, R):
  xt = x0
  xt1 = R * xt * (1 - xt)
  return xt1

#x0 is initial population, object 1
#xx0 is initial population, object 2
#R is growth rate for object 1
#RR is growth rate for object 2
x0 = .99999
blue = x0
xx0 = 0.00001
red = xx0
R = 3.6
# RR = 3.2
t = 100
arr_x = []
arr_xx = []
arr_t = []

for i in range(t):
  arr_x.append(x0)
  arr_xx.append(xx0)
  arr_t.append(i)
  x0 = lm(x0, R)
  xx0 = lm(xx0, R) #Replace R with RR for
                   two diferent growth rates

s = 'R = ' + str(R) + ', Initial Pop.
     (Blue = ' + str(blue) + ',
     Red = ' + str(red) +')'
plt.title(s, fontsize=24)
plt.xlabel('iterations (time)', fontsize=20)
plt.ylabel('X t+1 (population)', fontsize=20)
plt.xticks(fontsize=20)
plt.yticks(fontsize=20)
plt.rcParams["figure.figsize"] = [16.4, 4.8]

x = arr_t
y = arr_x
yy = arr_xx

plt.plot(x, y, linestyle='dashed', marker='o', color='blue')
plt.plot(x, yy, linestyle='dotted', marker='o', color='red')
plt.show()

df = pd.DataFrame(arr_x, arr_xx)
LM2 = df.to_csv()
print(LM2)
```

Listing 3. Python code for calculation MI, TE using PyInform.

```
import pandas as pd
import scipy
import math
import pyinform
from scipy.stats import chi2_contingency
from scipy.stats import binned_statistic

def calc_MI(x, y, bins):
    c_xy = np.histogram2d(x, y, bins)[0]
    g, p, dof, expected = chi2_contingency(c_xy,
    lambda_="log-likelihood")
    mi = 0.5 * g / c_xy.sum()
    return mi

def lib_te(x_vals, y_vals, num_bins, k):
    min_val_x = min(x_vals)
    max_val_x = max(x_vals)
    min_val_y = min(y_vals)
    max_val_y = max(y_vals)

    x_binned=binned_statistic(x_vals,x_vals,'sum',
    bins=num_bins,range=[min_val_x,max_val_x]).binnumber
    y_binned=binned_statistic(y_vals, y_vals, 'sum',
    bins=num_bins, range=[min_val_y, max_val_y]).binnumber
    return pyinform.transferentropy.transfer_entropy(
    x_binned, y_binned, k=k)
```

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