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Dynamic extracellular space alters spatiotemporal distribution of chemical signals in brain: experiment and modeling

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Brain can be considered as a porous medium. The brain cells form a *solid* phase while the liquid-filled extracellular space (ECS) forms a *porous* phase that surrounds each individual cell. Brain ECS is of a fundamental importance for brain function [1]. It serves as a reservoir for ions and a channel for diffusion-mediated transport of biologically significant molecules and therapeutics. ECS volume is the main factor governing the extracellular concentrations of these substances. Any ECS volume change may lead to a change in concentration of ions and transported substances, and this has consequences for brain function.

Volumes of extracellular and cellular phases undergo reciprocal changes during certain physiological and pathological events in brain. For example, transition from sleep to awake state is associated with a reduction in ECS volume [2, 3] and expansion of one type of brain cells [3]. Here we introduce a new phenomenon, the Transient Volume Reductions (TVR) in the ECS that appear to play an important role in sustaining epileptic seizures. Epileptic seizures represent abnormal synchronous excitatory activity in neurons. While they are often thought of as mediated by *cellular* mechanisms, there are *extracellular* mechanisms too, such as a rise in extracellular potassium and ephaptic (field) interactions. When studying epileptic seizures in hippocampus, we found TVRs that occurred in concert with epileptiform potentials (Fig. 1). We hypothesize that TVRs promote epileptiform activity and its propagation by enhancing the *extracellular* mechanisms.

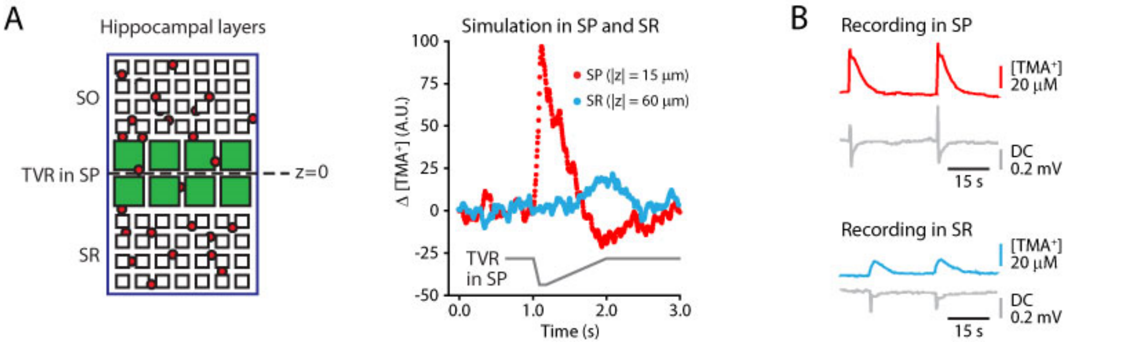

Figure 1: Transient Volume Reductions (TVR) of brain ECS. **A.** Modeling with MCell in hippocampal layers (SO, SP, SR). TVR in SP created a wave that was detected in SR. **B.** TVRs and field potentials (DC) recorded during epileptiform activity in hippocampal layers with tetramethylammonium (TMA) sensing microelectrode.

Here we ask how do the TVRs propagate in space and time and influence local diffusion and concentration of different molecules. The MCell simulator [4] recently acquired capability to incorporate time-dependent geometry. This enabled us to explore how concentration waves in the ECS can be generated by localized TVRs, possibly acting as a novel engine driving the diffusion flux. Preliminary numerical experiments with MCell suggest that TVR can generate interesting and unexpected effects. If a TVR occurs only in one layer of hippocampus, this layer acts as a transient macroscopic diffusion source and generate concentration wave of molecules endogenous to the ECS that spreads to the surrounding layers (Fig. 1). Numerical modeling is in agreement with the experiments in brain and helps us to understand the relationship between TVRs and epileptiform activity in brain.

References:

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