Projects for Tumor Dynamics Module *

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Projects

Projects. Instructor's Notes: The goal of these projects is to provide open-ended, exploratory exercises, so that the students can become more deeply involved with the modeling process. They could be done in groups or individually. We recommend that adequate time be given to these projects, and that the results be presented both orally and in written form. It is important to be able to critically evaluate the outcome of the modeling process, and to communicate any results to a rather wide audience. Some references have been provided, but the students should be encouraged to search the literature for other related articles. It is assumed that the students are familiar with most, if not all, of the material presented in the module before embarking on the projects. However, in order to expedite the completion of the projects, some of the exercises provide preliminary investigations which could provide some of the groundwork for a more in-depth exploration of the topic. We have tried to indicate which exercises inform particular projects. It might also be expedient to have the students select a project early on, and to begin some background reading on their particular subject. For example, some background reading on cancer vaccines could be done before modifying the mathematical model to incorporate this type of therapy.

1. **Purpose:** To compare different models of tumor growth with data from breast cancer patients. References: [DTV+94], [VAJ82], [HSA98] Note: The data itself if not included in the actual article. This project reproduces and extends the analysis of the data discussed in the article.

   ProjectThis project uses the data described in the article *"Local Recurrences Following Mastectomy: Support for the Concept of Tumor Dormancy* by R. Demicheli et al., published in the Journal of the National Cancer Institute. The actual data was acquired from the authors, through Dr. Bill Thayer. The data is available in an Excel file, as well as in the table titled: "Demicheli Data". The study consists of measurements made on 121 patients with breast cancer. All 121 patients underwent mastectomies, and the tumors subsequently regrew in all 121 patients. Some of the patients also received adjuvant treatment (chemotherapy or radiation) after the mastectomy. The table consists of six columns: 1) The patient's case number, 2) TM: the time since the patient's mastectomy, measured in weeks; 3) TC: the time since the end of any adjuvant therapy, measured in weeks; 4) D: the diameter of the recurring tumor when it was first observed, measured in millimeters; 5) TE: the time since the previous *negative* exam, i.e. since the last exam when no tumor was detected, measured in weeks and 6) V: the volume of the tumor at recurrence, measured in cm^3, calculated from the measured diameter assuming that the tumor is a perfect sphere.

   The goal of this project is to use this data to explore the validity of different models of tumor growth. The authors of the article argue that a single growth function *cannot* adequately explain the data, whether the function be an exponential or a logistic function. They conclude that breast tumors must undergo a period of dormancy, or retarded growth. Do you agree? Discuss the following models of tumor growth:

   (a) Exponential growth (no immune response): $\frac{dT}{dt} = aT$.

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(b) Growth on the tumor surface (no immune response): $\frac{dT}{dt} = aT^{2/3}$. See the Exercise on Von Bertalanffy growth.

(c) Logistic growth (no immune response): $\frac{dT}{dt} = aT(1 - bT)$.

(d) Growth on the surface with crowding (no immune response): $\frac{dT}{dt} = aT^{2/3}(1 - bT)$.

(e) Gompertz growth (no immune response): $\frac{dT}{dt} = aT(1 - \ln(bT))$.

(f) Add an immune response to any, some, or all of the above models of tumor growth. You will need to extend the model to a system of two differential equations by adding an immune population, as we did in the model development in class. Note: Since the data does not include any information about the immune cell population, you have some freedom in choosing parameters for that part of the model. One approach would be to use the parameters values we already estimated, but to leave the initial value of the immune population as a free parameter. It might be worth noting that some of the patients (the first 26) did not receive any adjuvant therapy, since in their case TM = TC. It is well known that both radiation and chemotherapy are harmful to the immune system, so that one would expect that patients 27-121 would have a poorer immune response. This might show up in the model as lower initial immune populations, a higher immune cell death rate, or a lower immune cell source rate.

