Mathematics 4MB3/6MB3 Mathematical Biology PROJECT 2017

Contents

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1 Important Preliminary Notes

(i) Please re-read all the General Notes and Technical Notes on assignments.

(ii) A preliminary draft of this project is due in class 9 days before the end of term: **Monday 27 March 2017 @ 11:30am**.
Please submit a hardcopy of the preliminary version of your main paper. Please submit the rest (`pdf` files of main paper and supplementary material, and a compressed folder containing all source files) by e-mail only.

(iii) The final version of this project is due in the last class of the term: **Wednesday 5 April 2017 @ 11:30am**.

(iv) Carefully read the instructor's solutions to all assignments.

(v) Start your personal project notebook in which you keep track of what work you have done personally on the project. Use the project notebook template available on the course wiki. You will be required to e-mail this notebook to the instructor twice (once when the preliminary version of the project is submitted and again when the final version of the project is submitted). The subject line of your e-mail must be one the following:

```
Math 4MB3 Project Notebook:  Default Name:  My Name (27 March 2017)
Math 4MB3 Project Notebook:  Model Students:  My Name (27 March 2017)
Math 4MB3 Project Notebook:  Models R Us:  My Name (27 March 2017)
Math 4MB3 Project Notebook:  The Tangentially Hip:  My Name (27 March 2017)
```

Please copy and paste the version with your group's name into the subject line of your e-mail and then replace "My Name" with your name. This will reduce the chance for typos that make it harder for me to find your e-mail by subject. Please attach both the LaTeX source file and the compiled `pdf` file to your e-mail message. The filename for your project notebook must be `MyNameGroupNameNotebook.pdf`, where `MyName` and `GroupName` are substituted with your name and your group's name, respectively.

(vi) A number of different possible directions for your project are described in §2. You can also suggest your own direction for a project. In any case, you must discuss and have your plans approved by the instructor.

(vii) Information about the required structure of your project is given in §4.

(viii) Check the course wiki for updates of this document.

2   Possible Research Directions

Choose one of the following research directions, propose a modified version of one of the directions below, or propose your own. Your research direction must be approved by the instructor.

2.1   Why are influenza epidemics seasonal?

Background: "The underlying cause of seasonal oscillations in influenza incidence remains unclear despite at least 80 years of investigation" (Dushoff *et al.* 2004, [1]). This possibly surprising statement remains valid today, though quite a bit has been learned since 2004.

Your challenge: For context, read the short review article on the ecology and evolution of influenza by Earn *et al.* [2]. Then read the very brief (two page) paper by Dushoff *et al.* [1] and do the following.

(a) Explain in your own words why an SIRS model is suitable to address the problem under consideration.

(b) Prove the claim that the intrinsic period of oscillation for an SIRS model (as defined in [1]) is approximately

$$T = 2\pi \sqrt{\frac{DL}{\mathcal{R}_0 - 1}},$$

where D and L are the mean durations of infectiousness and immunity, respectively. How good is this approximation?

(c) Explain in your own words the concept of "dynamical resonance" and why this might explain influenza seasonality.

(d) Using ®, reproduce the two figures in the paper of Dushoff *et al.* [1]. This involves solving both the deterministic and stochastic SIRS models in ®.

   Notes:

   - The "resonance prevented" lines in Figure 1 of Dushoff *et al.* [1] are obtained by imagining that at each time t, the system reaches the equilibrium that would be associated with $\beta(t)$ if t were a constant. You should explain why this achieves what Dushoff *et al.* [1] intended.

   - The appropriate initial state for your stochastic simulations is the endemic equilibrium of the unforced deterministic model (or at least near to this state). You should explain why.

   - Running large numbers of Gillespie simulations with a population size $N = 500,000$ (as in Dushoff *et al.* [1]) will be too slow to be practical for you given the time available for this project. You can use $N = 50,000$ instead (and much smaller than that when debugging your code). Alternatively, you can use a hybrid algorithm that is available in the `adaptivetau` ® package; this algorithm is certainly to use for

stochastic simulations with $N = 500,000$. If you use `adaptivetau` then you should read the vignette about this package (type `vignette("adaptivetau")` from the ℝ prompt) and explain why it is OK to use the adaptive algorithm for the problem you are addressing.

