Application for Funding (VIU RESEARCH FUND)

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Project title:

Tumor Growth Models with Time Lags (New Models of Chronic Myelogenous Leukemia and Growth Models with Angiogenesis)

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Summary.

Recent Contributions

1. P. Amster and L. Idels, Periodic Solutions of Nonautonomous Mackey-type Systems with Delay, submitted to SIAM Journal on Applied Dynamical Systems (SIADS)
2. L. Berezansky, L. Idels and L. Troib, Global Dynamics of One Class of Nonlinear Nonautonomous Systems with Time-Varying Delays, Nonlinear Analysis: Theory, Methods & Applications, Volume 74, Issue 18, December 2011, Pages 7499-7512
3. P. Amster, L. Berezansky and L. Idels, Periodic Solutions of Angiogenesis Models with Time Lags, Nonlinear Analysis Series B: Real World Applications, Volume 13, Issue 1, February 2012, Pages 299-311.
4. P. Amster, L. Berezansky and L. Idels, Stability of Hahnfeldt Angiogenesis Models with Time Lags, submitted to Math. and Computer Modelling (2011).
5. L. Berezansky, L. Idels and M. Kipnis, Mathematical Model of Marine Protected Area, IMA Journal of Applied Math, 76 (2) 2011 312-325.
6. (2011) L. Berezansky, L. Idels and M. Kipnis, Mathematical Model of Marine Protected Area, IMA Journal of Applied Math , 76
7. (2011) L. Berezansky, L. Idels and L. Troib, Global Dynamics of Nicholson-Type Delay Systems with Applications, Nonlinear Analysis: Real World Applications, 12 436-445.
8. (2010) L. Berezansky, E. Braverman and L. Idels, Nicholson's Blowflies Differential Equations Revisited: Main Results and Open Problems, Applied Math Modelling , 34 (6) 1405-17.

Potential impact of the research

- Enhance the reputation of VIU through the international conferences and workshops

- Involves collaboration with VIU (Dr. Allan Gibson, Biology Department), and outside VIU.

- We have preliminary agreements to start collaboration with

  Michael C. Mackey Joseph Morley Drake Professor of Director of the Centre for Applied Mathematics in Bioscience and Medicine

  Research Areas

  Biological, physical and economic systems whose dynamics are described by delay- differential or functional differential equations.

  Current biological research includes:

  An examination of hematological dynamics in cyclical neutropenia

  Modeling periodic chronic myelogenous leukemia

  Modeling of the regulation of the Lac operon

- Publishing articles in scientific journals and international conferences proceedings.
- Has potential to attract more graduate and undergraduate students from UBC, SFU and UVic.

Research abstract

The broad goal of this work

a) Develop new Tumor Growth Models with Angiogenesis and Chronic Myelogenous Leukemia with Time Lags
b) Create a network of specialists in Mathematical Modeling (Workshops and Collaboration).
c) Train HQP in Biology and help top undergraduate students to start a research program.

In the limited scope of the present proposal, short-term objectives are focused on:

a) Introduction of a new equilibrium delayed models of Chronic Myelogenous Leukemia and Tumor Growth Models with Angiogenesis
b) Theoretical studies of the qualitative behaviour of the mathematical models, interpretation of our mathematical findings and possible implementation of the developed models.
c) Give a start up for undergraduate students involved in Biology.

OUTLINE OF THE PROPOSED RESEARCH PROGRAM

Mathematical modeling and simulation can potentially provide insight into the underlying causes of tumor invasion and metastasis, help understand clinical observations, and be of use in designing targeted experiments and assessing treatment strategies.
Angiogenesis is the process which enables a solid tumor to make the transition from the relatively harmless, and localized, avascular state to the more dangerous vascular state, wherein the tumor possesses the ability to invade surrounding tissue and metastasize to distant parts of the body with the assumption that cellular feeding is controlled only by diffusive processes, i.e. that the tumor is in a pre-vascular stage.
To incorporate the spatial effects of the diffusion factors that stimulate and inhibit angiogenesis, the following two-compartmental model for cancer cells and vascular endothelial cells was developed.
According to , a stimulator/inhibitor tumor growth dynamics should provide a time dependent carrying capacity under angiogenic control and include the distinct mechanisms for angiogenic stimulation and inhibition. Let x(t) be the tumor mass and K(t) be a variable carrying capacity, that is defined as the effective vascular support provided to the tumor as reflected by the size of the tumor potentially sustainable by it.

