



Uncovering Genes Associated with the Process of Aging

The cerebellum is essential for the control of balance, posture, and motor coordination. During normal aging, the cerebellum can become progressively dysfunctional, which may be attributed to alterations of specific molecular components. Progressive dysfunction of the cerebellum can lead to life-threatening accidents. In a follow-up to the MBI workshop on Gene Expression Data Analysis (Fall 2004) several MBI visitors and a postdoc launched a journal club with the aim of uncovering genes whose expression levels in the cerebellum change during aging. Andre Rotter from OSU (Pharmacology) conducted Serial Analysis of Gene Expression (SAGE) experiments using a mouse as an animal model to study its cerebellum to identify such genes. He sought to identify the change in expression levels of genes in the cerebellum by comparing adult and aged mice. The other participants in the journal club included long-term visitors Shili Lin (OSU, Statistics), Vincent Melfi (Michigan State, Statistics and Probability), Bertram Zinner (Auburn University, Discrete and Statistical Sciences), Lynn Friedman (OSU, Statistics), Zailong Wang (MBI postdoc), and Adrienne Frosthalm and Magdalena Popesco from Rotter's lab.

One of the outstanding problems in SAGE is the lack of available methods that can handle multiple libraries (A SAGE library is a collection of up to tens of thousands of tags (genes) and their corresponding counts) per group, multiple groups, and all tags simultaneously, which was the challenge visitor Lin and Postdoc Wang undertook. Defining the problem as clustering all tags into a differentially expressed group and a similarly expressed group, and casting it as a model selection problem, Wang and Lin developed a Bayesian hierarchical model and a Markov chain Monte Carlo sampling procedure for tackling the high dimensionality.

In collaboration with Dr. Rotter's lab, the method was applied to the mouse cerebellum data generated by Popesco. Nine tags were found to be up-regulated (that is, more highly expressed) in the aged cerebella, while eight were down-regulated. To discern whether the genes selected as differentially expressed are meaningful biologically, the identified genes were used for further analysis using the Gene Ontology to annotate their functions and classify them into functional categories. As can be seen from the Figure, several of the enriched categories (shaded categories with names in black) were "oxygen" related. Oxygen binding heme proteins may protect neurons from hypoxic-ischemic injury in vitro and in vivo. While neuroglobin expression in the cerebellum decreases with age, our finding suggests that this process may be counteracted by an increased expression of hemoglobin mRNA: **According to Rotter, an elevated presence of this oxygen-binding transporter protein may serve to protect cerebellar cells from age dependent neurodegeneration.** These results, together with those from other studies, may help uncover the specific molecular changes during normal aging.