- Your figures do not need to look identical to those of Dushoff *et al.* [1]. In particular you can make your own aesthetic choices and you should also be aware that it would be impossible to reproduce precisely the same stochastic realizations shown in [1]. Nevertheless, the message of your figures should be the same as those in [1].

(e) At the time of publication of the Dushoff *et al.* paper [1], $\mathcal{R}_0$ for influenza was thought to be fairly high ($4 \lesssim \mathcal{R}_0 \lesssim 16$), whereas most more recent work has suggested a substantially lower range ($1.2 \lesssim \mathcal{R}_0 \lesssim 6$). How does this affect the inferences of Dushoff and his collaborators? Is dynamical resonance still relevant to influenza seasonality?

(f) Use the Web of Science and/or Google Scholar to search for research papers published since 2004 that shed light on biological and/or environmental processes that affect influenza seasonality. Note that not all relevant papers will contain the word "influenza" in the title or keywords (*e.g.*, [3]). Summarize what you discover and, if possible, comment on the relationships among the biological and environmental mechanisms and the dynamical mechanism proposed by Dushoff *et al.*.

2.2 Mechanistic models vs statistical time series models

Background: In class we discussed two very distinct types of epidemic models, in the context of recurrent epidemics of childhood infectious diseases.

(i) **Mechanistic mathematical models** such as the SIR and SEIR models. These models, whether deterministic or stochastic, explicitly formalize the biological processes associated with disease transmission (*e.g.,* contact, infection, recovery, *etc.*) and demographic processes (*e.g.,* birth, death, migration).

(ii) **Statistical time series models** such as auto-regressive (AR), moving average (MA) and auto-regressive-integrated-moving-average (ARIMA) models. These models are based on the assumption that the observed disease time series are generated by temporally correlated random processes and that knowledge of past observations is sufficient to forecast the future.

Your challenge: Provide evidence for or against each of the following claims:

(a) It is relatively easy to fit an ARIMA model to a time series that was truly generated by an ARIMA process.

(b) It is hopeless to forecast future measles epidemics using a statistical time series model, but possible using a deterministic, mechanistic mathematical model.

(c) Chicken pox epidemics can be forecast equally effectively with either type of model.

(d) For time series of reported infectious disease incidence, to obtain fits of similar quality, far more parameters are required for statistical time series models than for mechanistic mathematical models.

In addition:

(d) Use the Web of Science and/or Google Scholar to search for research papers that use time series models to forecast infectious disease epidemics. Summarize what you discover and comment on it in relation it to your work.

Note: As mentioned in Lecture 12, Ⓡ has built-in functions for fitting statistical time-series models to time-series data. In particular, the `ar()` function fits auto-regressive models, while the `arima()` function fits much more general ARIMA models. Particular ARIMA simulations can be generated with `arima.sim()`.

Warning: The instructor has never used Ⓡ to fit statistical time series models. Consequently, he is not familiar with any specific challenges associated with using Ⓡ's `ar()` and `arima()` functions. Of course, he will do his best to help you resolve any technical difficulties as quickly as possible.

2.3 The challenge of eradicating polio

Background: "Poliomyelitis vaccination via live Oral Polio Vaccine (OPV) suffers from the inherent problem of reversion: the vaccine may, upon replication in the human gut, mutate back to virulence and transmissibility resulting in circulating vaccine derived polio viruses (cVDPVs)." (Wagner and Earn 2008, [4])

Your challenge: Read the paper by Wagner and Earn [4]. Then do the following.

(a) Explain in your own words why the model depicted in Fig. 1 of the paper is suitable to address the problem under consideration. What is your opinion of the assumption that a fixed proportion of those vaccinated will become infected by the revertant virus?

(b) Using ®, reproduce the Figs. 4 and 5 in Wagner and Earn [4] and explain their significance in your own words.
Note: Your figures do not need to look identical to those of Wagner and Earn[4]. You can make your own aesthetic choices.

(c) Measles vaccine (which is injectible, not oral) is also a live-attenuated vaccine. Is reversion more or less of a concern for eradication of measles?