2. Outline of proposed research
To model processes in nature it is frequently
required to know system states from the past i.e. models incorporating memory .
Depending on the phenomena under study the after-effects represent duration of some hidden processes, e.g. time lags of transit through one state to another; transit time through compartments, or time lags associated with the growth rates (cell division).
In general, delay differential equations (DDE) provide
a richer mathematical framework (compared with ordinary differential
equations) for the analysis of biosystems dynamics.

Chronic myelogenous leukemia is cancer that starts inside bone marrow, the soft tissue inside bones that helps form blood cells. The cancer grows from cells that produce white blood cells. Chronic leukemia progresses more slowly than acute leukemia; and allows greater numbers of more mature, functional cells to be made. CML causes rapid growth of the immature blood-forming cells (myeloid precursors) in the bone marrow, blood, and body tissues. The accelerated phase is a more dangerous phase, during which the leukemia cells grow more quickly. The important characteristics of the dynamics are the existence of a slow-progressing chronic phase, the following instability, and with a very rapid transition to the acute phase. Chronic myelogenous leukemia is grouped into several phases: Chronic, Accelerated and Blast crisis. The chronic phase can last for months or years, but the chronic phase of pCML (Periodic Chronic Myelogenous Leukemia) differs slightly in that the chronic phase involves periodic oscillations with a period of about three months.

The important feature of the mathematical models of angiogenesis is the self-limiting growth phenomena; such properties are exhibited by Gompertz and logistic models in which the growth is limited by the carrying capacity. Hahnfeldt et al. (1999) proposed to define the Gompertz and logistic carrying capacity, which constrains the tumor growth, as a varying tumor volume sustainable by the vessels, approximately proportional to the vessel volume.

Although the equation proposed by Hahnfeldt to model the tumor growth appear similar to the Gompertz equation, the carrying capacity is not constant but varies with changes of the volume of the vessels. The dynamics of the growth of the vessel volume represented by its doubling time depend on the stimulators of angiogenesis, inhibitory factors secreted by tumor cells and natural death rate of the endothelial cells. In Hahnfeldt et al. (1999) it has been assumed that the inverse of the doubling time is the sum of these three factors.

Considering factors influencing growth and decay of tumor vasculature, Hahnfeldt et al. (1999) asserted that tumor-driven inhibitors from all sites act systemically, whereas tumor-derived stimulators act locally. On the other hand analyzing a diffusion–consumption equation for the concentration of stimulator or inhibitor inside and outside the tumor, Hahnfeldt et al. (1999) concluded that the inhibitor influences target endothelial cells in the tumor at a rate that grows ultimately as the area of the active surface between the tumor and the vascular network which in turn is propotional to the square of the tumor diameter. This leads to the conclusion that the inhibitory factor is proportional to the power 2/3 of tumor volume since the volume is proportional to the cube of the diameter. The modification of this model proposed by D'Onofrio and Gandolfi (2004) assumes that the effect of stimulators and natural mortality on the inverse of the doubling time is constant while the effect of inhibitors is proportional to the active surface of the area of tumor being in contact with the vascular network and therefore to the square of the tumor radius. Combinations of tumor growth models given by Gompertz-type and logistic-type equations with vascular network models proposed by Hahnfeldt et al. (1999) and D'Onofrio and Gandolfi (2004) result in four nonlinear models of tumor angiogenesis. Ergun et al. (2003) proposed yet another simplified model: in which the growth of the vascular network is independent of the tumor size. Nevertheless to obtain a complete model of the tumor growth in the vascular stage we should add one of the two proposed previously models of growth (Gompertz or logistic-type). The interesting finding is that all these models have the same nontrivial equilibrium point. The models are strongly nonlinear but by a logarithmic change of variables and scaling transformations, it is possible to simplify them and find their asymptoptic properties using the standard Lyapunov type analysis of stability (local and global) following the line of reasoning presented in D'Onofrio and Gandolfi (2004).

