Quantitative Analysis of Stochastic Axon Systems

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The brain contains many "point-to-point" projections that originate in known anatomical locations, form distinct fascicles or tracts, and terminate in well-defined destination sites. These projections are the focus of current connectomics projects and can be thought to represent the "deterministic brain." This brain coexists with a "stochastic brain" that is comparable in magnitude. The axons of the "stochastic brain" may initially travel in fascicles, but they eventually disperse in meandering trajectories, space-filling entire brain regions. Their cell bodies are typically located in the brainstem, as a component of the ascending reticular activating system (ARAS). ARAS axons (fibers) release serotonin, dopamine, norepinephrine, acetylcholine, and other neurotransmitters. They regulate perception, cognition, and affective states, and they also play major roles in human mental disorders (e.g., Major Depressive Disorder and Autism Spectrum Disorder).

Our interdisciplinary program [1, 2] seeks to understand at a rigorous level how the behavior of individual ARAS fibers determines their equilibrium densities in brain regions. These densities are commonly used in fundamental and applied neuroscience and can be thought to represent a macroscopic measure that has a strong spatial dependence (conceptually similar to temperature in thermodynamics). This measure provides essential information about the environment neuronal ensembles operate in, since ARAS fibers are present in virtually all brain regions and achieve extremely high densities in many of them.

A major focus of our research is the identification of the stochastic process that drives individual ARAS trajectories. Fundamentally, it bridges the stochastic paths of single fibers and the essentially deterministic fiber densities in the adult brain. Building upon state-of-the-art microscopic analyses and theoretical models, the project investigates whether the observed fiber densities are the result of self-organization, with no active guidance by other cells. Specifically, we hypothesize that the knowledge of the geometry of the brain, including the spatial distribution of physical "obstacles" in the brain parenchyma, provides key information that can be used to predict regional fiber densities.

In this presentation, we focus on serotonergic fibers. We demonstrate that a step-wise random walk, based on the von Mises-Fisher (directional) probability distribution, can provide a realistic and mathematically concise description of their trajectories in fixed tissue. Based on the trajectories of serotonergic fibers in 3D-confocal microscopy images, we present estimates of the concentration parameter (κ) in several brain regions. These estimates are then used to produce computational simulations that are consistent with experimental results. We also propose that other stochastic models, such as the superdiffusion regime of the fractional Brownian motion (fBm), may lead to a biologically accurate and analytically rich description of ARAS fibers, including their temporal dynamics. Since many properties of the fBm remain poorly understood, this interaction between neuroscience and stochastic analysis can stimulate both fields.

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References

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