For each of these models, use the data to estimate parameter values. You may consider each patient to have different parameter values, or you may decide to do some averaging. Describe in detail the method you use, and include any statistics you think are relevant. Answer the following questions. Be precise in your justifications.

(a) Does one model give results which fit the data better than the others?

(b) Is it possible to explain the data *without* including an immune response?

(c) Is it possible to distinguish between the various models? Which ones are similar, and which ones are distinctly different?

(d) What measurements would allow you to determine the form of the model? Is it possible to perform these measurements? (A literature search might be in order here.)

(e) Are the patients who received no adjuvant therapy markedly different from the rest in any way? Does this inform the mathematical model? (In particular, if therapy is harmful to the immune system, does this tell us anything about the tumor-immune interaction?)

Demicheli Data

TM	=	Time since masectomy (in weeks)
TC	=	Time since chemotherapy (in weeks)
D	=	Diameter at recurrence (in mm)
TE	=	Time since previous exam (in weeks)
TV	=	Volume at recurrece (in cm^3)

Case No.	TM	TC	D	TE	V
1	65	65	34	4	20.57950889
2	316	316	8	4	0.268082347
3	43	43	5	5	0.065449792
4	66	66	5	11	0.065449792
5	555	555	16	43	2.144658773
6	44	44	10	10	0.523598333
7	28	28	15	1	1.767144375
8	120	120	21.2	5	4.988911941
9	86	86	5	14	0.065449792
10	106	106	8.5	6	0.321554826
11	177	177	5	13	0.065449792
12	67	67	52.3	9	74.90370882
13	151	151	35	7	22.44927854
14	19	19	30	13	14.137155
15	156	156	20	12	4.188786667
16	180	180	35	16	22.44927854
17	142	142	50	13	65.44979167
18	270	270	16.3	43	2.267571911
19	56	56	18	4	3.05362548
20	19	19	12	5	0.90477792
21	29	29	9	6	0.381703185
22	71	71	21.2	5	4.988911941
23	27	27	20	3	4.188786667
24	26	26	12	13	0.90477792
25	32	32	40	5	33.51029333
26	45	45	8	6	0.268082347
27	843	787	20	30	4.188786667
28	144	88	5	3	0.065449792
29	86	31	12	8	0.90477792
30	111	43	7	9	0.179594228

Case No.	TM	TC	D	TE	V
31	708	656	12	28	0.90477792
32	205	146	15	9	1.767144375
33	151	131	5	13	0.065449792
34	116	61	10	19	0.523598333
35	328	268	3	17	0.014137155
36	312	261	28	13	11.49403061
37	266	216	7	26	0.179594228
38	226	198	10	17	0.523598333
39	87	37	2	1.5	0.004188787
40	647	591	33.7	46	20.03954968
41	130	79	6.2	13	0.124788144
42	354	301	10	6	0.523598333
43	173	120	21.2	4	4.988911941
44	78	46	5	15	0.065449792
45	111	60	50	11	65.44979167
46	117	64	2	12	0.004188787
47	694	644	20	21	4.188786667
48	76	40	11.2	24	0.735617959
49	135	92	4	26	0.033510293
50	165	118	9.7	23	0.477874062
51	209	162	10	12	0.523598333
52	183	145	20	25	4.188786667
53	234	194	42.4	17	39.91129552
54	42	9	10	4	0.523598333
55	119	79	22.5	12	5.964112266
56	70	39	5	16	0.065449792
57	90	54	10.5	12	0.606130521
58	260	223	5	25	0.065449792
59	174	135	8	16	0.268082347
60	138	103	5	26	0.065449792