Application of antiangiogenic therapy can be incorporated in the model using a factor multiplicatively increasing the death rate of the vessels. For the constant dose of the drug it is possible to find a dose such that the equilibrium point is equal to zero. According to

the conditions of stability given in D'Onofrio and Gandolfi (2004) this leads to the conclusion that the vascular network and in turn the tumor can be eradicated. This conclusion is crucial for the analysis. It is enough to ensure that the population of endothelial cells responsible for angiogenesis behaves in a required way, because the size of tumor population tracks similar transients. In D'Onofrio and Gandolfi (2004) it has been proven that the same effect might be reached for periodic therapy with mean value satisfying an equality or nonequality condition, which is however generally only necessary. It is not sufficient, since the original Hahnfeldt model of eradication of the tumor depends on the shape of pulses in the periodic protocol. For some other models, this condition is necessary and sufficient.

Although during simulation all the models discussed lead to similar behavior if uncontrolled, their behavior in the presence of control, corresponding to different therapeutic protocols, may differ significantly. Moreover, clinical interpretation of the results also depends on the choice of the model.

Another class of models based on ordinary differential equations was proposed and analyzed by Agur and coworkers ([Agur et al., 2004], [Arakelyan et al., 2002], [Arakleyan et al., 2005] and [Forys et al., 2005]). The main purpose of these models is to reflect instability of the newly formed vessels structure. The models consist of a module of tumor dynamics and two others, the angiogenesis and vessel maturation modules, coupled through the action of regulatory proteins. The model simulations demonstrate the role of micro-environmental conditions in the metastatic potential of the tumor. The simplified version of the model enables analytical considerations, which reflect instability and cycles observed in the angiogenesis process. The drawback of this class of models is that they do not reproduce the stable behavior observed in less aggressive tumors.

(1)

The model (1) would allow us to examine a variety of interesting questions. For example, It is interesting to compare dynamics presented by three model.
Do any of those models exhibit CML dynamics: After a relatively quick rise in the cell count, the system reaches a seemingly steady state. After several years, this steady state gives rise to oscillatory instability. Finally, this leads to a sharp, usually fatal, increase in the cell count.

3. Methods of investigation

Qualitative and theoretical methods: optimization of dynamical systems, equilibrium analysis, stability and oscillation theorems for systems of ordinary differential equations.

Numerical methods: Computer simulations using Matlab and other modern scientific software packages.

4. References

1. S. Andrew, C. Baker, G. Bocharov, Rival approaches to mathematical modelling in immunology, Journal of Computational and Applied Mathematics, 205, 2, 2007, 669-686
2. R. Araujo, D. McElwain, A history of the study of solid tumour growth: the contribution of mathematical modelling, Bulletin of Mathematical Biology, 66, 5, 2004, 1039-1091
3. H. Byrne, T. Alarcon, M. Owen, S. Webb, P. Maini, Modelling Aspects of Cancer Dynamics: A Review, Philosophical Transactions: Mathematical, Physical and Engineering Sciences, Vol. 364, No. 1843, Biomathematical Modelling II (Jun. 15, 2006), pp. 1563-1578.
4. Ergun, K. Camphausen, L. Wein, Optimal Scheduling of Radiotherapy and Angiogenic Inhibitors,Bulletin of Mathematical Biology, 65, 2003, 407-424.
5. Hahnfeldt P., Panigraphy D., Folkman J., Hlatky L. Tumor
6. development under angiogenic signaling: a dynamical theory of tumor
7. growth, treatment response, and postvascular dormancy. Cancer Res 59, 1999, 4770-4775.
8. P. Hardenbergh, P. Hahnfeldt, L. Hlatky, C. Takemoto, A. Shimamura, G. McGill, Claire Y. Fung, Stephan Bodis, David E. Fisher, Distinct mathematical behavior of apoptotic versus non-apoptotic tumor cell death, International Journal of Radiation Oncology-Biology-Physics, Volume 43, Issue 3, 1 February (1999), Pages 601-605.
9. U. Ledzewicz, H. Schattler, Optimal and suboptimal protocols for a class of mathematical models of tumor anti-angiogenesis, Journal of Theoretical Biology, 252, 2, 2008, 295-312
10. U. Ledzewicz, H. Schaettler, On an extension of a mathematical model for tumor anti-angiogenesis, Nonlinear Analysis: Theory, Methods and Applications, 71, 2009, e2390-e2397
11. S. Maggelakis, The effects of tumor angiogenesis factor (TAF) and tumor inhibitor factors (TIFs) on tumor vascularization: A mathematical model, Mathematical and Computer Modelling, 23, 1996, 121-133
12. J. Nagy, Competition and natural selection in a mathematical model of cancer, Bulletin of Mathematical Biology, Volume 66, Issue 4, July 2004, Pages 663-687
13. d'Onofrio, U. Ledzewicz, H. Maurer, H. Schattler, On optimal delivery of combinatio therapy for tumors, Mathematical Biosciences, 222, 1, 2009, 13-26.
14. A. d'Onofrio, A. Fasano, B. Monechi, A generalization of Gompertz law compatible with the Gyllenberg-Webb theory for tumour growth, Mathematical Biosciences, In Press, 11 January 2011.

