POWER programme

Introduction to bioinformatics (Summer term 2019)

1. Dr hab. Bogdan Kazmierczak - 1.5 h: 26.02.2019

Systems of ordinary differential equations in Mathematica.

2. Dr Jan Poleszczuk - 4 x 1.5 h: 05.03.2019, 12.03.2019, 19.03.2019, 26.03,2019

Mathematical modeling of cancer development and treatment: Introduction to mathematical oncology

Modern oncology is facing many challenges, most of which are related to the constantly increasing number of approved drugs and the amount of available clinical data. Back in 2014 there were about 1000 new anti-cancer drugs under investigation in the United States alone. Moreover, new drugs are rarely used alone and every drug combination needs to be clinically tested before it can be used in practice. As an example, in 2016 in the United States alone there were about 500 clinical trials in which new immune checkpoint inhibitors were tested with other, already available therapies. Some of the data gathered during those trials (and during routine clinical practice) is stored in a large public repositories, maintenance and analysis of which requires a lot of resources (both human and computational). In "The Cancer Genome Atlas" alone there is almost 2.5 petabytes of data available to researchers. Finally, there ia a constant development of new diagnostic methods which are generating new type of not fully understood data.

Mathematical methods are invaluable tools that could be used to solve some problems of the modern oncology. This has been already recognized by the scientific and medical communities with the establishment of the field named "mathematical oncology" [1] The idea behind it is to create models of two types: 1) those that can test the assumptions and protocols of clinical trials before they start, and 2) those that can help to predict patient's response to a given treatment. The former type of models can be compared to the virtual crash test that are nowadays performed by the car industry before building first prototypes. The second type of the models can be compared to so-called "spaghetti models" that are nowadays used to predict path of hurricanes.

During the lectures I will present exemplary mathematical oncology models and show how can they be applied to specific problems. Many different types of the models will be presented, starting from relatively simple equations describing cellular response to radiation [2], through elaborated agent-based models describing interactions of multiple populations [3, 4], finishing with models based on ordinary or partial differential equations [5, 6]. I will show difficulties associated with building models as well as problems with comparing them to the experimental and clinical data. Therefore, during the lecture I will show also some statistical and optimization methods. The lectures will finish with the presentation of some open problems of the mathematical oncology.

References

[1] Anderson ARA, Quaranta V. Integrative mathematical oncology. Nature Reviews Cancer. 2008;8(3):227–234.

[2] Sachs RK, Hahnfeld P, Brenner DJ. The link between low-LET dose-response relations and the underlying kinetics of damage production/repair/misrepair. International Journal of Radiation Biology. 1997;72(4):351–374.

[3] Kather JN, Poleszczuk J, Suarez-Carmona M, et al. In silico modeling of immunotherapy and stroma-targeting therapies in human colorectal cancer. Cancer Research. 2017;77(22):6442–6452.

[4] Kather JN, Charoentong P, Suarez-Carmona M, et al. High-throughput screening of combinatorial immunotherapies with patient-specific in silico models of metastatic colorectal cancer. Cancer Research. 2018;78(17):5155–5163.

[5] Kuznetsov VA, Makalkin IA, Taylor MA, Perelson AS. Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcation analysis. Bulletin of Mathematical Biology. 1994;56:295–321.

[6] Enderling H, Chaplain MAJ, Anderson ARA, Vaidya JS. A mathematical model of breast cancer development, local treatment and recurrence. Journal of Theoretical Biology. 2007 may;246(2):245–259.

3. Prof. Bartłomiej Wilczynski - 2 x 1.5 h: 02.04.2019, 09.04.2019

Global approaches gene regulation modeling

Mathematical modeling gene regulation has been done for almost 50 years and there is a long history and rich literature on the subject. In particular, a number of models have been proposed to address the question of what the expected level of the gene product should be given the regulatory state of the cell. This state of the cell can be very simple, as in the logical models (1,2) where the cell state is a binary vector of regulator gene's states, or much more complex, including quantitative gene expression levels and the occupancy state of transcription factor binding sites in gene promoters as in more quantitative models (3). In any case, it is assumed that the output of the gene of interest is a function of the state of the cell, even if some form of stochastic element is frequently included in this function.

