A multi-scale view of skin thermal pain: from nociception to pain sensation

BY Y. J. ZHU1,2 AND T. J. LU2,*

1 Stomatological Hospital, College of Medicine, and 2 Ministry of Education Key Laboratory for Strength and Vibration, Xi’an Jiaotong University, Xi’an 710049, People’s Republic of China

All biological bodies live in a thermal environment, including the human body, where skin is the interface with a protecting function. When the temperature is out of the normal physiological range, skin fails to protect, and the pain sensation is evoked. Furthermore, in medicine, with advances in laser, microwave and similar technologies, various thermal therapeutic methods have been widely used to cure disease/injury involving skin tissue. However, the corresponding problem of pain relief has limited further application and development of these thermal treatments. Skin thermal pain is induced through both direct (i.e. an increase/decrease in temperature) and indirect (e.g. thermomechanical and thermochemical) ways, and is governed by complicated thermomechanical–chemical–neurophysiological responses. However, a complete understanding of the underlying mechanisms is still far from clear. In this article, starting from an engineering perspective, we aim to recast the biological behaviour of skin in engineering system parlance. Then, by coupling the concepts of engineering with established methods in neuroscience, we attempt to establish multi-scale modelling of skin thermal pain through ion channel to pain sensation. The model takes into account skin morphological plausibility, the thermomechanical response of skin tissue and the biophysical and neurological mechanisms of pain sensation.

Keywords: skin tissue; temperature; thermal stress; thermal damage; nociception; thermal pain

1. Introduction

All creatures live in a thermal environment, including the human body. Skin is the largest single organ of the body, serving as an interface between the outside environment and the inside body. It plays a variety of important roles, including sensory, thermoregulation and defence, etc. In extreme environments, an uncomfortable feeling or sensation of pain is evoked due to extreme heat...
or cold. Skin fails to protect the human body when the temperature moves out of the normal physiological range. In medicine, various thermal therapeutic methods (e.g. microwave and laser techniques) have been widely used to help cure disease/injury involving skin tissue. However, the corresponding problem of pain relief has limited further application and development of these thermal treatments.

Why do human beings feel pain in extreme thermal environments? What is happening to the human body in extreme thermal environments? How can the human body be protected in extreme thermal environments? In order to address these issues, a new research area, ‘skin biothermomechanics and thermal pain’, was introduced (Xu et al. 2008\textsuperscript{b},c). This is an interdisciplinary problem, involving subjects of heat transfer, mechanics, biology and neurophysiology. This article presents a state-of-the-art review on research carried out hitherto on skin thermal-pain. There have been several good reviews on skin pain sensation (Caterina & Julius 1999; Millan 1999; Julius & Basbaum 2001; Brooks & Tracey 2005); however, all these start from the physiology background and few are focused on the skin thermal-pain sensation. Instead, in this review, starting from an engineering perspective, we hope to recast the biological behaviour of skin in engineering system parlance. Then, by coupling the concepts of engineering with established methods in neuroscience, we hope to build a multi-scale model for quantifying skin thermal pain, by considering the skin morphological plausibility, the biotermomechanical response of skin tissue and the biophysical and neurological mechanisms of pain sensation.

The review is outlined as follows: the physiology of pain is first introduced, followed by features of thermal-pain sensation. Currently available mathematical pain models are presented, and the development of a multi-scale model is introduced. The major problems, issues and topics for further studies are also outlined.

2. Physiology of pain

As one of the most important sensations, pain has been studied extensively for a long time. The International Association for the Study of Pain (IASP) defines pain as ‘an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage’ (Loeser & Treede 2008). According to aetiology, pain can be classified as: (i) nociceptive pain: activation or sensitization of peripheral nociceptors,\textsuperscript{1} (ii) inflammatory pain: inflammatory and tumour cells release chemical mediators that activate or modify the stimulus response properties of nociceptor afferents, and (iii) neuropathic pain: result of injury or acquired abnormalities of peripheral or central neural structures. In this paper, we mainly focus on nociceptive pain.

Thermal stimulation, as one of the three noxious stimulations (thermal, mechanical and chemical), has been widely used in pain study (Arendt-Nielsen & Chen 2003), such as in examination of tissue injury and sensitization mechanisms and the quantification of therapeutic effects of pharmacological, physical and psychological interventions (Borckardt et al. 2006; Mao-Ying et al. 2006).

