

Derivation of First-Order Ordinary Differential Equation (ODE) Models for Alternative Splicing Events

Alternative splicing is a fundamental phenomenon in cell biology that enables a single gene to code for and produce multiple proteins. The dysregulation of alternative splicing has been heavily linked to cancer and several developmental diseases. In recent years, SKaTER-seq (Splicing Kinetics and Transcript Elongation Rates through sequencing), a novel assay designed to study how polymerase II elongation rate affects alternative splicing has been developed. The assay uses the transcription inhibitor DRB to simultaneously restart the transcription process of each cell in the sample. Using sequencing technology, the amount of nascent RNAs at each position was measured at multiple points in time.

Once experimental data has been collected, mathematical models need to be developed to describe how the amount of nascent RNAs are related to key parameters of the transcription process. These parameters include the elongation rate, splicing rates, cleavage rates at the termination and cleavage sites. Next, these parameters are estimated by fitting the observed sequencing data to the created model.

A mathematical model was developed to represent the alternative splicing of an exon between two termination sites at the end of a gene. This specific configuration is a common phenomenon in many species, and is the most common types of alternative splicing events that has yet to be modeled. To derive this model, a set of nine differential equations and boundary conditions that describe the amount of nascent RNA as a function of the time at different state of gene transcription process was set up. As this is a system of First-Order Ordinary Differential Equations (ODE) involving only exponential and polynomial terms, closed form solutions can be shown to exist. However, as this ODE system is too complicated to be solved by the symbolic computation software Mathematica, a closed form solution must be manually computed. This process was painstaking and meticulous, as a small mistake could nullify two hours of integration and differentiation. Lastly, the manually computed solutions had to be re-organized into a series of functions so they could be efficiently implemented into computer programs. Future studies include testing the accuracy equations investigating and modeling the remaining types of alternative splicing events associated with two termination sites.