Parallel Session

Genetics and Genomics II

THE INFLUENCE OF THE STOCHASTIC GENE SWITCHING ON EFFECTIVENESS OF THE METRONOMIC THERAPIES

Krzysztof Puszynski

krzysztof.puszynski@polsl.pl

Silesian University of Technology

Keywords: Stochastic gene switching, Metronomic therapy, Mathematical modelling, Simulations.

In this work we analyze the impact of the stochastic fluctuation of genes switching between their ON and OFF states on the effectiveness of a potentially large class of drugs given by metronomic regime.

We investigate two elementary molecular circuits to reveal the basic mechanisms underlying the experimentally observed dose-response curves. Both circuits consist in the transcription of a gene and in the successive mRNA translation into the corresponding protein. The difference between them lays in the gene deactivation mechanism. While in the first on gene deactivation is spontaneous, in the second it is dependent on the protein level, which constitutes negative feedback loop.

To avoid the influence of the complicated, especially non-linear dynamics of the complex systems we want to keep our as simple as possible. Therefore we consider a simple therapy: given drug is delivered by the oral administration and its function is to lower the protein level by enhancing its degradation rate. Assumed therapy is considered successful when the protein level stays below given threshold for a given time. During our simulations we set the threshold to be a half of the protein level in the steady state in case without drug and the time to 12 hours. This kind of pharmacodynamics (with various thresholds and time periods) is observed in many antibiotics and antitumor drugs. Moreover, because each therapy causes side effects, which has to be minimized, we consider therapies for which the total dose is limited to the values resulting in protein level closely below threshold in deterministic approximation.

As a result we have a system with two interplaying sources of signals which influence protein level. First is the stochastic gene switching in which we can modulate the switching time understood as the waiting time to the next stochastic event. Second is the drug administration. Because we consider metronomic therapies we can modulate the total dose, the number of fractions the total dose will be split into and the time interval between two successive doses.

We investigated a various combinations of the above in the wide range of the gene switching time and drug administration parameters. Our numerical simulations suggest that the gene

switching plays a primary role in determining the shape of the dose-response curves and reveals some interesting phenomena. Especially for very slow gene switching a significant fraction of cells may respond also in absence of drug. For the faster gene switching cells may respond to the therapy even when the drug dose is insufficient for the response in deterministic case. In contrast for the fast gene switching the stochastic prediction follows the deterministic approximation.

Our results suggest that metronomic therapies protocols may be ineffective when based on the population data which by its nature corresponds to the deterministic case in our model, neglecting the stochasticity of the gene switching. Especially, when the gene switching is slow such therapies protocol should be correlated with the gene switching times.

Acknowledgements: This work was partially supported by the grant number 2016/23/B/ST6/03455 founded by National Science Centre, Poland

Parallel Session

Genetics and Genomics II

A COMPARISON OF SINGULAR VALUES DECOMPOSITION AND FUNCTIONAL STATISTICS FOR THE ANALYSIS OF OMICS DATA

Alessandra Micheletti

alessandra.micheletti@unimi.it

Department of Environmental Science and Policy, Universitá degli Studi di Milano, via Saldini 50, 20133 Milano, Italy

Keywords: Functional statistics, Singular value decomposition, Omics data.

Many practical problems in the "omics" (genomic, proteomic, metabolomic) sciences are related with discrimination and comparison between groups: scientists are often interested to determine which genes, or metabolites, or proteins are significantly modified in groups of subjects affected by specific pathologies, in order to identify biomarkers or relationships between metabolic or genetic alterations and pathology development.

Omics data are characterized by large set of measurements performed on a small number of probes or experiments. In this setting, usual multivariate statistical techniques for groups comparison, like MANOVA or Hotelling T^2 tests, are not applicable, since the covariance matrix of high dimensional data, in presence of small samples, can not be computed without strong approximations, which may result unrealistic. Thus, other techniques for dimensionality reduction must be applied. Such techniques must preserve all the relevant information needed to discriminate with respect to different groups, and filter out the noise.

A rather consolidated technique in genomic is singular value decomposition (SVD) [1, 2], applied to genetic expression arrays. We here propose to represent omics data through functions, in spite of their non-longitudinal nature, and then we apply functional statistical techniques [3], like functional ANOVA (fANOVA), to compare the different groups. We compare the results of the functional data analysis with the one obtained through SVD on real genomic and metabolomic datasets.

References

[1] O.Alter, P.O. Brown, D. Botstein. (2000) *Singular value decomposition for genome-wide expression data processing and modeling*, PNAS, 97 (18), 10101-10106.

[2] F. Font-Clos, S. Zapperi, C.A.M. La Porta. (2017) *Integrative analysis of pathway deregulation in obesity*, npj Systems Biology and Applications, 3:18, doi:10.1038/s41540-017-0018-z

[3] J.O. Ramsay, B.W. Silverman. *Functional Data Analysis*. Springer, 1997.

Parallel Session

Genetics and Genomics II

A HYBRID ANALYTICAL-NUMERICAL METHOD FOR PARAMETER INFERENCE IN STOCHASTIC GENE EXPRESSION MODELS

Frits Veerman

f.veerman@ed.ac.uk

School of Mathematics, University of Edinburgh, James Clerk Maxwell Building, Peter Guthrie Tait Road, Edinburgh EH9 3FD, United Kingdom

Joint work with Carsten Marr (ICB, Helmholtz Centre Munich) and Nikola Popović (U. Edinburgh).

Keywords: Stochastic gene expression, Dynamical systems, Perturbation techniques, Probability generating function.

