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A multiscale model to inform the design of nerve repair conduits

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Peripheral nerve damage afflicts 1 M people p.a. in Europe and the USA [1]. In the most severe cases, patients experience major loss of function. The gold-standard treatment for patients with severe cases is surgery using a graft based on a healthy section of nerve taken from the patient, however, only 50% of patients experience functional recovery [2].

After a nerve is severed, the distal stump produces chemotactic cues that can stimulate neurite regeneration. At the proximal stump, neurites start growing and their direction is informed by these cues. If the gap is short enough, the neurites are able to respond to their environmental cues and grow across the injury site to enter the distal stump. However, if the gap is larger than 5 mm, the regenerative process is unable to establish a supportive environment for neurite growth.

The limitations of the current gold-standard therapy to establish functional recovery have motivated the development of engineered replacement tissues and repair conduits to promote regeneration. Several designs have been proposed that vary not only in terms of material and therapeutic cell composition but also in their spatial distribution. Despite promising results in animal models, these conduits have not yet progressed to clinical use, in part because of the expanse of different variables that need to be tested using experimental models [3].

Here a multiscale mathematical model is proposed to streamline the design of these conduits. The model comprises of two components. The first is a continuous 3D model of the chemotactic field within the conduit. The release of chemotactic factors from the distal stump is captured using a flux boundary condition, as well as the permeability of the conduit wrap.

Within this geometry, at the proximal stump, a random walk model for individual neurites is initiated. Neurite growth is simulated as a random variable that is biased towards the direction of increasing cue; this cue could either be chemotactic (as described using the continuum model above), or durotactic (due to the underlying material distribution). Neurite branching is incorporated into the model, as this is a fundamental feature during regeneration, which determines how neurites sense the underlying gradient fields. Morphological features of branching are accounted for by implementing the model by Van Pelt *et al.*, whilst branches can also recede if they encounter a sub-optimal environment, modelled using a Markov chain process [4,5].

The discrete-continuum framework is parameterised against *in vitro* and *in vivo* data on neurite progression through engineered conduits, including neurite counts at the proximal and distal end as well as measurements of neurite lengths. The parameterised framework can be used to explore the optimal arrangement of materials and cells to promote efficient neuronal regeneration following injury.

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