\textsuperscript{1}A nociceptor is a receptor preferentially sensitive to a noxious stimulus or to a stimulus that would become noxious if prolonged (Loeser & Treede 2008).
However, the understanding of underlying mechanisms of thermal pain is still far from clear, with the main reason being that pain can be influenced by many factors, including both physiological factors, such as stimulus intensity (LaMotte & Campbell 1978; Torebjörk et al. 1984) and duration (Pertovaara et al. 1996; Nielsen & Arendt-Nielsen 1998a,b; Pertovaara 1999), and psychological factors, such as attention (Miron et al. 1989; Jones & Derbyshire 1997; Brooks et al. 2002) and empathy (Kakigi et al. 2004).

(a) Pain pathways

The neuroanatomical pathway involved in pain is generally considered to be composed of two parts (Cesare & McNaughton 1997; Caterina & Julius 1999; Millan 1999; Julius & Basbaum 2001; Brooks & Tracey 2005): (i) the peripheral nervous system: pain or nociception is initiated when the nociceptors are activated by noxious chemical, mechanical or thermal stimuli, and then transmitted from primary afferent axons (axons from cell bodies in a spinal ganglion) → the spinal cord dorsal horn (marginal nucleus or nucleus proprius) → the thalamus → the cerebral cortex and (ii) the central nervous system: pain sensation elicited by noxious inputs from the peripheral nerve after modulation by facilitatory or inhibitory regions. However, it should be noted here that nociception and pain are two different terms, as nociception is defined as the neurophysiological/neurobiological mechanisms evoked by a nociceptive stimulus, while pain is the perceptual correlate to this nociceptive stimulus.

The physiological pathway of pain is schematically shown in figure 1 and can be simply described as four processes: (i) transduction: when a stimulus is applied to the skin, the nociceptors located there trigger action potentials

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2A nociception is a measurable physiological event of a type usually associated with pain, agony and suffering (Loeser & Treede 2008).
by converting the physical energy from a noxious thermal, mechanical or chemical stimulus into electrochemical energy, (ii) transmission: the signals are subsequently transmitted in the form of action potentials (similar to pulse trains) via nerve fibres from the site of transduction (periphery) to the dorsal root ganglion, which then activates the interneuron, (iii) perception: the appreciation of signals arriving in specified areas in the cerebral cortex as pain, and (iv) modulation: descending inhibitory and facilitory input from the brainstem that influences (modulates) nociceptive transmission from the spinal cord.

(b) Features of nociceptors

Nociceptors, the receptors of pain, are the first unit in the series of neurons related to nociceptive pain (Sherrington 1906). Nociceptors transduce mechanical, chemical and/or thermal energy to ionic current (noxious stimuli into depolarizations that generate action potentials), conduct the action potentials from the peripheral sensory neurons to the central nervous system and convert the action potentials into neurotransmitter release at the presynaptic terminal (McCleskey & Gold 1999).

(i) Classification of nociceptors

Peripheral free nerve endings are nociceptors, where most nociceptors are either myelinated Aδ-fibres or unmyelinated C-fibres. Thermal pain is mediated by both thin myelinated Aδ- and unmyelinated C-fibres (Meyer et al. 1994).

Generally, Aδ-fibres have a medium diameter (2–6 μm) with a conduction velocity (CV) of 12–30 m s\(^{-1}\). In comparison, C-fibres have a small diameter (0.4–1.2 μm), and their CV is in the range 0.5–2 m s\(^{-1}\), while the CV in large-diameter Aβ-fibres is 30–100 m s\(^{-1}\) (Harper & Lawson 1985; Millan 1999). The CV is directly related to fibre diameter (Julius & Basbaum 2001), with the conduction velocities of Aδ- and C-fibres accounting for the first (fast) and second (slow) pain responses, respectively (Julius & Basbaum 2001). There are also so-called ‘silent’ nociceptors that, in general, cannot be activated (Bessou & Perl 1969; Lynn & Carpenter 1982; McMahon & Koltzenburg 1990a, b; Pini et al. 1990; Treede et al. 1992; Schaible & Grubb 1993; Cervero et al. 1994; Koltzenburg & Torebjörk 1995; Schmidt et al. 1995, 2000; Gee et al. 1996; Kress et al. 1996; Messlinger 1997; Siddall & Cousins 1997; Treede et al. 1998; Torebjörk 2000; Watanabe et al. 2002). For example, in the survey of cutaneous C-fibres, Bessou & Perl (1969) found that only 10 per cent of the skin sample was inexcitable, while Lynn & Carpenter (1982) and Pini et al. (1990) found that up to 28 per cent of the nerve units in rat skin were inexcitable. Under conditions of inflammation or tissue injury, however, these silent nociceptors are sensitized and activated by a variety of chemical mediators (Reeh et al. 1987; Sengupta & Gebhart 1994a, b; Koltzenburg & Torebjörk 1995; Schmidt et al. 1995; Dmitrieva & McMahon 1996; Siddall & Cousins 1997). This recruitment of previously silent nociceptors under pathological states may contribute to temporal and spatial summation and considerably enhances the C-fibre afferent discharges to the dorsal horn. It may also
contribute both to primary hyperalgesia,\(^3\) due to heat and pressure after chemical irritation, and secondary hyperalgesia,\(^4\) as a consequence of central sensitization (Schmidt et al. 1995, 2000; Kress et al. 1996; Millan 1999).