(d) Implement both deterministic and stochastic (Gillespie) versions of your model in ® and check that both generate reasonable results. In particular, verify that the deterministic model approaches the equilibrium (for any initial conditions you choose). In addition, the ensemble mean of many stochastic realizations should agree with the associated deterministic solution.

(e) In their Figs. 7 and 8, Wagner and Earn [4] show the effects of various "end game" strategies designed to eradicate polio in a relatively short time. But they do not show the corresponding curves for the case of continuous OPV vaccination. Construct the "missing curves" for Figs. 7 and 8, and comment on what you learn. *Note:* Do not attempt to run Gillespie simulations with a population size 100 million. Either use a much smaller population size or use the `adaptivetau` package mentioned in §2.1.

(f) The model you have investigated includes only the (negative) effect of reversion, but not the (positive) effect of "contact vaccination". Explain the meaning of "contact vaccination" and construct a model that includes both effects.

(g) Graphically compare the equilibrium prevalence in both (deterministic) models as a function of the OPV vaccination proportion p. (Note that it is always possible to find an equilibrium numerically even if you do not succeed in finding it analytically.)

(h) Use the Web of Science and/or Google Scholar to search for research papers published since 2008 that shed light on feasible strategies for polio eradication. Also look at the World Health Organization (WHO) web site. Summarize what you discover and, if possible, comment on the relevance of your analysis to polio eradication in light of recent developments.

2.4 Effects of medieval practices on epidemic dynamics

Proposed by "Puns $\mathcal{R}_0$ 4 Us" in 2013.

Background: Many medieval medical practices are now known to have done more harm than good, at least insofar as they helped individual patients. Depending on the practice in question, transmission of infection to others might have been increased or decreased. What were the population level (epidemiological) effects of medieval medical practices that were harmful to the individuals being treated?

Your challenge: Address this question as follows.

(a) Use the Web of Science, Google Scholar and/or other means to research infectious disease treatments that were common in the Middle Ages. Select a disease (or class of diseases) for which the transmission dynamics can be reasonably approximated by an SIR model, and for which the common treatments often caused patients to die. Explain the rationale for your choice, and back it up with appropriate references.

(b) Explain clearly the biological process or processes that you need to formalize mathematically in order to explore the epidemiological effects. You will need to ask yourself many questions. For example, you might consider the following (and other questions).

   (i) Does everyone get treated? If not, are individuals selected at random to be treated?

   (ii) When does treatment begin? As soon as symptoms are evident? Only if the patient becomes extremely ill? Before illness as a prophylactic measure?

   (iii) Is everyone equally susceptible to the harmful effects of treatment? If not, why not? Is this determined genetically, environmentally or by some other means?

   (iv) How does treatment affect transmission? Death of the patient? Increase in infectiousness? Degree of contact with others?

You do not need to take every aspect of biological reality into account, but you do need to be crystal clear about what you are assuming. Ideally, you would consider a variety of different scenarios, but for the purpose of this project it is probably best to focus on one.

(c) Formalize your assumptions in a deterministic model that generalizes the SIR model. Express your model both as a flow chart and as a system of ODEs. Discuss your model with the instructor ASAP before continuing your research.

(d) Consider the special case of your model without vital dynamics, which is appropriate for studying a single epidemic. Find the expected final size of the epidemic and compare it to the final size predicted by the basic SIR model. Using ℝ, make a graph that compares the predicted final sizes, and explain what you learn from this graph.

(e) For the full model (including vital dynamics), find all equilibria and determine their local stability. If possible, find conditions under which each equilibrium is globally

stable. Graphically compare the equilibrium prevalence of infection in the population with and without treatment. Explain what you learn from your figure(s).

(f) Implement both deterministic and stochastic (Gillespie) versions of your model in ℝ and check that both generate reasonable results. In particular, if the deterministic model has an equilibrium then your solutions should converge to it, at least if sufficiently close. In addition, the ensemble mean of many stochastic realizations should agree with the associated deterministic solution.

(g) Compare the mean time to extinction predicted by your model with that of the standard SIR model. Discuss the implications (*e.g.,* ethical) of what you find. What advice would you have offered to medieval politicians and health workers?

