Mathematical Modelling of Chaos in Cancer Cells

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Abstract

Analyzing cancer growth can be overwhelming and confusing when dealing with host cells, effector immune cells, and tumour cells. Mathematical modelling is an effective way of organizing and understanding these chaotic systems. The objective of the model proposed by de Pillis and Radunskaya in 2003 is to make the behaviour of these competing species clearer and more concise. Dissecting the model's parameter values is a practical technique that provides more information about the inner workings and sensitivities of the system. Cancer is a harsh disease that needs to be fully understood in order for treatment to be effective. This paper will study the chaotic cancer model and how to efficiently modify the system to control tumour growth.

Contents

1 Introduction

Mathematical modelling is a useful tool when exploring cancerous cells and assessing the biology involved. The human body undergoes the process of cell division when old, damaged cells die and new one's form in their place. The unusual behaviour occurs when these abnormal cells continuously multiply and form growths in the organs or tissues of the body. Modelling trends in these cellular systems can indicate what the problem is and pinpoint how to effectively control the tumours. Mathematical modelling is a great advantage in science today and can help overcome these cruel diseases while also preparing for the future.

A tumour can be classified as a benign non-cancerous tumour or a malignant cancerous tumour. Benign tumours generally do not spread and can often be fully removed with the expectation to not grow back. Some benign tumours can be concerning if they are large or are located within the brain. Malignant tumours however can cause serious damage when they grow uncontrollably. When cancerous tumours are removed, there is a chance that they will come back. Cancerous cells spread throughout the blood or lymph systems in the body causing new tumours to form through a process called metastasis, the new cancer is called metastatic cancer. Once a cell is ready to die, it experiences signals through apoptosis which a cancerous cell may not receive. The cancerous cells continue to multiply out of control ignoring these signals.

It is only natural to use the term 'chaos' when describing cancerous cells. Tumours are often unpredictable even with the use of mathematical modelling and various testing. An infinitesimal modification in a cancerous system can produce an immense change that is nearly impossible to predict.

2 Chaos Theory

Chaos is a form of order disguised as disorder, proposed to produce the diversity and plasticity response within self-organized units that provides the fitness advantage to complex adaptive systems (Coffey, 1998). Chaos is highly sensitive to initial conditions and exhibits determinism since the system behaviour follows simple rules of interaction. There are six principles of chaos that allow for a better analysis and understanding of this behaviour. One principle is the butterfly effect, which involves small changes in the initial conditions that lead to drastic effects in results. The second principle is unpredictability which speaks to the fact that predicting the fate of a complex system is not possible since all of the initial conditions are not defined. The third principle is order which states that chaos transitions between order and disorder. The fourth principle is mixing, which is where two adjacent points in a complex system eventually end up in different positions over time. The fifth principle is feedback which involves systems that are made chaotic when feedback is present. The sixth and final principle is fractals, which are the never-ending, complex, and self-similar patterns seen across different scales, created by repeating a simple process in an ongoing feedback loop.

Chaos theory is the "qualitative study of unstable aperiodic behaviour in deterministic nonlinear dynamical systems" (Bishop, 2015). The key features include instability and aperiodicity. The theory was coined in 1963, when Edward Lorenz, an American mathematician and meteorologist from MIT, discovered it when looking at uncontrolled approximations aiming at predicting the weather (Bishop, 2015). He originally expected that a small variation at the start of a calculation would trigger a small difference in the result, but through a sensitivity analysis, he discovered the chaotic behaviour of a nonlinear system.

Below is the Lorenz system that models stable and chaotic behaviour.

$$\frac{dx}{dt} = \sigma(y - x)$$
$$\frac{dy}{dt} = x(\rho - z) - y$$
$$\frac{dz}{dt} = xy - \beta z$$