(ii) Polymodality of nociceptors

According to the response to different stimulations, nociceptors can be further classified as high-threshold mechanoreceptors, chemoreceptors, temperature-sensitive receptors (heat/cold nociceptors), polymodal nociceptors and mechanoinensitive (silent) nociceptors. In an animal study, Leem et al. (1993) found approximately 70 per cent of A\(\delta\)-nociceptors as mechanical nociceptors, 20 per cent as mechano-heat nociceptors and 10 per cent as mechano-cold nociceptors. The cutaneous nociceptors responding to thermal stimulations are largely polymodal, as they can be activated by thermal, mechanical and/or chemical stimuli, and can be grouped into six classes of distinctive afferents (Simone & Kajander 1997; Arendt-Nielsen & Chen 2003): (i) C-cold nociceptors (approx. \(<10^\circ\)C), (ii) A-cold and possible C-cold afferents (approx. \(>20^\circ\)C), (iii) type I AMH (A-fibre mechano-heat nociceptors; \(>53^\circ\)C), (iv) type II AMH (\(>46^\circ\)C, mediator of first pain), (v) C-warm afferent (\(>40^\circ\)C), and (vi) C-fibre mechano-heat nociceptors (CMHs; \(>45^\circ\)C, mediator of second pain).

(iii) Distribution of nociceptors in skin tissue

As for nociceptors in skin, C-, A\(\delta\)- and A\(\beta\)-fibres are typically present in proportions of about 70, 10 and 20 per cent, respectively, although these ratios may vary (Millan 1999). Many C-fibres can be traced far into the epidermal layer. Vertical sections reveal that free nerve endings emerge from superficial dermal nerve plexuses to epidermis (Patapoutian et al. 2003), as shown by the black points in figure 2. The study of myelinated mechanical nociceptor endings in cat

\(^3\)Hyperalgesia refers to an increased response to a stimulus that is normally painful, where primary hyperalgesia refers to the hyperalgesia within an injury, which is characterized by spontaneous pain and an increased sensitivity to stimuli (Loeser & Treede 2008).

\(^4\)Secondary hyperalgesia refers to the hyperalgesia in the undamaged tissue surrounding the injury.
hairy skin showed that the free nerve endings exist at around a depth of 50 μm (Kruger et al. 1981), while the receptors effective in mediating the pain sensation are calculated to be at a depth of approximately 200 μm (Stoll & Greene 1959). In comparison, the receptor depth in the hairy skin of monkey, estimated from responses to ramped stimuli, was approximately 200 μm (Tillman et al. 1995a,b). C-fibres have a higher density of distribution than Aδ-fibres (Ochoa & Mair 1969; Tran et al. 2002). Depending on the species and the methods for quantification, the density distribution of C-terminals is approximately 2–8 fibres mm⁻², while that of Aδ-fibres is less than 1 fibre mm⁻² (Lynn & Baranowski 1987).

