New views of gene expression in the brain
Focus on “Gene expression tomography”

ROBERT W. WILLIAMS1 AND SUSAN B. GLUECK2
1University of Tennessee Health Sciences Center, Memphis, Tennessee 38163; and 2Deputy Editor, Physiological Genomics

TOMOGRAPHIC IMAGE RECONSTRUCTION is used in combination with some of the most sophisticated imaging techniques, including ultrasound, X-ray, and positron emission scans, to visualize anatomic structures in much greater detail than can typically be achieved using conventional techniques. Positron emission tomography (PET), for example, computationally reassembles full three-dimensional (3-D) images from a large set of virtual “slices” of the body cut in many different planes and angles of section. How are the brain’s 3-D structures constructed, and which genes are responsible? In this online release of Physiological Genomics, an article by Brown et al. (Ref. 1; see page 159 in this release) describes a new research methodology, gene expression tomography (GET), which exploits a clever and literal adaptation of tomography to provide a 3-D reconstruction of gene expression in the mouse central nervous system.

Brown et al. tested the GET method using three complementary tactics. The authors compared the expression of the tyrosine hydroxylase (TH) gene, the rate-limiting enzyme in dopamine synthesis, using several different detection methods. First, they generated a reference series of histological sections of TH activity using a TH-β-galactosidase reporter line of mice. Then, C57BL/6J brains were sliced in several orientations, and TH gene expression was measured in a total of 90 spatially defined samples. These serial slices, obtained in nine different planes of section from a set of nine genetically identical mice, provided the tissue necessary for two forms of gene expression detection, an RNase protection assay and quantitative real-time reverse transcriptase PCR (QRT-PCR). Standard tomographic mathematical methods were used to assemble nearly complete 3-D maps of brain regions expressing TH, with ~1.5 mm resolution. By warping these images onto atlases of the mouse brain and their own reference sections, Brown et al. were able to make side-by-side comparisons of the accuracy and validity of the position of regions with high TH expression. The substantia nigra and locus coeruleus, for example, were readily resolved. They found that the two gene detection methods, the RNase protection assay and QRT-PCR, agreed quite well with the reporter gene expression profile.

Why not just use in situ hybridization? The primary advantage of GET is that it scales extremely well and can easily be adapted for use with gene array technology. When combined with high-density oligonucleotide microarrays, GET should make it possible to simultaneously map the 3-D expression patterns of 10,000–20,000 genes with resolution better than 1 mm, even in a brain as small as that of a mouse. The precision of anatomic tomography of this type depends on the number of sections, their angular coverage, and the congruence of the set of brains used in the tomography. Isogenic mice make ideal subjects, but the method should eventually be adaptable to other species (perhaps even humans), provided that a set of brains can be accurately warped into a common frame of reference.

REFERENCES