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A model of space-fractional-order diffusion in the glial scar

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HIGHLIGHTS

- Cell migration and diffusion of species about an implant have been modeled.
- Asymptotic behavior of the model has been investigated.
- Closed form solutions of fractional order have been obtained.
- Impact of the boundary conditions has been established.

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ABSTRACT

Implantation of neuroprosthetic electrodes induces a stereotypical state of neuroinflammation, which is thought to be detrimental for the neurons surrounding the electrode. Mechanisms of this type of neuroinflammation are still poorly understood. Recent experimental and theoretical results point to a possible role of the diffusing species in this process. The paper considers a model of anomalous diffusion occurring in the glial scar around a chronic implant in two simple geometries – a separable rectilinear electrode and a cylindrical electrode, which are solvable exactly. We describe a hypothetical extended source of diffusing species and study its concentration profile in steady-state conditions. Diffusion transport is assumed to obey a fractional-order Fick law, derivable from physically realistic assumptions using a fractional calculus approach. Presented fractional-order distribution morphs into integer-order diffusion in the case of integral fractional exponents. The model demonstrates that accumulation of diffusing species can occur and the scar properties (i.e. tortuosity, fractional order, scar thickness) and boundary conditions can influence such accumulation. The observed shape of the concentration profile corresponds qualitatively with GFAP profiles reported in the literature. The main difference with respect to the previous studies is the explicit incorporation of the apparatus of fractional calculus without assumption of an ad hoc tortuosity parameter. The approach can be adapted to other studies of diffusion in biological tissues, for example of biomolecules or small drug molecules.

1. Introduction

Implantation of neuroprosthetic electrodes induces a sustained state of neuroinflammation and scarring, which is thought to be detrimental for the neurons surrounding the electrode (McConnell et al., 2009). The formation of the glial scar is a complex reactive process involving interactions between several types of cells, including astrocytes and activated microglia, and is mediated by plethora of bio-active molecules. Over 100 studies have described stereotypic features of the brain response to microelectrodes that occur irrespective of the type of implant, method of sterilization, species studied, or implantation method (recent reviews in Jorfi et al., 2015; Prodanov and Delbeke, 2016). The literature demonstrates that in chronic conditions the recording longevity of such electrodes in experimental animals is highly variable. Wire electrodes tend to have longer use times compared to multielectrode cortical arrays (for wire electrodes see for example Liu et al., 1999, cortical arrays – Ward et al., 2009).

Attachment of *microglia* on the implant surface is a well documented phenomenon in all in vivo studies. This attachment is thought to be mediated by the adsorption of albumin on the implant surface or due to the release of chemo-attractants by serum factors, such as monocytes chemotactic protein-1 (MCP-1) and macrophage inflammatory protein (MIP-1) at injury sites (Saadoun et al., 2005). The number of ED-1 (a specific cellular marker for activation of rat macrophages) labeled cells increases progressively for several days after implantation, suggesting the potential

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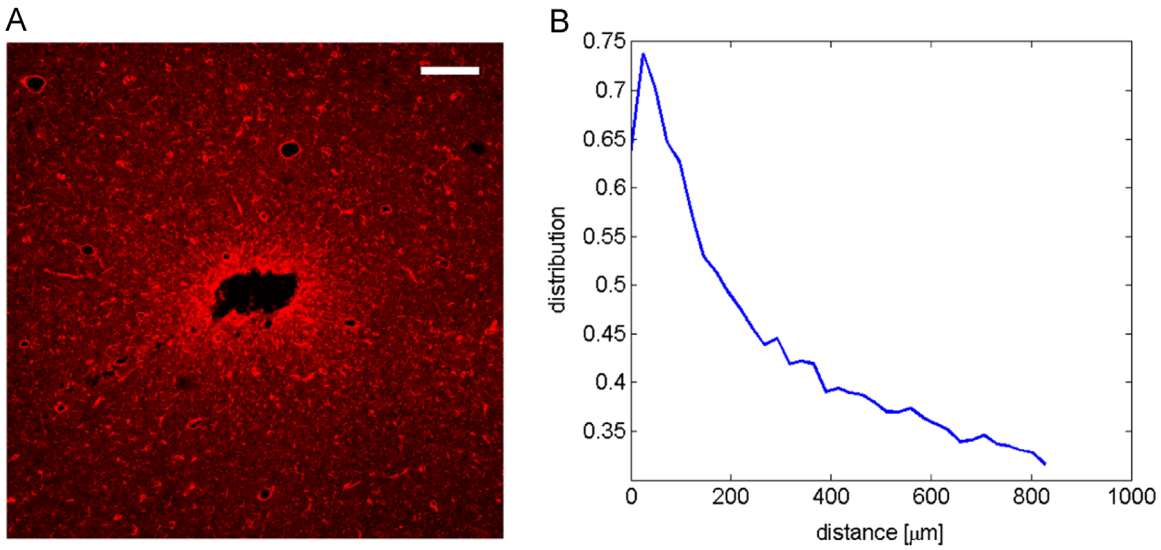