(iv) Ion channels of nociceptors

All the essential functions of nociceptors depend on ion channels (Caterina & Julius 1999; McCleskey & Gold 1999), which are proteins located in cell membrane that selectively mediate the transmembrane transportation of specific ions or molecules (Alberts et al. 1994). The ion channels include: heat-activated channels (Cesare & McNaughton 1996; Kirschstein et al. 1997; Dittert et al. 1998; Nagy & Rang 1999a,b); capsaicin receptor-dependent channels (Caterina et al. 1999; Nagy & Rang 1999a,b); adenosine triphosphate (ATP)-gated channels (Burnstock 1996; Burnstock & Wood 1996; Hamilton 2002; Hilliges et al. 2002); proton-gated channels (Krishtal & Pidoplichko 1980, 1981; Waldmann 2001); nociceptor-specific voltage-gated Na⁺ channels (Waxman et al. 1999); and mechano-sensitive channels, among others. In spite of these different channels, they are generally converted from closed to open states by mainly three types of stimulus, namely, thermal (hot or cold), mechanical and chemical stimuli, with thresholds of 43°C and approximately 0.2 MPa for the first two. Although not directly activated by stimuli, voltage-gated channels form a very important class of channels. These voltage-gated channels that respond to membrane depolarization or hyperpolarization are substantial to the generation and transmission of electrical signals along axons (Elmore 2004).

When a noxious stimulus is applied to a nociceptor, the corresponding ion channels will be opened, which will induce a transmembrane current and increase the membrane voltage. When the membrane voltage increases to the threshold, specified sodium channels will be open in a positive feedback mode that results in the depolarization of the membrane, eventually generating an action potential. For example, when a thermal loading is applied to a nociceptor, the heat-activated channels will be opened.

(c) Gate control theory of pain

The gate control theory (GCT), proposed by Melzack & Wall (1965), was more successful than many others in explaining the important features of pain process. Figure 3 shows a schematic of the original version of the theory. In general, it is the small (C, Aδ) fibres (S) that carry information about noxious stimuli, while the large (Aβ) fibres (L) carry information about less-intense mechanical stimuli. As the signal from the (C, Aδ) fibres is routed through substantia gelatinosa (SG) to central transmission (T) cells and onwards, the double-inhibition (indicated by the minus signs) strengthens the signal, and the sensation of pain is more easily evoked. However, the signal from Aβ-fibres activates the inhibitory function...
of SG, which will reduce the firing to transmission (T) cells and suppress the pain finally. The theory was later modified by Melzack & Wall (1983). The new model included excitatory and inhibitory links from SG to T-cells, as well as descending inhibitory control from some structures in brainstem. The round knob at the end of the inhibitory link implies that its actions may be presynaptic, postsynaptic or both. All connections are excitatory, except the inhibitory link from SG to T-cells.

The neuromatrix theory, proposed by Melzack (1999), integrates multiple inputs to produce the output pattern that evokes pain. The body-self neuromatrix comprises a widely distributed neural network that includes somatosensory, limbic and thalamocortical components.

3. Features of thermal-pain sensation

Skin thermal-pain sensation exhibits physiological and psychological features and is influenced by different factors. As engineers, we want to know the different features of skin thermal pain and how they are evoked. This will be helpful in applying engineering methods to solve biological and neural problems. In this section, we mainly discuss definitive factors involved in pain or physiological features of pain. Psychological features are not included in this review.

(a) Differences between C- and Aδ-nociceptors

Differences in the histological structure of myelinated and unmyelinated nociceptors (Raja et al. 1999; Lawson 2002) suggest that they play different physiological roles in pain perception. For example, there appears to be a clear
difference in the response thresholds between Aδ- and C-nociceptors in monkeys to cold stimuli (Simone & Kajander 1997): the response thresholds for most Aδ-nociceptors were <0°C, whereas those of most C-nociceptors were >0°C (Simone et al. 1994). This supports the notion that C-nociceptors contribute to the sensation of dull pain produced by cold stimuli ≥0°C and that Aδ-nociceptors contribute to pricking pain evoked by cold stimuli <0°C and by skin freezing.

The threshold, magnitude and reaction time of heat-induced pain best correlate with the activity of C-nociceptors recorded in monkeys and in humans (LaMotte & Campbell 1978; Meyer & Campbell 1981; Campbell & Meyer 1983; LaMotte et al. 1983; Torebjörk et al. 1984), and are not altered significantly by the conduction block of Aδ-fibres (Torebjörk et al. 1984; Jorum et al. 1989; Yarnitsky & Ochoa 1991). It has also been found that C-fibres responsive to intense cold stimuli are located along vein walls, whereas the thermosensory Aδ-fibres responsive to cooling are localized cutaneously (LaMotte & Thalhammer 1982; Klement & Arndt 1992; Chen et al. 1996; Craig et al. 1996). Generally speaking, upon exposure of the skin to a noxious stimulus, myelinated Aδ-fibres elicit a rapid, first phase of pain, which is ‘sharp’ in nature, whereas unmyelinated C-fibres evoke a second wave of ‘dull’ pain (Torebjörk & Hallin 1973; Mackenzie et al. 1975; Ochoa & Torebjörk 1981, 1983, 1989; Schady et al. 1983; Torebjörk & Ochoa 1990; Treede 1992; Handwerker & Kobal 1993; Meyer et al. 1994; Belemonte & Cervero 1996). However, the microstimulation of C-polymodal fibres also produced dull pain depending on the skin areas they innervate (Ochoa & Torebjörk 1989).

