Project: **Role of diffusion of local anaesthetics through tissue barriers in the mode of action of interfascial plane blocks and non-invasive transmucosal blocks**
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Local anaesthetics (LA) are widely used in medical practice for pain control during surgical procedures. They can be used for infiltration anaesthesia, where they are injected directly into the tissue of the operation site, or for regional anaesthesia, where they are administered near a specific nerve or bundle of nerves. The current advances in regional anaesthesia techniques are especially important given the increasing recognition of the need to re-evaluate opioid use as a mainstay of anaesthesia and acute pain management.

There has been a progressive expansion in the clinical techniques and applications of regional anaesthesia. Of particular note is the rise in popularity of techniques that involve an injection of LA into the fascial planes rather than around the nerves and the transmucosal application of LA. Although current evidence indicates that fascial plane blocks are primarily analgesic in nature, their efficacy is generally unpredictable, limiting their reliability for surgical anaesthesia. Currently, the spread of local anaesthetics within tissues is studied by using different water-soluble dyes and contrast agents that cannot easily cross the biological membranes. In contrast, LAs are highly lipid-soluble and can rapidly diffuse through membranes and tissue barriers, which could account for significant discrepancies between the extent of the clinically observed sensory blockade and the spread of injectate. Furthermore, there is no standard cadaveric model to study injectate spread, and fresh, fresh frozen, and formaldehyde fixed cadavers have been used interchangeably.

Although LAs are chemically similar compounds, their pharmacokinetic properties, like onset and duration of action, vary widely. Depending on the site of injection and method of measurement, the effect of local anaesthetics may last from 50 minutes for short- to 14 hours for long-acting LAs. Mechanistic explanations suggest that the more lipophilic LAs can more readily cross the hydrophobic membrane. As a result, they accumulate in the membrane and are, therefore, more slowly removed by diffusion; however, this has not been proven by experimental studies. Comparative data on mechanistic studies of the onset of action of different LAs remain even scarcer. Nevertheless, the consensus in the literature is that a shorter onset of action is related to lower pK_a since, at physiological pH, a higher percentage of the LA would be present in the neutral form and, therefore, available to cross the membrane. However, there are numerous inconsistencies between the time of onset and pK_a values. Therefore, a more robust explanation of LA pharmacokinetic properties and mechanisms is imperative to refine and improve the clinical applications of regional anaesthesia, especially in the context of novel block techniques.

The proposed project accordingly aims to accomplish five broad objectives by combining experimental and computational methods: 1) Use molecular dynamics simulations and mathematical modelling to study the thermodynamics and kinetics of local anaesthetics crossing biological membranes. 2) Build a computational model of the peripheral nerve and surrounding tissue to understand how different tissue compartments store and transfer local anaesthetics, supported by experimental pharmacokinetic data. 3) Investigate the suitability of dyes and radiographic contrast agents for studying local anaesthetic spread in human tissue and the effects of cadaver storage conditions on it. 4) Study whether local anaesthetics can diffuse through tissue barriers such as fasciae, skeletal muscles, and mucous membranes. The ultimate goal is to understand the potential role of diffusion of local anaesthetics through tissues in the unpredictable clinical effects of certain interfascial plane and transmucosal blocks, i.e. quadratus lumborum block type 2 and non-invasive transnasal (transmucosal) pterygopalatine ganglion block respectively.