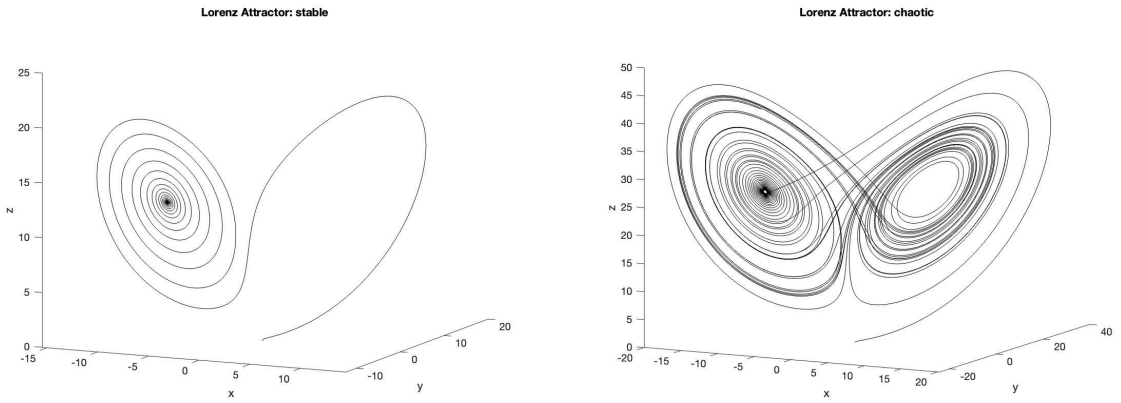

Figure 1: Left: Stable. $\sigma = 10$, $\beta = 8/3$, and $\rho = 14$
Right: Chaotic. $\sigma = 10$, $\beta = 8/3$, and $\rho = 28$

From these simulations, it is apparent that when $\rho = 14$, the system is stable but when $\rho = 28$ the system exhibits chaotic behaviour. When $\rho = 28$, the model produces a butterfly pattern which is an instance of a fractal. The pattern seems to be repeating itself, but it is hard to predict when the trajectory will switch sides, thus the chaotic behaviour.

Today, chaos theory is a relevant topic that has a broad scope and can be applied to many different fields of study such as meteorology and fluid dynamics that are modelled by the Lorenz system. There are also many useful applications of chaos theory in medicine. Living species can increase complexity as they organize from order to disorder without any external inputs, so they produce a complex chaotic system. Another example of chaotic behaviour in medicine is cardiac rhythm, as it is sensitive to initial conditions and dimensions of attractors. Brain disorders and artificial neural networks are more areas that display chaotic behaviour as seen in epilepsy and other diseases. With the cancer model, there are interactions between healthy and cancerous cell populations which create chaos. This chaotic cancer model will be explored in depth throughout this paper.

3 Chaos in Cancer Cells

Cancer is detected when there is an uncontrollable growth of tumour cells that invade blood, organs, and tissues throughout the body. When cancerous cells are present, they compete for space and resources that healthy cells need to thrive. Cancerous cells are also able to withstand the effector immune cells that are momentarily activated to defend the body and fight off the invading diseased cells. Due to the lack of knowledge on key parameters and the unpredictability of tumour growth, carcinogenesis population-based models can aid in the understanding of the dynamics and treatment of tumours. Some factors to consider are competition and predation between healthy and cancerous cells. If the tolerability of cancer cells on healthy cells is increased while also decreasing the tolerability of healthy cells on cancer cells, then the body can effectively fight against the tumour growth by gaining control over the space and resources and killing off the unhealthy cells.

The model proposed by de Pillis and Radunskaya in 2003 describes interactions between the populations of host cells, effector immune cells, and tumour cells. Host cells are healthy living cells that are susceptible to being invaded by infectious agents. The competing species produce chaotic behaviour. Analyzing this model will provide insight on cellular interactions that are verified in experimental as well as clinical studies. These results help with determining which parameters should be the focus when planning an effective treatment strategy.

3.1 Model

The following qualitative model by de Pillis and Radunskaya is based on the Lotka-Volterra equations which describes interacting species where one is a predator, and one is the prey.

$$\dot{H} = \tilde{p_1} H(1 - \frac{H}{\tilde{\kappa_1}}) - \tilde{\alpha_{13}} TH$$

$$\dot{E} = \frac{\tilde{p_2} TE}{T + \tilde{\kappa_2}} - \tilde{\alpha_{23}} TE - \tilde{\delta} E$$

$$\dot{T} = \tilde{p_3} T(1 - \frac{T}{\tilde{\kappa_3}}) - \tilde{\alpha_{31}} TH - \tilde{\alpha_{32}} TE$$

This describes the relationships between the host cells H, the effector immune cells E, and the tumour cells T. All parameters are assumed to be positive.