Studies of first and second pain produced by heat have shown that first pain is quickly suppressed with repeated heating (Price & Dubner 1977). The myelinated and unmyelinated nociceptive primary afferents play different roles in the establishment and maintenance of secondary hyperalgesia (Fuchs et al. 2000; Magerl et al. 2001), suggesting that they have different functions in chronic pain states.

However, considerable controversy also exists concerning the true selectivity of this technique (Wall & McMahon 1985). For example, LaMotte & Thalhammer (1982) found no differences in the responses of Aδ- and C-polymodal nociceptors to noxious cold reaching 2°C. Harrison & Davis (1999) found that absolute thresholds at different cooling rates become more similar with the C-fibre estimate than with the Aδ-fibre estimate, but still vary with cooling rate. In normal individuals, a cold stimulus delivered during experimental A-fibre block feels hot and burning, suggesting a complex interaction between A- and C-fibre primary afferents (Mackenzie et al. 1975; Fruhstorfer 1984; Wahren et al. 1989; Yarnitsky & Ochoa 1990a,b; Davis 1998). In studies of a small sample of C- and Aδ-nociceptors in rat, Simone & Kajander (1996) found that the response thresholds for cold stimuli and the responses evoked by suprathreshold stimuli did not differ from each other. As for cold pain, it is likely that pricking pain produced by cold stimuli is mediated, at least in part, by excitation of Aδ-nociceptors. C-fibre nociceptors may also contribute to the sensation of cold pain because a portion of C-nociceptors in animals (Bessou & Perl 1969; Georgopoulos 1976, 1977; Kumazawa & Perl 1977; LaMotte & Thalhammer 1982; LaMotte et al. 1982) and humans (Torebjörk 1974; Torebjörk & Hallin 1974; Campero et al. 1996) was excited by noxious cold.
(b) Influence of stimulus temperature on pain

It is well known that the magnitude of temperature has a great effect on pain. For example, LaMotte & Campbell (1978) found that heat pain increases monotonically with stimulus intensities between 40 and 50°C, while Torebjörk et al. (1984) observed a linear relationship between the mean responses of CMHs recorded in awake humans and median ratings of pain over the temperature range of 39–51°C. It was also shown that the intensity of cold pain is linearly correlated with that of a cold stimulus (Iggo 1959; Georgopoulos 1976, 1977; Chery-Croze 1983a,b). For example, Georgopoulos (1976, 1977) found that the stimulus-response functions were approximately linear, with mean slopes of power functions of 1.15, while Simone & Kajander (1997) obtained a slope of 1.07.

(i) Influence of temperature-change rate on pain

It has been shown that higher firing frequencies are evoked by higher rates of temperature change in warm- and cold-specific afferents (Beitel et al. 1977; Kenshalo & Duclaux 1977; Duclaux & Kenshalo 1980). However, studies on the effect of stimulus ramp rate on suprathreshold pain sensation have given conflicting results.

It has been found that the threshold increases with faster rates of change in skin temperature (Neisser 1959; Bessou & Perl 1969; Croze et al. 1976; Kumazawa & Perl 1977; Croze & Duclaux 1978; Lynn 1979, 1980; LaMotte et al. 1983; Pertovaara & Kojo 1985; Yarnitsky & Ochoa 1990a,b; Tillman et al. 1995a,b; Palmer et al. 2000; Defrin et al. 2006). For example, the surface temperature thresholds were found to be 41.9°C for a stimulus ramp rate of 5.8°C s⁻¹, 40.1°C for a rate of 0.85°C s⁻¹ and 39.6°C for a rate of 0.095°C s⁻¹ (Tillman et al. 1995a,b). Treede et al. (1990, 1995) found that the threshold for detecting an action potential in the C-fibre of the monkey increased with ramp rate in the range of 0.1, 1 and 10°C s⁻¹. Defrin et al. (2006) found that the pain threshold difference was as large as 4°C measured in the range of 0.5–40°C s⁻¹, and a much steeper stimulus-response function for pain sensation was observed for stimuli with a faster rise rate, while the slopes for the slow rate resemble those of the power functions for C-fibre discharge evoked by noxious heat in rats. Bessou & Perl (1969) found higher discharge rates in cat polymodal nociceptors for faster heating rates. In humans, faster heating rates to suprathreshold temperatures evoke higher C-fibre activity and higher peak magnitude estimates of pain (Yarnitsky et al. 1992). Tillman et al. (1995a,b) found that the peak discharge frequency of CMHs during the heat ramp increased with stimulus ramp rate.