Stochastic models for gene expression frequently exhibit dynamics on several different scales. One potential time-scale separation is caused by significant differences in the lifetimes of mRNA and protein; the ratio of the two degradation rates gives a natural small parameter in the resulting chemical master equation, allowing for the application of perturbation techniques. We present an analytical method for the analysis of a family of 'fast-slow' models for gene expression that is geared to provide fully time-dependent propagators that describe the evolution of the stochastic model, in order to make full use of experimental time series data obtained by real-time tracking of gene expression in single cells as an input for a Bayesian parameter inference scheme, whose implementation provides the numerical part of the hybrid analytical-numerical approach [1]. We present the results of the application of the analytical-numerical method on a gene expression model that incorporates autoregulation through gene switching. We highlight the consequences of the perturbative approach for the parameter inference procedure, and give an overview of the possibilities and limitations of our analytical perturbative approach. We discuss the performance of the method on experimental single cell data from microfluidics experiments on budding yeast.

Acknowledgements: This work has been supported by the Leverhulme Trust, through Research Project Grant RPG-2015-017 ('A geometric analysis of multiple-scale models for stochastic gene expression').

References

[1] F. Veerman, C. Marr and N. Popović. (2017). *Time-dependent propagators for stochastic models of gene expression: an analytical method*, Journal of Mathematical Biology, doi:10.1007/s00285-017-1196-4

Parallel Session

Genetics and Genomics II

UNLOCKING THE STEM CELL PHENOTYPE: A MULTI-SCALE MODEL OF THE EPIGENETIC REGULATION OF CELL FATE AND PLASTICITY

Núria Folguera-Blasco

nfolguera@crm.cat

Centre de Recerca Matemàtica (CRM). Campus de Bellaterra, Edifici C. 08193 Bellaterra (Barcelona), Spain.

Joint work with Rubén Pérez-Carrasco (University College London), Elisabet Cuyàs (Institut Català d'Oncologia (ICO)), Javier A. Menéndez (Institut Català d'Oncologia (ICO)) and Tomás Alarcón (ICREA and Centre de Recerca Matemàtica (CRM)).

Keywords: Plasticity, Epigenetics, Reprogramming, Robustness.

A model of a two gene regulatory network with self-activation and competitive inhibition, with one gene promoting differentiation and one gene promoting pluripotency, is presented. The variation on the number of binding sites at the promoter regions of the genes, which can be originated by the stochastic epigenetic regulation (ER) dynamics, drives noise-induced transitions between the open and the silenced state of the genes, giving rise to plastic behaviour. This switch between the open and closed state lets us to describe a situation of partial cell reprogramming, where the differentiation-promoting gene gets closed, and a scenario of full reprogramming, where not only the differentiation-promoting gene gets silenced but also the pluripotency-promoting gene gets open. The robustness of each of these states can be analysed by computing its exit time, which allows to show that spontaneous reprogramming is a much rarer event than epigenetically-induced reprogramming. Furthermore, we also are able to find which properties a system must have in order to be more poised for (de)differentiation or self-renewal, and match them with some factors known to affect the ER system, such as aging and cancer.

Parallel Session

Genetics and Genomics II

EXTRINSIC NOISE LEADS TO PHENOTYPIC TRANSITIONS IN STOCHASTIC GENE EXPRESSION

Abhishek Gupta

s1478186@sms.ed.ac.uk

Centre for Synthetic and Systems Biology, University of Edinburgh, Edinburgh, United Kingdom

Joint work with Dr. Ramon Grima (Centre for Synthetic and Systems Biology, University of Edinburgh, Edinburgh, United Kingdom).

Keywords: Stochastic Gene Expression, Extrinsic Noise, CME/CFPE/CLE, Unified Colored Noise Approximation.

Phenotypic switching in gene regulatory networks is a well known phenomenon with relevance to cellular decision-making. It is typically marked by bimodal distributions of protein expression levels where each of the modes is associated with a particular phenotype. While it has been shown that intrinsic noise due to low copy number of promoters can induce bimodality under certain conditions, the influence of extrinsic noise is presently largely unexplored. Here we show using model systems of gene expression that the addition of extrinsic noise to certain reactions can shift the system's phenotype, i.e. the bimodal distribution switches from its mass being largely in one mode to the other mode. We also discuss a simplistic novel approximation of chemical master equation to capture these transitions. This phenomenon has relevance to synthetic biology, particularly to the design of biomolecular circuits whose function can be switched by external signals.

Parallel Session

Genetics and Genomics II

DATA DRIVEN MODEL SELECTION AND PARAMETER ESTIMATION FOR DNA METHYLATION

Nikos Kavallaris

n.kavallaris@chester.ac.uk

University of Chester

Joint work with Karen Larson (Brown University), Mark Mc Auley (University of Chester), Anastasios Matzavinos (Brown University), Jason Roberts (University of Chester) and Loukas Zagkos (University of Chester).

Keywords: DNA methylation, Model selection, Bayesian parameter estimation, Gene promoter, CpG dyads.

Epigenetics is coming to the fore as a key process which underpins health. In partic- ular emerging experimental evidence has associated alterations to DNA methylation status with healthspan and aging. Mammalian DNA methylation status is maintained by an intricate array of biochemical and molecular processes. It can be argued changes to these fundamental cellular processes ultimately drive the formation of aberrant DNA methylation patterns, which are a hallmark of diseases, such as cancer, Alzheimers disease and cardiovascular disease. In recent years mathematical models have been used as effective tools to help advance our understanding of the dynamics which underpin DNA methylation. In the current talk we will present some linear and nonlinear models which encapsulate the dynamics of the molecular mechanisms which define DNA methylation. Using our recently developed Bayesian algorithm for model analysis we will identify a set of model parameters which satisfy the biological requirements as well as we will propose an easy way of choosing the more efficient of the constructed models.