Case No.	TM	TC	D	TE	V
61	141	90	5	5	0.065449792
62	117	61	45	25	47.71289813
63	119	64	5	18	0.065449792
64	155	123	20	6	4.188786667
65	380	292	20	27	4.188786667
66	139	80	15	15	1.767144375
67	280	231	25	28	8.181223958
68	98	43	20	30	4.188786667
69	348	303	3	6	0.014137155
70	80	58	8	45	0.268082347
71	317	293	6	8	0.11309724
72	82	18	6	14	0.11309724
73	98	33	12	14	0.90477792
74	107	65	19.2	13	3.70597036
75	88	55	20	11	4.188786667
76	90	43	20	16	4.188786667
77	97	54	5	17	0.065449792
78	422	373	13	2	1.150345538
79	329	267	8	37	0.268082347
80	69	20	30	15	14.137155
81	74	25	21	28	4.849044165
82	167	119	6	25	0.11309724
83	90	62	5	11	0.065449792
84	199	143	3	25	0.014137155
85	140	87	3	24	0.014137155
86	76	18	8	8	0.268082347
87	329	279	20	21	4.188786667
88	129	79	15	6	1.767144375
89	207	155	25	20	8.181223958
90	88	26	6.2	26	0.124788144
91	389	318	20	37	4.188786667

Case No.	TM	TC	D	TE	V
92	78	34	35	24	22.44927854
93	126	89	15	25	1.767144375
94	138	103	8	28	0.268082347
95	57	20	10	13	0.523598333
96	69	32	6	17	0.11309724
97	121	106	10	27	0.523598333
98	58	21	3	13	0.014137155
99	68	30	15	13	1.767144375
100	66	23	5	2	0.065449792
101	233	199	4	1	0.033510293
102	53	14	20	14	4.188786667
103	79	34	32.5	26	17.97414904
104	121	84	5	9	0.065449792
105	113	70	3	27	0.014137155
106	134	92	15	22	1.767144375
107	99	48	5	22	0.065449792
108	53	23	6	21	0.11309724
109	105	74	10	27	0.523598333
110	55	16	4	10	0.033510293
111	114	77	10	18	0.523598333
112	133	96	10	30	0.523598333
113	79	36	10	24	0.523598333
114	164	121	25	22	8.181223958
115	48	10	70	9	179.5942283
116	100	74	21.2	13	4.988911941
117	194	154	5	12	0.065449792
118	81	42	7	8	0.179594228
119	99	60	10	26	0.523598333
120	230	187	20	23	4.188786667
121	83	43	15	25	1.767144375
122	99	51	30	9	14.137155

2. **Purpose:** To explore a well-known model of a chemical reaction which can produce oscillations. From [Dan85], Model 4.80, pp 186-189. See also [J.D93], Chapter 6, and the original article by Field and Noyes, [FN74].

   Note: This model gives rise to a *stiff* system. See, in particular, the Computing Project Exercise on nonlinear chemical reactions.

   Project: The "Oregonator" is so-called because the research done on it by Field and Noyes was performed at the University of Oregon. Field et al. developed this mathematical model of an oscillatory chemical reaction which was discovered in 1951 by Belousov, whose original paper was "contemptuously rejected by a journal editor", ([J.D93]). However, the study of this reaction was continued by another Russian, Zhabotinski, and the reaction itself is now known as the Belousov-Zhabotinskii, or the BZ reaction. Since its discovery, the BZ reaction has prompted a great deal of research, and Belousov was finally recognized (after he died) when he was awarded the Lenin Prize in 1980.

   We will set up the model without going into great detail. The interested reader is invited to read the paper by Field and Noyes, [FN74]. The variables of the model are the concentrations of three molecules. Let X denote the amount of bromous acid, $HBrO_2$; let Y denote the amount of bromide ion, Br^-, and let Z denote the amount of cerium ion, Ce(IV). All three of these substances are both reactants as well as products of the reaction, much as the effector and tumor cells in the tumor-immune reaction. Any other reactants are assumed to be available at constant concentrations, and any other products are assumed to be inert. These are labeled A, (BrO_3^-) and P, (HOBr).