However, others found no influence of the temperature-change rate (Hardy et al. 1952; Croze et al. 1976; Pertovaara et al. 1996; Nielsen & Arendt-Nielsen 1998a,b; Pertovaara 1999). For example, Croze et al. (1976) observed no change in nociceptor threshold between rates of 0.2 and 1.5°C s⁻¹ in monkey; Nielsen & Arendt-Nielsen (1998a,b) did not find any change in the human C-nociceptor firing threshold between the three rates of temperature rise used (0.3, 2 and 6°C s⁻¹); and Pertovaara (1999) found that the magnitudes of sensory and spinal neuronal response were independent of the stimulus ramp rate (2.5, 5 and 10°C s⁻¹).
Conflicting results have also been reported. For example, with increasing rate of rising temperature stimuli, Yarnitsky *et al.* (1992) found the magnitude estimates of pain increased, while Nielsen & Arendt-Nielsen (1998a,b) observed a decrease in the magnitude estimate.

(ii) Influence of stimulus duration

With an increase in the duration of the noxious heat stimulus, the heat pain threshold was decreased (Birren *et al.* 1951; Hardy *et al.* 1952; Arendt-Nielsen & Bjerring 1988; Pertovaara *et al.* 1988, 1996; Nielsen & Arendt-Nielsen 1998a,b; Pertovaara 1999), and the sensory magnitude estimate of suprathreshold heat pain and the spinal neural responses were considerably increased (Nielsen & Arendt-Nielsen 1998a,b; Pertovaara 1999; Wu *et al.* 2001). However, in these studies, the stimulus-duration changes always entailed an associated change in the delivered energy (Iannetti *et al.* 2004). By using lasers with the same energy but different duration applied to skin, it was found that shorter stimulus durations yielded steeper slopes in the skin temperature profiles and higher pain ratings (Iannetti *et al.* 2004).

Coghill *et al.* (1993a,b) reported that pain did not decrease substantially during the course of prolonged, repetitive nociceptive stimulation, the responses of nociceptive specific neurons declined significantly. Pertovaara (1999) found that the onset latencies of pain reactions and spinal neuronal responses were independent of the peak stimulus duration, whereas the latency of the maximum discharge in spinal neurons increased with prolongation of the peak stimulus. Moreover, the peak frequency of spinal neuronal response increased significantly with prolongation of the heat stimuli after spinalization, but not in animals with an intact spinal cord. Iannetti *et al.* (2004) found that shorter stimulus durations shortened the latency.

(iii) Influence of baseline temperature

The time required for pain to be detected varies inversely with the base temperature (Birren *et al.* 1951; Hardy *et al.* 1951; Arendt-Nielsen & Bjerring 1988; Pertovaara *et al.* 1988), and a decrease in adapting skin temperature may significantly elongate the minimal latency or energy needed to produce a threshold response, since more heat energy is needed to reach the critical threshold temperature (Duggan *et al.* 1978; Hole & Tjolsen 1993; Luukko *et al.* 1994; Pertovaara *et al.* 1996). Studies have shown that the base skin temperature substantially influences heat pain response when a constant-power stimulator is used, while heat pain sensitivity is independent of baseline skin temperature, as tested with heat pulses delivered via a temperature-controlled contact stimulator (Whyte 1951; Croze *et al.* 1976, 1977; Kojjo & Pertovaara 1986, 1987; Pertovaara *et al.* 1996). For example, Pertovaara *et al.* (1996) indicated that heat pain threshold, unlike the pain magnitude estimate of suprathreshold pain, was not significantly modified by a change in the adapting temperature in the range of 25–35°C. Therefore, the influence of initial skin temperature on the heat pain threshold appears to be dependent on the type of heat stimulus used (Wu *et al.* 2001).

