Parallel Session

Genetics and Genomics I

STOCHASTIC MODELING AND INFERENCE OF TEMPERATURE-DEPENDENT TRANSCRIPTION SUPERCOILING DYNAMICS

Andre S. Ribeiro

andre.ribeiro@tut.fi

Laboratory of Biosystem Dynamics, Multi-Scaled Biodata Analysis and Modelling Research Community and BioMediTech Institute and Faculty of Biomedical Sciences and Engineering, Tampere University of Technology, PO Box 553, 33101 Tampere, Finland

Joint work with Vatsala Chauhan and Cristina S.D. Palma (Laboratory of Biosystem Dynamics, BioMediTech Institute, Tampere University of Technology, PO Box 553, 33101 Tampere, Finland)

Keywords: Stochastic model, Transcription dynamics, Temperature shift, Supercoiling.

Based on a stochastic biophysical model of multi-step transcription based on empirical parameter values of the rate constants of a fully induced $LacO_3O_1$ promoter at optimal temperature, we hypothesize that temperature downshifts increase promoter escape times from supercoiled states as they enhance the energy barrier of this process. Next, from simulations of the model and statistical inference, we predict the consequences of this hypothesis on the mean and cell-to-cell variability in RNA numbers at low temperatures and on the rate-limiting steps of the multi-step transcription process. To validate our results, we produced empirical *in vivo* single RNA-level data from a single-copy $LacO_3O_1$ promoter, when chromosome-integrated and when plasmid-borne (impervious to supercoiling due to lack of topological barriers). We show that the original hypothesis and the predicted transcription kinetics alterations are highly accurate, in a statistical sense. The data further supports that this phenomenon is solely biophysical, as its kinetics rapidly changes following the temperature shifts. Thus, we conclude that our temperature-dependent transcription model is accurate within the range of 37 ^{o} C and 10 ^{o} C. In the future, we expect this validated temperature-dependent stochastic model of transcription for chromosome-integrated promoters to be of use in predicting the plasticity of temperature-sensitive synthetic genetic circuits.

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A SIMULATION STUDY OF THE RELATIONSHIP BETWEEN DNA DAMAGE DETECTION PATHWAYS AND THE CELL CYCLE

Monika Kurpas

monika.kurpas@polsl.pl

Faculty of Automatic Control, Electronics and Computer Science, Silesian University of Technology, Gliwice, Poland

Joint work with Krzysztof Puszynski (Faculty of Automatic Control, Electronics and Computer Science, Silesian University of Technology, Gliwice, Poland).

Keywords: Ataxia telangiectasia mutated protein kinase, Ataxia telangiectasia mutated and Rad3-related protein kinase, p53 tumor suppressor protein, Cell cycle, Mathematical model.

Daily, in each cell of human organism thousands of DNA lesions are formed. They may be caused by exogenous or endogenous factors. Ataxia telangiectasia mutated (ATM) protein is activated by DNA double-strand breaks (DSBs), while ataxia telangiectasia mutated and Rad3-related (ATR) detects single-stranded DNA areas (ssDNA). Both pathways cooperate inducing p53 tumor suppressor protein, which regulate apoptosis, DNA damage repair and cell cycle arrest.

Using mathematical modeling we examined how detection of DNA lesions influences the cell cycle and what is the impact of cell cycle phase on DNA damage detection processes. We combined deterministic version of our previously created mathematical model of ATM-p53-Wip1 pathway [1] with cell cycle core. We implemented resection process as a part of homologous recombination repair mechanism present in S and G2 phases of the cell cycle. We take into account stochastic cell cycle length and particular phases duration. Simulated cells are treated with ionizing radiation in random time points in order to recreate conditions in asynchronous cell population.

Our model confirms that the cell cycle phase, during which DNA damage arise, has the impact on genetic material susceptibility to damage. Our results indicate that during cell cycle progression, with increasing cell size, cellular DNA becomes more prone to damage than in early stages of cycle. Changing amount of DNA, and degree of its condensation have an impact on strength of DNA damage response. Also DNA damage repair type and speed are different in various cell cycle phases. In S and G2, resection process causes formation of ssDNA, which is the reason of experimentally observed activation of ATR module after ionizing irradiation.

Taken together, our results may explain why cells from heterogeneous population exhibit different responses to radiation, what is commonly observed during biological studies performed on the cell culture.

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EXPERIMENTAL VERIFICATION OF A COARSE-GRAINED MODEL PREDICTS PRODUCTION RATE LIMITS MRNA LOCALIZATION

Jonathan Harrison

harrison@maths.ox.ac.uk

University of Oxford

Joint work with Richard Parton, Ilan Davis and Ruth Baker (University of Oxford).

Keywords: Bayesian inference, mRNA localisation, Coarse-grained model.