From experiments, we know that, at least in the case of multi-cellular eukaryotes, the process of gene regulation depends on many events. Some of these events, such as transcription initiation or elongation, are mostly local with respect to a single gene and could be modeled with gene-oriented variables. However, there are other events that have implications for gene expression, that cannot be solely associated with a single gene. Two such phenomena are distal regulatory elements and global chromatin changes. In case of distal regulatory elements, it has been observed that concurrent binding of several transcription factors to a single DNA element can trigger a transcriptional response of one or more target genes(4). While distal regulatory elements are not strictly gene-associated, and are known to reside sometimes very far from their target genes, they are still localized, in the sense, that any regulatory element has a fixed position in the genome. However, there exist more global chromatin changes, mostly related to developmental processes, but also very well described in case of the heat shock stress, where large parts of chromosomes change their state to either enable or disable transcriptional activation of many genes.

In terms of mathematical modeling of both these phenomena – i.e. regulation of genes by multiple distal regulatory elements and larger scale chromatin changes – it is still an active area of research, however, there are already some quite clear trends. In our lectures, we will discuss several studies that have dealt with these issues. In particular, we will discuss approaches for identification and activity prediction of regulatory elements (5,6) based on different experimental measurements of the chromatin state, as well as the more global approaches to modelling the chromatin state – both in the supervised manner using Bayesian Networks(7) and unsupervised with Hidden Markov Models (8)

References

[1] Kauffman, Stuart (11 October 1969). "Homeostasis and Differentiation in Random Genetic Control Networks". Nature. 224(5215): 177–178.

[2] Thomas, R (1973). "Boolean formalization of genetic control circuits". Journal of Theoretical Biology. 42: 563–85.

[3] Janssens, H., Hou, S., Jaeger, J., Kim, A. R., Myasnikova, E., Sharp, D., & Reinitz, J. (2006). Quantitative and predictive model of transcriptional control of the Drosophila melanogaster even skipped gene. Nature genetics, 38(10), 1159.

[4] Wilczyński, B., & Furlong, E. E. (2010). Challenges for modeling global gene regulatory networks during development: insights from Drosophila. Developmental biology, 340(2), 161-169.

[5] Bonn, Stefan, Robert P. Zinzen, Charles Girardot, E. Hilary Gustafson, Alexis Perez-Gonzalez, Nicolas Delhomme, Yad Ghavi-Helm, Bartek Wilczyński, Andrew Riddell, and Eileen EM Furlong. "Tissue-specific analysis of chromatin

state identifies temporal signatures of enhancer activity during embryonic development." Nature genetics 44, no. 2 (2012): 148.

[6] Podsiadło, A., Wrzesień, M., Paja, W., Rudnicki, W., & Wilczyński, B. (2013). Active enhancer positions can be accurately predicted from chromatin marks and collective sequence motif data. BMC systems biology, 7(6), S16.

[7] Wilczyński, B., Liu, Y. H., Yeo, Z. X., & Furlong, E. E. (2012). Predicting spatial and temporal gene expression using an integrative model of transcription factor occupancy and chromatin state. PLoS computational biology, 8(12), e1002798.

[8] Ernst, J., & Kellis, M. (2012). ChromHMM: automating chromatin-state discovery and characterization. Nature methods, 9(3), 215.

4. Dr hab. Tomasz Zielinski - 3 x 1.5 h: 16.04.2019, 30.04.2019, 07.05.2019

   Theoretical and practical introduction to COMSOL program

5. Dr Pawel Kocieniewski - 2 x 1.5 h: 14.05.2019, 21.05.2019

   Modeling Combinatorial Complexity - Rule-based Modeling

6. Prof. Tomasz Lipniacki - 3 x 1.5 h: 28.05.2019, 04.06.2019, 11.06.2019

   Analysis of selected regulatory pathways in cells