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Finite element analysis of thermal laser skin stimulation for a finer characterization of the nociceptive system

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ABSTRACT

Thermal laser stimulation of the skin is an efficient exploratory tool to characterize the nociceptive system. In the present study, finite element simulations are done to calculate the intra-cutaneous spatio-temporal temperature profiles following the delivery of such laser stimuli. The proposed computer-aided modeling considers a number of important parameters that have been disregarded in previous approaches: (i) variability of water content across the skin in both hairy and glabrous skin, (ii) temperature dependency of optical and thermal skin parameters, (iii) laser wavelength and corresponding absorption coefficient, (iv) beam shape (Gaussian vs. flat top) and (v) power emission (closed vs. open loop). Numerical simulations allow determining at each instant of time the volume and area of skin tissue whose temperature exceeds a given nociceptor activation threshold. This knowledge allows a finer characterization of the subpopulations of primary afferents that encode and convey nociceptive signals to the central nervous system. As an example, the approach is used to obtain an estimate of intraepidermal nerve fiber density in both physiological and pathological conditions. Moreover, a better knowledge of the heat distribution also reduces the risk of injury to the skin. Finally, in order to make the finite element simulations accessible to investigators with no prior background in numerical analysis, a specific open-source user-interface has been developed with the ONELAB software.

1. Introduction

Primary somatosensory neurons terminating in the epidermal layers of the skin encode one or several stimulus modalities (mechanical, thermal and chemical) into an afferent signal for the central nervous system (CNS). When they respond to stimuli that are potentially noxious, they are called primary nociceptors. When these nociceptors cross the dermo-epidermal junction, they become part of a 3D intra-epidermal nerve fiber (IENF) network of "free nerve endings" with frequent branching (on average 2.3 ± 0.5 per fiber, according to Reilly et al., 1997) that may extend over tens of μm in the thickness of the vital epidermal layers but remain below the stratum corneum. Besides encoding noxious stimuli, they also maintain complex relationships with the surrounding tissue for their mutual functional and structural advantage. During the last decades, heat has been the most widely used stimulus to study nociception. Radiant heat is preferred over conducted heat, as the latter produces the confounding factor of skin contact. However, most conventional methods (e.g. light bulbs) lack the power to produce stepped heat stimuli for the recording of time-locked responses to the stimulus, such as reaction times or event-related brain potentials (ERPs). This was resolved in the mid seventies with the introduction of the CO_2 laser as a nociceptor stimulator by Carmon et al. (1976) and Meyer et al. (1976). The CO_2 laser offers the advantage of producing a collimated beam of monochromatic electromagnetic waves resulting in a high power density several orders of magnitude higher than any conventional light source. Furthermore, at the wavelength of the CO_2 laser (10.6 μm), the radiated energy is completely absorbed within a small volume of skin (for a review see Plaghki and Mouraux, 2003). Brief (ms) laser stimuli can thus be used to elicit time-locked responses related to the selective activation of phasic heat-sensitive IENFs. In normal non-sensitized states, these can be either rapidly adapting Type 2 Aδ-fiber mechano-sensitive and heat-sensitive nociceptors, referred to as Type 2-AMH nociceptors by Treede et al. (1995) or rapidly adapting C-fiber afferents (C-warm receptors and/or quickly-adapting Q-C nociceptors). Indeed, studies with single-fiber micro-stimulation techniques have shown that short bursts of electrical pulses delivered to a single rapidly adapting Aδ- or C-fiber unit innervating the glabrous skin of the hand usually reach consciousness, whereas activity in slowly adapting units practically never does (Torebjörk and Ochoa, 1980). It is generally agreed that the capsaicin receptor TRPV-1, a non-selective ligand-gated channel that responds to heat, constitutes the main mechanism for

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the neural transduction of thermal stimuli in these free epidermal nerve endings.

To better characterize the subpopulations of primary afferents that encode and convey nociceptive signals to the CNS, it is important to define as accurately as possible the spatio-temporal parameters of the stimulus. For instance, the number of nociceptors contributing to the CNS response is determined by the distribution density of nociceptors as well as by the duration and the volumetric or areal extent of the supra-threshold thermal stimulus in the skin. Inversely, accurate knowledge of the stimulus may allow inferring from the CNS response an estimate of nociceptor density (Mouraux et al., 2012). However accurate estimation of the duration and the volumetric or areal extent of the stimulus is difficult to achieve, even with advanced tools. Indeed, direct measurement of the temperature in epidermal layers with ultra thin thermocouples, although feasible in principle, inevitably distorts the thermal field and damages the skin (Bromm and Treede, 1983). Currently, infrared (IR) cameras can measure fast temperature transients at the skin surface but they give no direct access to the temperature at the depth of nociceptors. Consequently, we must rely on modeling and simulation to estimate intracutaneous temperatures of skin exposed to laser stimuli. Several useful approaches have been reported (Bromm and Treede, 1983; Haimi-Cohen et al., 1983; Frahm et al., 2010; Tillman et al., 1995), but all lack one or more important features. First, these approaches model the epidermis and dermis as a homogenous structure, neglecting the fact that the water content varies from about 20% below the stratum corneum to 70% at the dermo-epidermal junction, and the fact that this distribution differs greatly between hairy and glabrous skin (Caspers et al., 2003; Warner et al., 1988). This is not trivial as it is the water present in the skin that absorbs most of the IR radiation. Second, the temperature dependency of optical and thermal parameters of the skin is usually considered as constant. Third, these approaches always assume laser stimulators with a Gaussian beam, although flat-top beams are now available that are potentially more efficient as they allow a more straightforward estimation of the duration and the volumetric or areal extent of the stimulus. Finally, these approaches only consider laser sources with a constant power emission, although temperature controlled closed loop laser stimulators are now commercially available (Geuzaine and Henrotte, 2011; Geuzaine and Remacle, 1996; CSC-IT Center for Science, 1995).

