

RESEARCH ARTICLE

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Detecting sequence dependent transcriptional pauses from RNA and protein number time series

Frank Emmert-Streib¹, Antti Häkkinen² and Andre S Ribeiro^{2*}

Abstract

Background: Evidence suggests that in prokaryotes sequence-dependent transcriptional pauses affect the dynamics of transcription and translation, as well as of small genetic circuits. So far, a few pause-prone sequences have been identified from in vitro measurements of transcription elongation kinetics.

Results: Using a stochastic model of gene expression at the nucleotide and codon levels with realistic parameter values, we investigate three different but related questions and present statistical methods for their analysis. First, we show that information from in vivo RNA and protein temporal numbers is sufficient to discriminate between models with and without a pause site in their coding sequence. Second, we demonstrate that it is possible to separate a large variety of models from each other with pauses of various durations and locations in the template by means of a hierarchical clustering and a random forest classifier. Third, we introduce an approximate likelihood function that allows to estimate the location of a pause site.

Conclusions: This method can aid in detecting unknown pause-prone sequences from temporal measurements of RNA and protein numbers at a genome-wide scale and thus elucidate possible roles that these sequences play in the dynamics of genetic networks and phenotype.

Background

Noise is inherent in gene expression and affects the behavior of genetic circuits and thus phenotype determination. It is unknown to what extent this noise is evolvable. One mechanism that likely contributes to transcriptional noise in prokaryotes is RNA polymerase (RNAP) pausing during elongation [1,2]. Pausing enhances the propensity for collisions between consecutive RNAPs in the template [3] and, in some cases, of premature terminations [4], particularly when hairpin loops form in the transcript, facilitating the recruitment of Rho-factor, a protein that dissociates the RNA from the DNA template and RNA polymerase [5]. The distance of the hairpin from the RNA 3' end and the RNA sequence affect pause duration and proneness for premature termination [4], indicating that the kinetics of this process is sequence dependent [6]. This

feature makes transcriptional pausing a plausible mechanism via which natural selection may act upon noise in gene expression.

Long-duration pauses usually occur only at specific DNA sequences [4], while short-duration pauses occur at random locations [7]. Observations in bacteria suggest that the RNAP pauses, on average, every 100 to 200 bp, for a few seconds [6] and, less frequently, for one to several minutes [4].

One of the best studied long-pause sites is the *his* pause sequence. This sequence causes the RNAP to pause for, on average, 47 s, with an efficiency that can go up to 80% [5]. The long duration of this event relies on the formation of a hairpin loop in the elongating RNA sequence that stabilizes the RNAP [7]. By removing the region of the DNA that codes for loop, the duration is reduced to 4.6 s, and becomes exponentially distributed [7]. Unlike *his* pauses, other sequence dependent long pause sites do not require the formation of RNA secondary structures [8].

Studies of transcriptional pausing have focused on the physical-chemical causes and its physiological role in

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Detecting The Sequence

Michael Gertz, Bertram Ludäscher



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Handbook John M. Walker, Ralph Rapley, 2008-11-04 Recent advances in the biosciences have led to a range of powerful new technologies particularly nucleic acid protein and cell based methodologies The most recent insights have come to affect how scientists investigate and define cellular processes at the molecular level **Molecular Biomethods Handbook 2nd Edition** expands upon the techniques included in the first edition providing theory outlines of practical procedures and applications for a range of techniques Part A of the book describes nucleic acid methods such as gene expression profiling microarray analysis and quantitative PCR In Part B protein and cell based methods are outlined in subjects ranging from protein engineering to high throughput screening Written by a well established panel of research scientists **Molecular Biomethods Handbook 2nd Edition** provides an up to date collection of methods used regularly in the authors own research programs This book will prove to be an invaluable reference for those engaged in or entering the field of molecular biology and will provide the necessary background for those interested in setting up and using the latest molecular techniques **DNA Technology in Forensic Science** Committee on DNA Technology in Forensic Science, Commission on Life Sciences, Division on Earth and Life Studies, National Research Council, 1992-01-15 Matching DNA samples from crime scenes and suspects is rapidly becoming a key source of evidence for use in our justice system **DNA Technology in Forensic Science** offers recommendations for resolving crucial questions that are emerging as DNA typing becomes more widespread The volume addresses key issues Quality and reliability in DNA typing including the introduction of new technologies problems of standardization and approaches to certification DNA typing in the courtroom including issues of population genetics levels of understanding among judges and juries and admissibility Societal issues such as privacy of DNA data storage of samples and data and the rights of defendants to quality testing technology Combining this original volume with the new update **The Evaluation of Forensic DNA Evidence** provides the complete up to date picture of this highly important and visible topic This volume offers important guidance to anyone working with this emerging law enforcement tool policymakers specialists in criminal law forensic scientists geneticists researchers faculty and students

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have hives shingles and an outbreak of psoriasis

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