- $\tilde{p_1}$, $\tilde{p_2}$, and $\tilde{p_3}$ are the respective growth rates.
- $\tilde{\kappa_1}$, $\tilde{\kappa_2}$, and $\tilde{\kappa_3}$ are the respective maximum species capacities.
- $\tilde{\delta}$ is the natural death rate of the effector immune cells.
- $\tilde{\alpha_{13}}$ is the death rate of host cells by tumour cells.
- $\tilde{\alpha_{23}}$ is the death rate of effector immune cells by tumour cells.
- $\tilde{\alpha_{31}}$ is the death rate of tumour cells by host cells.
- $\tilde{\alpha_{32}}$ is the death rate of tumour cells by effector immune cells.

The first equation is the rate at which the population of the host cells are growing modelled with a logistic function. The second equation is the rate of change of the effector immune cells where the first term represents the stimulation of the immune system by the tumour cells. The third equation exhibits the growth rate of the tumour cells with a logistic model when the tumour cells are alone.

When the model is normalized, the direct mapping is $(x, y, z) \mapsto (H, E, T)$ where x is the normalized population of the host cells, y is the population of the effector immune cells, and z is the population of the tumour cells. In this case, ρ_3 and α_{31} are set to equal one.

$$\dot{x} = \rho_1 x(1 - x) - \alpha_{13} xz$$
$$\dot{y} = \frac{\rho_2 yz}{1 + z} - \alpha_{23} yz - \delta y$$
$$\dot{z} = z(1 - z) - xz - \alpha_{32} yz$$

This system of equations represents the highly competitive model seen in Figure 2. Solid lines represent linear interactions and dashed lines represent nonlinear interactions. The '+' indicates that the interaction promotes the growth and '-' means the interaction represses the growth of the species. In this case, none of the species are seen as a particular prey, they are not contributing to the growth of the other species but rather all populations are diminishing. Also illustrated by the model is the fact that the host cells and the effector immune cells do not directly interact with each other.

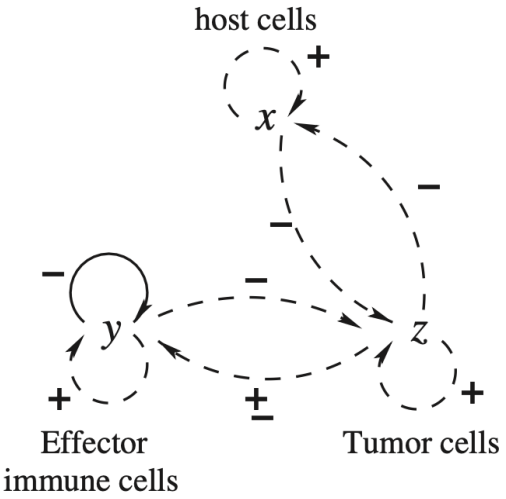

Figure 2: Model [Letellier et al, (2013)]

3.2 Simulation

Set the normalized model parameters to be: $\rho_1 = 0.6$, $\alpha_{13} = 1.5$, $\rho_2 = 4.5$, $\alpha_{23} = 0.2$, $\delta = 0.5$, $\alpha_{32} = 2.5$.