15. V. Quaranta, A. Weaver, P. Cummings, A. Anderson, Mathematcal modeling of cancer: The future of prognosis and treatment, Clinica Chimica Acta, 357, 2, 2005, 17-179
16. J.M. Mahaffy, J. Bélair, & M.C. Mackey. "Hematopoietic model with moving boundary condition and state dependent delay", J. Theor. Biol. (1998), 190, 135-146.
17. P. Fortin & M.C. Mackey. "Periodic chronic myelogenous leukemia: Spectral analysis of blood cell counts and aetiological implications", Brit. J. Haematol. (1999), 104, 336-345
18. Louise Kold-Andersen & M.C. Mackey. "Resonance in periodic chemotherapy: A case study of acute myelogenous leukemia", J. Theor. Biol. (2001), 209, 113-130
19. Fowler & M.C. Mackey. "Relaxation oscillations in a class of delay differential equations ", SIAM J. Appl. Math. (2002), 63, 299-323
20. L. Pujo-Menjouet & M. C. Mackey. "Contribution to the study of periodic chronic myelogenous leukemia", Comptes Rendus Biologiques (2004), 327, 235–244
21. M.C. Mackey, C. Ou, L. Pujo-Menjouet, & J. Wu. "Periodic oscillations of blood cell populations in chronic myelogenous leukemia", SIAM J. Math. Anal. (2006), 38(1), 166–187
22. M.J. Piotrowska, H. Enderling, U. an der Heiden & M.C. Mackey. "Mathematical modeling of stem cells related to cancer", in Cancer and stem cells (eds. T. Dittmar & K. S. Zänker), Nova Science Publisher, Hauppauge, NY (2008, in press)
23. R. Sachs, L. Hlatky, P. Hahnfeldt, Simple ODE models of tumor growth and anti-angiogenic or radiation treatment, Mathematical and Computer Modelling, 33, 12-13, 2001, 1297-1305
24. Swierniak, M. Kimmel, J. Smieja, Mathematical modeling as a tool for planning anticancer therapy, European Journal of Pharmacology, 625, 1-3, 2009, 108-121
25. R. Sachs, L. Hlatky, P. Hahnfeldt, Simple ODE models of tumor growth and anti-angiogenic or radiation treatment, Mathematical and Computer Modelling, 33, 12-13, 2001, 1297-1305
26. So, J.W.-H., Tang, X.H. and Zou, X. Stability of linear delay system without instantaneous negative feedbacks. Society of Industrial and Applied Mathematics: Journal on Mathematical Analysis 33 2002, 1297-1304
27. Swierniak, M. Kimmel, J. Smieja, Mathematical modeling as a tool for planning anticancer therapy, European Journal of Pharmacology, 625, 2009, 108-121.

Timelines:

- Jan-Feb: to analyse and develop certain models of, develop and mathematically justify a new methodology of studying non-linear models, based on a new model.
- Feb-April : perform numerical simulations and qualitative analysis of the proposed models

- May-June a two-week trip to the Centre for Applied Mathematics in Bioscience and Medicine, Department of Physiology, McGill University to discuss the project
- Sep-Nov finalize all proofs and details preparation the obtained results for publication
- Dec 2012 preparation of the final report to the Committee.