(h) Research epidemiological models for the Black Death, which we now know was caused by bubonic plague [5] (the causative agent of which is the bacterium *Yersinia pestis*). What treatments and precautionary measures were used during the Black Death? Select one (or more) of these measures and construct a flow chart and derive a set of equations to represent the dynamics of this infectious disease. Note that the normal mode of transmission for bubonic plague is *rodent → flea → human*, with the primary transmission dynamics occurring in the rodent population. How would your model differ if the disease were pneumonic plague rather than bubonic plague? Could the Black Death have been an epidemic of pneumonic plague?

2.5 Spatial epidemic dynamics: Synchronization

Background: Synchronizing epidemics has the potential to reduce the eradication threshold for measles. But under what circumstances can we expect epidemics to synchronize? And how big is the effect if they do?

Your challenge: Read the paper of Earn *et al.* [6]. (If you want to learn more about the analytical theory, [7] and [8] might also be of interest to you.) Then do the following.

(a) Explain in your own words why synchronization might reduce the eradication threshold.

(b) Construct a spatial SIR model based on n identical patches (cities) with identical population sizes. Do not consider explicit movement of individuals among patches. Instead, assume that connectivity arises from individuals visiting other patches for short periods, which creates a source of infection into a focal patch from the other patches. Check your model structure with the instructor before you proceed further with the project.

(c) Implement both deterministic and stochastic (Gillespie) versions of your model in ℝ and check that both generate reasonable results. In particular, if the deterministic model has an equilibrium then your solutions should converge to it, at least if sufficiently close. In addition, the ensemble mean of many stochastic realizations should agree with the associated deterministic solution.

(d) Using the deterministic version, make the equivalent of Fig. 1 in Earn *et al.* [6] for your model. Your horizontal axis should be $\mathcal{R}_0$. What should the parameter on your vertical axis be?

(e) Based on Gillespie simulations of the stochastic version of your model, make the equivalent of Fig. 3 in Earn *et al.* [6] for your model.

(f) Make a conjecture concerning an analytical criterion that would guarantee synchrony in your system.

(g) Use the Web of Science and/or Google Scholar to search for research papers published since 2000 that shed light on epidemic synchrony and its relationship to eradication. Summarize what you discover and, if possible, relate it to your work.

Note: This project will generate boring results if you do not include seasonal forcing. Why? A reasonable implementation of seasonally forced transmission would be sinusoidal forcing, $\beta(t) = \langle \beta \rangle (1 + \alpha \cos(2\pi t))$, with a seasonal amplitude $\alpha = 0.1$.

2.6   Predicting transitions in epidemic patterns via bifurcation analysis using XPPAUT

Background: The bifurcation diagrams discussed in class were constructed by "brute force", meaning by direct simulation of the model in question and plotting a representation of the one-year stroboscopic map associated with the system. While this method identifies the attractors of the model, it cannot easily provide information about the period of damped oscillations onto those attractors.

Your challenge: Begin by learning the basics of XPPAUT using Bard Ermentrout's book (see the Software page on the course wiki).

(a) Read Chapter 2 and do Exercise 2.3 on page 26.

(b) Read Chapter 3, sections 3.1 to 3.4, and do Exercise 2 on page 34. Plot x, y and Q as a function of time for a particular parameter set.

(c) Read Chapter 7, sections 7.1 and 7.2, and do Exercise 1 on page 182. Produce a bifurcation diagram similar in style to the left panel of Figure 7.5 on page 180.

(d) Read Chapter 7, section 7.4.

Continue to enhance your skill with XPPAUT by reading and learning the methods described in "Bifurcation analysis of the seasonally forced SIR model using XPPAUT", which is one of the electronic supplements to a 2013 paper by Krylova and Earn [9].

(e) Obtain the source code for the electronic supplement to [9] from your instructor and make sure you can reproduce the results.

(f) Write code that computes the period of damped oscillations onto the attractors and reproduce Figure 2 in the main body of the paper by Krylova and Earn [9] or Figure 6 in the more recent paper by Hempel and Earn [10].