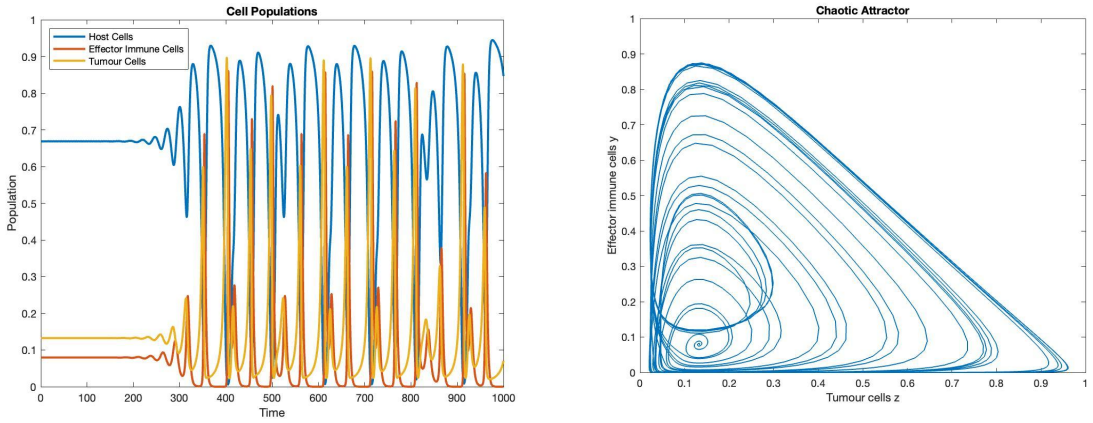

Figure 3: Species Populations and Chaotic Attractor

Displayed by Figure 3, when the population of tumour cells spikes, the population of host cells declines which is expected since the tumour cells take over the host cells. Also seen is the fact that the effector immune cell population is directly correlated with the tumour cell population. With the growth of tumour cells comes the growth of effector immune cells and equivalently, when tumour cells decrease, effector immune cells follow suit. This again is expected because

more tumour cells present require more immune cells to fight back. There however is a small lag between when the tumour cells grow and decrease and when the effector immune cells grow and decrease. This is because the effector immune cells cannot predict the tumour cells' behaviour, so it experiences a small reaction time.

These simulations are presumed to occur in a single tumour-cite compartment and start with the initial condition [0.66, 0.079, 0.132] for the best visual results where each cell type is coexisting. The point at the origin corresponds to the case where there are no cells. The point [1, 0, 0] would be the case when there are only host cells present and the point [0, 0, 1] is when there are only tumour cells present. A point such as [0, 0.347, 0.132] is the condition when only effector immune cells and tumour cells are in the compartment.