Fig. 1. Typical GFAP distribution around an implant site. (A) GFAP staining after 6 weeks of implantation in tethered configuration; (B) mean intensity distribution as a function of the distance to the insertion track (Prodanov and Verstreken, 2012). The dataset was published previously in Welkenhuysen (2011) and Welkenhuysen et al. (2011). Scale bar – 200 μm.

recruitment of peripheral blood-borne macrophages, as well as a transformation of endogenous microglia into brain macrophages (Barrese et al., 2013). The numbers of microglial cells initially increase sharply in the implanted region during the recovery phase reflecting a local microglial proliferation but the increase does not continue further during the chronic phase.

The reactive *astrocytes* form a dense web of interdigitated processes which over-expresses the Glial Fibrillary Acidic Protein (GFAP) and attach to the implant (see Fig. 1). Thus GFAP immunoreactivity is commonly used in neuroprosthetic studies as a marker of neuroniflammation. Astrogliosis and scar formation have sometimes been regarded as responses that are predominantly harmful. This belief is refuted by a large volume of in vivo experimental studies from many laboratories, which show that normally occurring astrogliosis and scar formation exert numerous essential beneficial functions that improve outcome, including wound closure, neuronal protection, blood–brain barrier (BBB) repair and restriction of CNS inflammation (recent review in Sofroniew, 2015). In the context of chronic implantation studies astrogliosis can be considered to be actually a compensatory reaction aiming to protect the neurons.

Concurrent with the glial scar formation, neuronal density within the recording radius of the microelectrodes decreases in certain circumstances, leading to even fewer distinguishable single-unit recordings (recent reviews in Jorfi et al., 2015; Prodanov and Delbeke, 2016). During this process the cells themselves substantially alter the composition, the morphology and the functional properties of the extracellular matrix. Roitbak and Syková (1999) also demonstrate changes of the diffusion path in reactive astrogliosis states and therefore in the extracellular space (ECS) properties.

Several hypotheses for the silencing of neurons have been put forward. Ward et al. (2009) attribute electrode failure to the traumatic injury resulting from insertion and a long-term foreign body response to the implant. Some authors proposed that formation of *glial scar results in a physical barrier* to diffusing substances released from the electrode, thus creating a toxic environment for the neurons. Other studies observed that many neurons around the electrodes die shortly after implantation (Edell et al., 1992; Biran et al., 2005). On the other hand, more recent observations link such cell death to the occurrence of hemorrhages during surgery (Biran et al., 2005; Grand et al., 2010). More recently McConnell et al. (2009) have proposed that the observed loss of signal can also result from the *progressive degeneration of nerve fibers and synapses* due to persistent local chronic inflammation.

Recent studies point to the role of the open *blood brain barrier* in the process. Potter et al. (2013) have shown some evidence that short-term attenuation of reactive oxygen species accumulation and stabilization of BBB can result in prolonged improvements in neuronal viability around implanted intracortical microelectrodes, while also identifying potential therapeutic targets to reduce chronic intracortical microelectrode-mediated neurodegeneration. Therefore, it is likely that reduction of the accumulation of reactive oxygen species at the intracortical microelectrode–tissue interface could result in a direct improvement in BBB stability and neuronal health.

Physiologically, BBB refers to the vascular segment of the capillaries that regulate diffusion of solutes, whereas in an inflammatory response, the term refers to the postcapillary venules, that is, the vessels from which leukocytes migrate into the CNS, which are distinct vascular segments (Owens et al., 2008). The process of leukocyte entry into the CNS parenchyma is controlled by different cellular components at the level of postcapillary venules. In order to reach the CNS parenchyma, leukocytes need to perform *two* differently regulated steps: first, to cross the vascular wall, and second, to traverse the *glia limitans* (Owens et al., 2008). Current research indicates that these steps are controlled by different mechanisms. It seems that activated lymphocytes regularly penetrate the endothelial barrier for immuno-surveillance of the CNS, but only upon penetration of the glia limitans and infiltration of the CNS parenchyma do leukocytes come into direct contact with the parenchyma, which leads to clinical symptoms.

While the process of glial scar formation has a tremendous complexity (review in Prodanov and Delbeke, 2016) some of its aspects can nevertheless be understood conceptually by derivation from first principles. In this paper we study accumulation of a diffusing species in steady-state conditions, produced as a reaction to the presence of another object, i.e. an implanted electrode. We hypothesize that such a simple conceptual model can describe diffusion phenomena occurring in the extracellular matrix following implantation of flat electrodes, for example Michigan type of silicon probes or cylindrical electrodes, such as microwires. In addition we compare so-derived model with the model of