(g) With the help of your figure, explain the observed dynamics of measles in New York City from 1890 to 1984 (see Figures 2 and 5 in [10]).

(h) Investigate the robustness of this "transition analysis" by making the equivalent of the figure you made in part (f) for modified SIR models as follows.

   (1) Replace the standard incidence term βSI with the "pseudo-heterogenous" incidence term $\beta S^h I$. Consider $h = 1/2$ and $h = 2$ and explain how these modified models mimic heterogeneous transmission without adding additional compartments (see the papers by Liu and co-workers [11, 12] for detailed discussions of these models). By carefully selecting values of the seasonal forcing amplitude α, can you force the $h \neq 1$ models to make the same transition predictions as you find with $h = 1$?

   (2) Replace the sinusoidal seasonal forcing function with a square wave. Is the square wave more realistic than a sinusoid? Is it now possible to choose values of α such that the $h \neq 1$ models make the same transition predictions as with $h = 1$?

Your solutions must include your `.ode` files and graphs (made in ℝ).

2.6.1 Notes on combining XPPAUT and Ⓡ

Embedding an XPPAUT.ode file in a knitr script. There are many ways to do this, but one convenient way is to use the LaTeX listings package. To do this include

```
\usepackage{listings}
```

in your LaTeX preamble, and then include the file (say mycode.ode) via

```
\lstinputlisting{mycode.ode}
```

If you want to get fancy, you can learn a lot about the listings package online (e.g., http://en.wikibooks.org/wiki/LaTeX/Source_Code_Listings). If you're very ambitious, you could write an XPPAUT style definition for the listings package and get beautifully highlighted code.

An alternative that is straightforward and yields aesthetically pleasing results is to let knitr think that XPPAUT code is actually Ⓡ code and typeset it accordingly. Provided the chunks of XPPAUT code are not evaluated (chunk option eval=FALSE), this will work just fine and will at least distinguish between comments and executable code. The principal disadvantage of this approach is that the XPPAUT code needs to be duplicated in the knitr document and in the .ode file, which tends to generate accidental inconsitencies between the two.

Making graphs in Ⓡ from XPPAUT output. Your knitr script (.Rnw file) should actually run the .ode files and then read and plot the data in the output files that XPPAUT produces. You can run XPPAUT in silent mode from within Ⓡ in the appropriate place in your project via

```
system("xppaut -silent mycode.ode")
```

By default, XPPAUT will produce an output file called output.dat, but you can change the name via the OUTPUT=filename option in your .ode file; you will need to do this so that when you run your project .Rnw file, the second execution of XPPAUT does not overwrite the output from the first. You will then need to read the XPPAUT output into Ⓡ and make the plots described in the exercises above. Note that it is important to learn to use XPPAUT interactively, since that's the easiest way to use it for initial exploration. But it is equally important to know how to create scripts that produce easily reproducible results.

By setting things up this way, your project will be exactly reproducible.

3   Executive Summary

In at most one page, summarize the aspects of your project that you think would be of greatest interest to the Public Health Agency of Canada (PHAC) in language that PHAC employees are likely to be able to understand.

Note: It is imperative that the one-page executive summary be printed on its own page. To start a new page in LaTeX, use the `\newpage` *command. Also, as usual, your summary should be in 12 point font. Don't try to cram in as much as possible. Make that page as clear and concise as you can, so that a public health planner can absorb its content quickly and easily.*

4   Structure of Your Final Project Document

Your project document must have the following form:

1. Cover page (2 marks), including the title of your paper, the name of your group, the names and e-mail addresses of all group members, and the word count for the main paper.

2. Executive summary (4 marks). See §3 above.

3. Main paper (24 marks). See further specifications below.

4. Supplementary material (10 marks), comprising a `knitr` script that reproducibly generates all of your results.

The hardcopy version that you bring to the final class must be provided as two documents, printed in colour, double-sided, and stapled together in the order indicated above. The first document must contain the first three parts above. The second document must contain the last part (the `knitr` supplement).