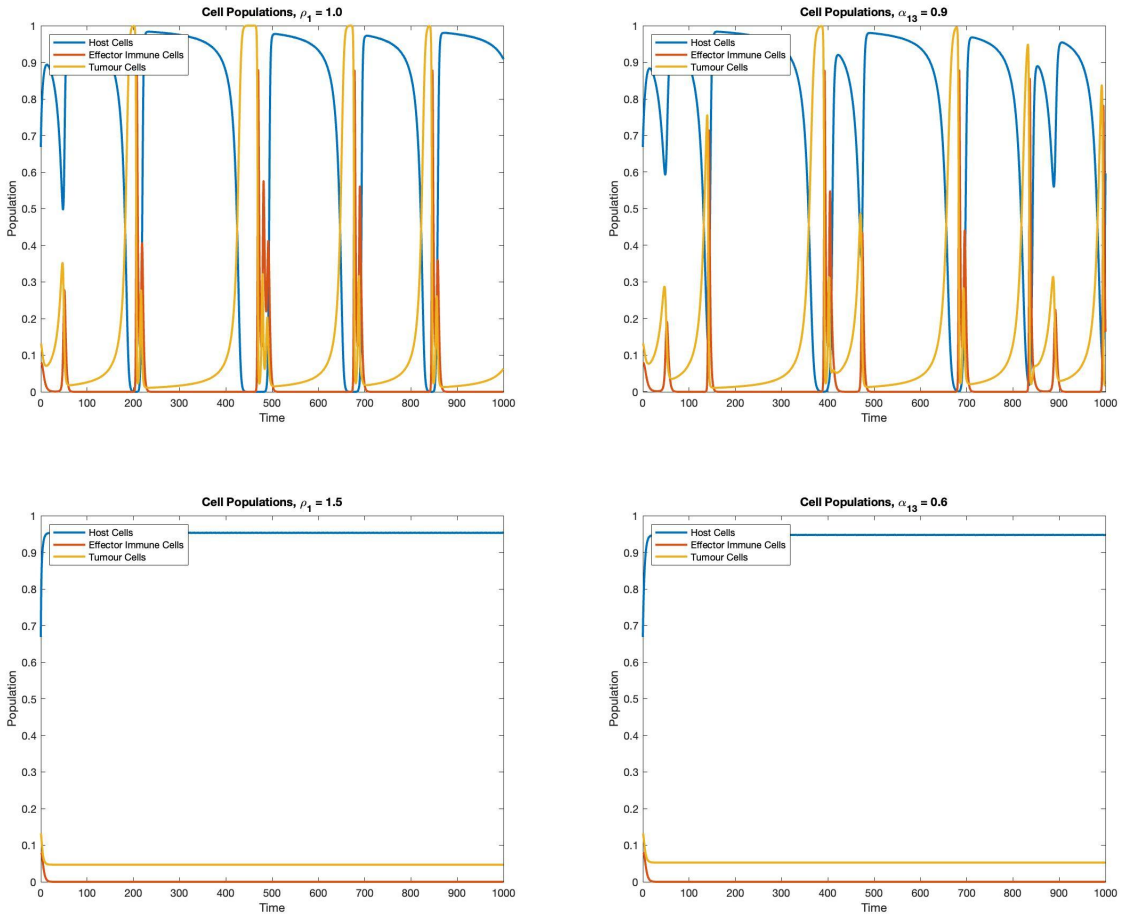

Figure 4: Left: Increasing ρ_1
Right: Decreasing α_{13}

In Figure 4, the left-hand side corresponds to increasing the parameter value ρ_1 (growth rate of the host cells) from 0.6 up to 1.0 and 1.5. The right-hand side corresponds to decreasing parameter value α_{13} (death rate of host cells by tumour cells) from 1.5 down to 0.9 and 0.6 while all other parameters remain the same.

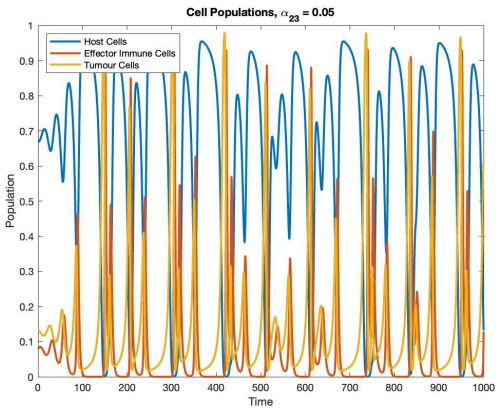

Figure 5: Decreasing α_{23}

Figure 5 explores the results of decreasing α_{23} (death rate of effector immune cells by tumour cells) from 0.2 to 0.05. This would mean that there are more effector immune cells in the system, but it still exhibits the same oscillatory behaviour. That is, reducing the death rate of effector immune cells by tumour cells does not have the same effect as increasing the growth rate of the host cells and decreasing the death rate of host cells caused by tumour cells.

3.3 Results

As discovered by Letellier, Denis, and Aguirre, increasing the growth rate of the host cells has a similar effect as decreasing the rate at which the tumour cells kill off the host cells. When the growth rate of host cells exceeds the death rate of host cells by tumour cells, the system is stable. Likewise, when the death rate of host cells caused by tumour cells drops below the growth rate of tumour cells the system is stable again. They found that the population of host cells is the most reliable when analyzing the dynamics of this model and the tumour cells are a close second in reliability. This means that the effector immune cells are the least reliable because they are not as easily assessed through these specific simulations and trials. An effective way of controlling the system would be to alter the host cell populations or destroying the tumour cells rather than adjusting the immune cells through a vaccine.

4 Model Extension: Sensitivity Analysis

Take nominal parameters to be $\rho_1 = 0.6$, $\alpha_{13} = 0.6$, $\rho_2 = 4.5$, $\alpha_{23} = 0.2$, $\delta = 0.5$, $\alpha_{32} = 2.5$. The steady state values are obtained by running simulations.