   Using traditional reaction notation, the reactions are approximated by this sequence:

$$\begin{aligned} A + Y &\xrightarrow{k_1} X, \quad X + Y \xrightarrow{k_2} P \\ B + X &\xrightarrow{k_3} 2X + Z, \quad 2X \xrightarrow{k_4} A + P, \quad Z \xrightarrow{k_5} Y \end{aligned} \tag{1}$$

   The *Law of Mass Action* states that **the rate of a reaction is proportional to the product of the concentrations of the reactants**. Following tradition, we denote the *concentrations* of each substance by lower case letters: x,y, and z.

   (a) Use the Law of Mass Action and the sequence above to get the following system of three differential equations for x, y, and z. Recall the assumptions on A and P.

$$\begin{aligned} \frac{dx}{dt} &= k_1 ay - k_2 xy + k_3 bx - 2k_4 x^2 \\ \frac{dy}{dt} &= -k_1 ay - k_2 xy + k_5 z \\ \frac{dz}{dt} &= k_3 bx - k_5 z \end{aligned} \tag{2}$$

   The rate constants $k_1, \ldots k_5$ are given in [FN74] as:

$$\begin{aligned} k_1 &= 1.34\text{M}^{-1}\text{sec}^{-1}, \quad k_2 = 1.6 \times 10^9 \text{M}^{-1}\text{sec}^{-1} \\ k_3 &= 4 \times 10^3 \text{M}^{-1}\text{sec}^{-1}, \quad k_4 = 8 \times 10^7 \text{M}^{-1}\text{sec}^{-1}, \quad k_5 = 1\text{sec}^{-1}. \end{aligned}$$

   (b) Non-dimensionlize the system 2 to get:

$$\begin{aligned} \frac{dx^*}{dt^*} &= \alpha(y^* - x^* y^* + x^* - \beta(x^*)^2) \\ \frac{dy^*}{dt^*} &= \alpha^{-1}(-y^* - x^* y^* + z^*) \\ \frac{dz^*}{dt^*} &= \gamma(x^* - z^*), \end{aligned} \tag{3}$$

   where α, β, and γ are new parameters. Show all the details of the transformation, and compute the values of the three new parameters, (the constants a and b drop out if the transformation is done a certain way).

(c) Verify that there is an equilibrium at $x_E^* = 488.68, y_E^* = 0.99796$, and determine its stability. Find any other positive equilibria, and determine their stability.

(d) Numerically integrate the system, for $t^* \in [0, 325]$. Explain why this system is considered "stiff". (You may need to adjust solver settings to get solutions over this interval. Use a higher-precision setting, or lower tolerances if the solver is having trouble.) Plot the concentrations over time on a logarithmic scale, since they will vary greatly in magnitude.

(e) Experiment with initial conditions close to the non-zero equilibrium given in 2c. Plot phase portraits using two of the three variables (you choose). Find a limit cycle.

(f) Set the parameter $\gamma = 0$. In [FN74] it is claimed that in this case there are no oscillations. Confirm this statement, both numerically and analytically.

(g) Change the parameter values in system 3, considering sets of values which are not so disparate in magnitude. What do you notice?

(h) This system has an equilibrium at the origin: (0,0,0). Determine the range of parameter values for which this equilibrium is stable.

(i) Show that there is always one other positive equilibrium, and perform a bifurcation analysis of this equilibrium. In particular, determine:

- for which range of parameter values is the equilibrium stable?
- for which range of parameter values might there be a limit cycle?
- at which parameter values does a Hopf bifurcation occur? Note: A Hopf Bifurcation occurs when a stable equilibrium becomes an unstable spiral, and a stable limit cycle is created. To find the Hopf bifurcation, determine the parameter values at which the eigenvalues of the Jacobian of the system at the equilibrium are *purely imaginary*, i.e. when do the eigenvalues cross the imaginary axis? As the real parts of the complex eigenvalues change from negative to positive, the equilibrium changes stability, and a limit cycle is created.
- Sketch in the $\gamma\alpha$-plane the "stability bifurcation curve", i.e. the parameter values at which the equilibrium becomes unstable.

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