The main paper and executive summary should be LaTeX documents, whereas the supplement must be written using `knitr`. The instructor must be able to create your final `pdf` files without modifying your `.tex` and `.Rnw` source files. Everything you want to be marked should be contained in your final project `pdf` files. When submitting the electronic version of your project, include both the final `pdf` files and zip archive or tarball of all the files required to generate your `pdf`s.

Further specifications for the Main paper:

(a) Structure. The main paper should be presented in the style of a research paper for publication, as a self-contained coherent document. It should have an abstract, introduction, body, discussion and references to literature cited. The body will contain multiple sections. You can name the sections of the body however you feel is appropriate. It is OK to use "Methods" and "Results" as section names but there is no need to do so. Design the paper with a sensible logical flow and section names that summarize their content.

(b) Abstract. Should not exceed 100 words.

(c) Reference list. Use BibTEX. Call your BibTEX library `GroupName`.bib. To obtain a formatted reference list at the end of your paper, use the following:

```
\bibliographystyle{vancouver}
\bibliography{GroupName}
```

(d) Replication of results. If you are replicating the results of a published paper then say so and cite the paper appropriately. Never give the impression that you are presenting new research unless you are.

(e) Typos and spelling errors. Run your documents through a spell-checker and have every group member proofread the final version. Do not submit a paper with obvious spelling errors. See the Software page on the course wiki for hints.

(f) **Word limit: 3000 words.** If you exceed the word limit for the main paper you will lose a full letter grade. In your electronic submission, you must include a script that reproduces your word count. See the Software page on the course wiki for hints.

Marking will be based on the following criteria:

- Correctness: of analysis (both analytical and numerical).

- Communication: clarity of thought, quality of exposition of methods and results.

- Thoroughness: were suggested directions completed? If not, were they discussed coherently as future directions for research, and were scientifically sensible alternative directions explored?

References

[1] Dushoff J, Plotkin JB, Levin SA, Earn DJD. Dynamical resonance can account for seasonality of influenza epidemics. *PNAS – Proceedings of the National Academy of Sciences of the U.S.A.*. 2004;101(48):16915–16916.

[2] Earn DJD, Dushoff J, Levin SA. Ecology and evolution of the flu. Trends in Ecology and Evolution. 2002;17(7):334–340.

[3] Grassly NC, Fraser C. Seasonal infectious disease epidemiology. Proceedings of the Royal Society Series B. 2006;273:2541–2550.

[4] Wagner BG, Earn DJD. Circulating vaccine derived polio viruses and their impact on global polio eradication. *Bulletin of Mathematical Biology*. 2008;70:253–280.

[5] Bos KI, Schuenemann VJ, Golding GB, Burbano HA, Waglechner N, Coombes BK, et al. A draft genome of *Yersinia pestis* from victims of the Black Death. Nature. 2011;478(7370):506–510.

[6] Earn DJD, Levin SA, Rohani P. Coherence and conservation. Science. 2000;290(5495):1360–1364.

[7] Earn DJD, Levin SA. Global asymptotic coherence in discrete dynamical systems. *PNAS – Proceedings of the National Academy of Sciences of the U.S.A.*. 2006;103(11):3968–3971.

[8] McCluskey C, Earn DJD. Attractivity of coherent manifolds in metapopulation models. *Journal of Mathematical Biology*. 2011;62(4):509–541.

[9] Krylova O, Earn DJD. Effects of the infectious period distribution on predicted transitions in childhood disease dynamics. *Journal of the Royal Society Interface*. 2013;10:20130098.

[10] Hempel K, Earn DJD. A Century of Transitions in New York City's Measles Dynamics. *Journal of the Royal Society Interface*. 2015;12(106):20150024.

[11] Liu WM, Levin SA, Iwasa Y. Influence of nonlinear incidence rates upon the behavior of SIRS epidemiological models. Journal of Mathematical Biology. 1986;23(2):187–204.

[12] Liu WM, Hethcote HW, Levin SA. Dynamical behavior of epidemiological models with nonlinear incidence rates. Journal of Mathematical Biology. 1987;25(4):359–380.

Note: Papers listed above that include Earn as an author can be downloaded from http://www.math.mcmaster.ca/earn/publications.php.

— END OF PROJECT DESCRIPTION —

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