Consider a 5% increase from ρ_1. $\Delta\rho_1 = 0.03$.
The sensitivity analysis on ρ_1 is the following,

Sensitivity coefficients:

$$\frac{dH^{ss}}{d\rho_1} = \frac{H^{ss}(0.6 + 0.03) - H^{ss}(0.6)}{0.03} = \frac{0.985214 - 0.947312}{0.03} = 1.2634$$

$$\frac{dT^{ss}}{d\rho_1} = \frac{T^{ss}(0.6 + 0.03) - T^{ss}(0.6)}{0.03} = \frac{0.0154266 - 0.0525972}{0.03} = -1.23902$$

Relative sensitivities:

$$\frac{\rho_1}{H^{ss}}\frac{dH^{ss}}{d\rho_1} = (\frac{0.6}{0.947312})(1.2634) = 0.8002$$

$$\frac{\rho_1}{T^{ss}}\frac{dT^{ss}}{d\rho_1} = (\frac{0.6}{0.0525972})(-1.23902) = -14.1341$$

Consider a 5% decrease from α_{13}. $\Delta\alpha_{13} = 0.03$.
The sensitivity analysis on α_{13} is the following,

Sensitivity coefficients:

$$\frac{dH^{ss}}{d\alpha_{13}} = \frac{H^{ss}(0.6 - 0.03) - H^{ss}(0.6)}{0.03} = \frac{0.985673 - 0.947312}{0.03} = 1.2787$$

$$\frac{dT^{ss}}{d\alpha_{13}} = \frac{T^{ss}(0.6 - 0.03) - T^{ss}(0.6)}{0.03} = \frac{0.014959 - 0.0525972}{0.03} = -1.2546$$

Relative sensitivities:

$$\frac{\alpha_{13}}{H^{ss}}\frac{dH^{ss}}{d\alpha_{13}} = (\frac{0.6}{0.947312})(1.2787) = 0.8099$$

$$\frac{\alpha_{13}}{T^{ss}}\frac{dT^{ss}}{d\alpha_{13}} = (\frac{0.6}{0.0525972})(-1.2546) = -14.3118$$

4.1 Analysis

Increasing the growth rate of tumour cells has a very similar effect as decreasing the death rate of host cells by tumour cells on the system as discussed previously. In both cases, the tumour cell populations are more sensitive to changes in these parameters compared to the host cell populations even though they directly affect the rate of change in the host cells. This shows that altering these two parameters would have a large impact on tumour cells and should be considered when planning treatment. The goal should be to increase the growth rate of host cells while also decreasing their death rate, resulting in more healthy cells which would be stronger against the tumour cells. The sensitivity analysis is useful when trying to effectively control tumour growth by making small adjustments while still being effective.

5 Conclusion and Open Problems

To conclude, mathematical modelling is a powerful tool when it comes to analyzing chaos in cancerous cells. The model designed by de Pillis and Radunskaya investigates how the host cells, effector immune cells, and tumour cells interact in a single tumour-cite compartment and how the competing species exhibit chaotic behaviour. Through analysis, it is evident that increasing the growth rate of host cells produced similar results as decreasing the rate of host cell death caused by tumour cells. Chaotic systems tend to be highly sensitive to small changes in parameter values resulting in vast differences in outcomes. This sensitivity can also be seen in initial conditions. At one point the system could be stable while at a different point nearby the system could experience sustained oscillations and grow out of control. These facts should be considered when experts decide the best way for effective treatment of tumours.

The model proposed by de Pillis and Radunskaya was published in 2013, so there are limitations in their research and conclusions. Their paper focuses on the host cell population of the chaotic cancer model. Due to the results being centred around the host cells, the treatment plans explored involve manipulating these cells and their rate of change rather than focusing on shrinking the tumour growth. The system is modelled with more of an ecological approach in the sense that the host cells have a prey-predator interaction with the tumour cells.

An interesting idea to build on this model would be to investigate whether or not this connection still applies in the biological field. Due to the scope of the paper, the connection between chaos theory and the cancer cell model was not explored in depth. Different types of cancers can exhibit different strengths of chaos and should be individually assessed when further analyzed.

