

**Stony Brook University
The Graduate School**

Doctoral Defense Announcement

Abstract

Genome Signals and Evolution for Fidelity and Regulation of Pre-mRNA splicing

By

Chaolin Zhang

Pre-mRNA splicing is the process by which introns from pre-mRNAs are removed and exons are ligated in eukaryotes. By different combinations of exons and splice sites, i.e. alternative splicing, one gene can produce multiple transcript isoforms, providing a major source of proteomic diversity, novel mechanisms of gene expression regulation, and new paths of gene evolution. Splicing and alternative splicing take place in a cellular machinery called spliceosome, through interactions of many *cis*-regulatory elements and *trans*-acting splicing factors. However, the splicing code that elucidates how these interactions determine the splicing outcome, sometimes specific for tissues, developmental stages, different species or populations, is still poorly understood. This study aims to advance our mechanistic understanding of the fidelity and regulation of both constitutive and alternative splicing, mainly through computational analysis of genomewide, high-throughput data, combined with experimental validations from collaborative bench biologists. I first demonstrate the limited fidelity of the splicing machinery and describe a new and usual type of alternative splicing, which suggests selective pressure to reduce splicing errors or evolutionary intermediates. Then I show how such selective pressure results in non-random distributions of splicing-regulatory elements to optimize exon and intron discrimination, as gauged by a neutral evolution model developed from strand-asymmetry patterns. To achieve a better understanding of the organization and functional impacts of splicing-regulatory networks, I use the tissue-specific splicing factors Fox-1/2 as a model. Using comparative analysis of 28 vertebrate species, I predict thousands of conserved Fox-1/2 targets, among which at least 50-60% of predicted targets can be experimentally verified *in vivo*. This analysis demonstrates a surprising extensiveness of tissue-specific regulation at the splicing level. The regulatory network is highly organized and modular, with many predicted targets playing important neuromuscular functions and disorders.

Date: May 2, 2008

Time: 1:30 pm

Place: Health Sciences Center, Level 3, Lecture Hall 6

Program: Biomedical Engineering

Dissertation Advisor: Michael Q. Zhang