Identifying bottlenecks in a biological process can enable the identification of key targets for regulation by the cell. mRNA localization by molecular motor driven transport is important for cell polarization, but the limiting bottleneck for efficiency of transport is not known in most cases. Here, we examine the rate-limiting steps in the localization of *gurken/TGF-alpha* mRNA in *Drosophila* egg chambers. We construct a coarse-grained model of the entire path of localization from mRNA production in nurse cell nuclei to the site of final localization in the interconnected oocyte. Using Bayesian inference, we relate this model to quantitative single molecule fluorescence in situ hybridization data, and draw three main conclusions. First, we characterize the formation of higher order assemblies of RNA-protein complexes in the oocyte by quantification of fluorescence in different regions. Second, by calculating steady state behaviour in the model, we estimate the extent of the bias in transport directionality through ring canals between cells. Finally, by parameterizing our full dynamic model, we provide estimates for the rates of the different steps of localization, and predict that the rate of production not transport is rate-limiting. We use our model to make a testable prediction about behaviour under perturbation to the production rate. Together, our results strongly suggest that production is rate-limiting for *grk* mRNA localization in *Drosophila* development.

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EIGENSOLUTIONS FOR A MODEL OF VERTICAL GENE TRANSFER OF PLASMIDS

Eva Stadler

eva.stadler@tum.de

Department of Mathematics, Technical University of Munich, Boltzmannstr. 3, 85748 Garching, Germany

Joint work with Johannes Müller (Department of Mathematics, Technical University of Munich).

Keywords: Growth-fragmentation equation, Hyperbolic partial differential equations, Spectral gap.

We consider a model for vertical gene transfer of genetic elements in bacteria called plasmids. The model incorporates non-constant cell division and death, plasmid reproduction, and segregation which is modeled by an integral operator that describes the fraction of plasmids the respective daughter receives from the mother. The dynamics of the system is determined by plasmid reproduction which increases the number of plasmids in the population and cell division and segregation which dilutes the plasmids and decreases the number of plasmids per cell. We obtain a growth-fragmentation equation for the bacterial population structured by the number of plasmids. The model equation is a hyperbolic partial differential equation with an integral term.

As we are interested in the long-term behavior of the distribution of plasmids we consider the associated eigenproblem and prove existence of eigensolutions along the lines of [1, 2] extending the results to models with non-constant cell death rates. In order to obtain stability results, we analyze the spectrum of the differential operator given by the model equation. We find a real dominating eigenvalue. The corresponding eigenfunction attracts all solutions.

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MOLECULAR EVOLUTION AND META-TRANSCRIPTOMIC APPROACHES TO ACCESS THE PLANT OXIDATIVE STRESS RESISTANCE ENZYMES

Alexey V. Doroshkov

ad@bionet.nsc.ru

Laboratory of Evolutionary Bioinformatics and Theoretical Genetics, Institute of Cytology and Genetics SB RAS, Novosibirsk, Prospekt Lavrentyeva 10, Russia and Novosibirsk State University, Novosibirsk, Pirogova 2, Russia

Joint work with Alexander V. Bobrovskikh (Institute of Cytology and Genetics SB RAS, Novosibirsk, Russia and Novosibirsk State University, Novosibirsk, Russia)

Keywords: Genes, Antioxidant system, Expression level, Evolution.

Reactive oxygen species (ROS) are some of the most damaging factors for living systems. Cells produce ROS during normal metabolism reactions, but ROS production increases under stressful conditions. Improving the antioxidant system in cultivated plants will increase their tolerance to abiotic stresses, such as salinity, drought and cold. However, the biochemical components of the system are redundant, each reaction is catalyzed by a series (up to 10) of enzymes encoded by different genes. This is an excellent model of a multicopy enzymatic system with complex regulation. Its study is of fundamental value. Simultaneously choosing the most perspective components of this system will help speed up evaluating the optimal breeding strategy for improving abiotic stress tolerance in economically valuable plants.

Here, we present the results of an integrative analysis of evolution- and expression-related characteristics. The work was carried out on a series of genes that belong to main functional groups (APX, GPX, SOD, CAT, etc.) of enzymatic components of the antioxidant defense system. We used a sample set of plant species consists of flowering plants (representing of main families in dicots and monocots), gymnosperms, mosses and green algae species. Also, we have collected the data on the cell localization of particular enzymes and the activities of individual components of the system in the favorable conditions and in response to stress.

As a result, more than 50 groups of orthologous genes were evaluated and described in terms of substitution rates, expression patterns and cellular localization. The data of phylogenetic analysis speak in favor of the theory that most part of diversification of individual components of the antioxidant system and their distribution by cellular compartments occurred at the early stages of the plant line evolution long before the appearance of multicellularity. Dramatic differences within series of the genes (for example, APX series) were detected in the pressure of purifying selection and in the level of mRNA expression. This pattern of

evolution and expression peculiarities is stable within species families and has significant differences between dicots and monocots species. At the next stage, the character of the expression changes in response to stress factors (drought, salt, cold) was described. It was found that the fraction of highly expressed genes responds to abiotic stress factors differently than the low-expressing fraction. A good correspondence was found between the particular activities of the atioxidant system and the mRNA levels of the corresponding components, which indicates a high relative contribution of expression regulation to the dynamics of the plant antioxidant system.

The highest gene expression level and the greatest pressure of purifying selection were found to characterize particular copies. Because these genes undergo the most conservative evolution and have the highest level of mRNA expression, we may assume that they contribute a lot to the antioxidant system functioning of the plants studied.

We have shown that the integration of evolutionary characteristics and expression data represents a promising approach access the fermentative system dynamics and to predict target genes for plant breeding.

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