In terms of treatment plans, there are many forms that exist in medicine such as anti-angiogenic therapy, hormonotherapy, early anti-periostin therapy, and more. These specific forms of treatment shrink tumours but there is currently no method that increases healthy cell growth without also increasing tumour cell growth (Letellier et al, 2013). The development of tumour cells is an ongoing topic of discussion and is continuously being researched and new models are being developed. Cell interactions are studied and deconstructed to better understand deterministic tumour growth, resistance, and treatment responses (Letellier et al, 2013).

Some interesting open problems include determining parameters that accurately describe the model based on real world biological experiments (Letellier et al. 2013) instead of running systems with parameters to match theoretical situations. Also pertinent to chaotic behaviour is the topic of stabilizing and controlling initial conditions to be less sensitive to changes (Coffey, 1998). Another important field to consider is understanding tumour cell heterogeneity to determine why cancers may resist treatment (Coffey, 1998).

Overall, using mathematical models to explore the chaotic cancer system helps with determining the specific parameter values needed to control the behaviour. However, the model may fail in larger cases since chaos can be quite unpredictable. This makes it difficult to come to conclusions in experiments and real-life settings that include many factors that are heavily external.

6 References

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Coffey, D. S. (1998). Self-organization, Complexity and Chaos: The new biology for medicine. *Nature Medicine*, *4*(8), 882–885. https://doi.org/10.1038/nm0898-882

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Letellier, C., Denis, F., & Aguirre, L. A. (2013). What can be learned from a chaotic cancer model? *Journal of Theoretical Biology*, *322*, 7–16. https://doi.org/10.1016/j.jtbi.2013.01.003

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7 Appendix A: MATLAB code

```
% Figure 1
% Parameters
Tend = 50.0;
sigma = 10.0;
rho = 14.0;
%rho = 28.0;
beta = 8.0/3.0;
h = 0.002;
% Initialization
n = 1;
t(n) = 0.0;
x(n) = 1.0;
y(n) = 0.0;
z(n) = 0.0;
% Recursive scheme
while (t(n) + h < Tend + 1.e-12)
   x(n+1) = x(n) + h * (sigma * (y(n) - x(n)));
   y(n+1) = y(n) + h * (x(n) * (rho - z(n)) - y(n));
   z(n+1) = z(n) + h * (x(n) * y(n) - beta * z(n));
   t(n+1) = t(n) + h;
   n = n+1;
end
plot3(x,y,z, ‘color’, ‘black’)
xlabel('x')
ylabel('y')
zlabel('z')
title('Lorenz Attractor: stable')
%title('Lorenz Attractor: chaotic')
```

```
% Figures 3, 4, and 5

function final_project

% declare model parameters

global p1;

global p2;

global a1;

global a2;

global a3;

global d;

p1 = 0.6;

%p1 = 1.0;

%p1 = 1.5;

a1 = 1.5;

%a1 = 0.9;

%a1 = 0.6;

p2 = 4.5;

a2 = 0.2;

%a2 = 0.05;

d = 0.5

a3 = 2.5;

% declare dynamics and set simulation options

ODEFUN=@chaos;

Tend=1000;

[t,S]=ode45(ODEFUN, [0,Tend], [0.66 0.079 0.132]);

% plot

plot(t, S(:,1), t, S(:,2), t, S(:,3),'lineWidth', 2)

xlabel('Time')

ylabel('Population')

title('Cell Populations')

legend('Host Cells', 'Effector Immune Cells' , 'Tumour Cells', 'location',
'northwest')

%plot(S(:,3),S(:,2), 'lineWidth', 1, ‘color’, ‘black’)

%axis([0 1 0 1])
```

```
%xlabel('Tumour cells z')
%ylabel('Effector immune cells y')
%title('Chaotic Attractor')
end
% declare right-hand-side
function dS = chaos(t,S)
global p1;
global p2;
global a1;
global a2;
global a3;
global d;
x = S(1);
y = S(2);
z = S(3);
% model equations
dx = (p1 * x * (1 - x)) - (a1 * x * z);
dy = ((p2 * y * z) / (1 + z)) - (a2 * y * z) - (d * y);
dz = (z * (1 - z)) - (x * z) - (a3 * y * z);
dS=[dx dy dz]';
end
```