In the present study, the intra-cutaneous temperature transients in response to various types of laser stimulation are calculated by means of finite element (FE) simulations, taking all above listed aspects into account. This allows determining with unprecedented accuracy the volume and duration of skin tissue exceeding a given nociceptor activation threshold. Simulation results can then be correlated with reaction times measured experimentally in order to establish quantitative estimates of the subpopulations of primary afferents.

It should be noted that the presented finite element model is not restricted to laser stimulators but could also be used for other types of controlled temperature devices (e.g. Peltier devices).

2. Materials and methods

2.1. CO_2 laser stimulation

Two different CO_2 laser stimulators have been considered in this study.

The first stimulator is a constant power CO_2 laser (maximum power output: 25 W) built in the Department of Physics (Université catholique de Louvain), operating in TEM_{00} (Transverse Electromagnetic Mode) mode and delivering an infrared Gaussian beam of wavelength 10.6 μm. Stimulus duration can be adjusted from 1 ms to continuous and beam diameter from less than 1 mm to 20 mm.

The second stimulator is power regulated with a temperature feedback control based on the measurement of the temperature of the skin at the site of stimulation (Laser Stimulation Device, SIFEC, Belgium) (Churyukanov et al., 2012). The conception of this laser was inspired by a similar feedback-controlled device developed by Meyer et al. (1976). The closed-loop control of laser power is performed by an online monitoring of skin temperature using a radiometer collinear with the laser beam, enabling to produce temperature steps with rise rates greater than 350 °C/s and pulse durations from 10 ms to 50 s. To be blind for the radiation of the CO_2 laser emitting at 10.6 μm, the radiometer of the stimulator is equipped with a bandpass filter ranging from 5 to 9.6 μm. This has also as consequence that the deeper skin layers have a very limited effect on the temperature measurement. In practice, the radiometer measures the temperature of the most superficial layer of the skin, i.e. that part of skin concerned by the laser pulse. The heat source is a 25 W radio frequency excited CO_2 laser (Synrad 48-2, Synrad, USA). Power control is achieved by pulse-width modulation at 5 kHz clock frequency. The stimuli are delivered through a 10 m long optical fiber. By vibrating this fiber at some distance from the source, a quasi-uniform spatial distribution of radiative power within the stimulated area is obtained (flat-top beam profile). At the end of the fiber, optics collimate the beam. The optics used in the present study provided a beams of 3 or 6 mm radius.

The protocol of the physiological studies was as follows. Heat stimuli were delivered to the dorsum of the hand. The volunteers were instructed to press a button held in the contralateral hand as soon as any sensation was felt, in order to give an indication of the latency of the percept elicited by the laser stimulus. Reaction times (RTs) were measured relative to the onset of the thermal stimulus. The average thermal activation threshold of C-fiber nociceptors ($\hat{T}_C$) is slightly lower than that of the quickly adapting $A\delta$ nociceptors ($\hat{T}_{A\delta}$). In a previous study, we showed that RTs compatible with the slow conduction velocity of C-fibers (RT > 650 ms) are obtained for surface stimulation temperatures $T_i > 41$ °C, whereas RTs compatible with the higher conduction velocity of Ad-fibers (RT ≤ 650 ms) are obtained for surface stimulation temperatures $T_i > 46$ °C. Therefore, a cut-off of 650 ms was used to discriminate between responses triggered by Aδ- and C-fiber input.

2.2. Infrared recording of skin surface temperature

A high-speed infrared camera (SC7000, FLIR, USA) was used to acquire surface skin temperature measurements at a 1000 Hz sampling rate with a spatial resolution of 7–10 pixels per centimeter.

2.3. Finite element modeling of the intra-cutaneaous temperature distribution

The domain of analysis is a cylinder centered on the laser beam axis, consisting of a thin epidermal layer on top of a 1.5 mm thick dermis layer, Fig. 1. The system is axi-symmetrical and the spatio-temporal temperature distribution obeys Fourier's partial differential heat equation, which writes in cylindrical coordinates:

$$\rho c_p \frac{\partial T}{\partial t} = \frac{1}{r}\frac{\partial}{\partial r}\left(k\frac{\partial T}{\partial r}\right) + \frac{\partial}{\partial z}\left(k\frac{\partial T}{\partial z}\right) + Q_v, \quad (1)$$

with $T(r, z, t)$ the temperature field, ρ [kg/m^3] the mass density, c_p [J/(kg K)] the specific heat, k [W/(m K)] the thermal conductivity and $Q_v(r, z, t)$ [W/m^3] the source term describing the power delivered by the laser beam. Heat exchange by blood perfusion can be shown