However, it has also been reported that there exists an influence of the baseline temperature on heat pain threshold and heat pain ratings to a constant-temperature heat stimulator (Tillman *et al.* 1995a,b; Dyck *et al.* 1996;
Nielsen & Arendt-Nielsen 1998a,b; Pertovaara 1999; Wu et al. 2001). Tillman et al. (1995a,b) demonstrated that the threshold temperature at the skin surface for initiating action potentials in CMHs in the monkey decreases as the baseline skin temperature is increased. Wu et al. (2001) found that the mean normalized pain ratings for suprathreshold stimuli applied from the higher base temperature were slightly greater than those from the lower base temperature in the range of 34–38°C. Wu et al. (2001) found nonetheless that a 1°C increase in skin stimulus temperature resulted in a significantly greater increase in pain magnitude than a 4°C increase in baseline temperature.

(iv) Influence of nociceptor depth

Haimi-Cohen et al. (1983) found that the temperature threshold of nociceptors was 45°C when the receptor layer was set between the epidermis and the dermis; however, Tillmann et al. (1995a,b) found the value of 40.4°C at a depth of 200 μm for a heat stimulus having the same magnitude. Tillmann et al. (1995a,b) also found that the heat threshold for C-fibre mechano-heat nociceptors was determined by receptor depth.

(c) Temporal summation

The temporal summation (TS) of repetitive noxious stimuli, or wind-up, refers to the enhancement of perceived pain intensity when noxious stimuli are applied repetitively (Mendell 1966; Price et al. 1971, 1977; Price 1972; Vierck et al. 1997; Tommerdahl et al. 1998; Li et al. 1999; Herrero et al. 2000). Not only are the phenomena of wind-up and TS of pain intensity regarded as dependent on activation of C-afferents (Price et al. 1977; Price & McHaffie 1988; Li et al. 1999), but it has also seemed likely that stimulation of nociceptors is required (Vierck et al. 1997).

However, the TS of thermal sensations to very strong levels of pain could be produced by the repetition of a stimulus that produced only sensations of warmth when presented at frequencies of ≤0.14 Hz (Vierck et al. 1997). This finding opens the possibility that the TS to painful levels does not depend on the activation of nociceptors. Alternatively, some nociceptors may be activated by temperatures that elicit only sensations of warmth, or nociceptor activity may be recruited especially by brief contacts of the preheated thermode at frequencies >0.14 Hz. Convincing evidence has been provided by a demonstration that peripheral nociceptor discharge is suppressed progressively by repetitive stimulation that produces wind-up of central cells (Price et al. 1977). Using ramped thermal stimulation (Price et al. 1994) or brief contacts by a preheated thermode (Vierck et al. 1997), an N-methyl-D-aspartate (NMDA) receptor antagonist (Church et al. 1985), clearly attenuated TS.

However, central neurons with receptive fields common to the two sites of alternating stimulation receive input at 0.33 Hz, which does produce summation for stimulation of a single site. The amount of summation from alternation should be less than that obtained from stimulation of a single site at 0.33 Hz, unless the

5Wind-up refers to the prolonged dorsal horn activity after repetitive C-fibre stimulation, also called neuroplasticity or reflex hyperexcitability.

Phil. Trans. R. Soc. A (2010)
Peripheral receptive fields overlap extensively. Also, the central summation could be enhanced by an NMDA-receptor-sensitive expansion of the central receptive fields (Ren 1994).

Peripheral sensitization of each site could be enhanced by mutual influences on the sites from a lateral spread of inflammation (LaMotte et al. 1992), but secondary hyperalgesia adjacent to a cutaneous injury is not revealed by thermal stimulation (Simone et al. 1989). In the experiment of Vierck et al. (1997), evidence in favour of central summation was obtained by the finding that alternating stimulation of adjacent sites on the thenar eminence at 0.33 Hz produced TS that was intermediate in rate, and had an amount between those obtained with stimulation of either site alone at interstimulus intervals of 3 or 6 s. This finding is suggestive of central radiation, but contrasts with another study using alternating ramped stimulation of adjacent sites on hairy skin that produced TS in excess of that observed with stimulation at a single site (Price et al. 1977). Thus, for the paradigm involving extended series of stimuli to one site and then another, repetitive excitation of a subset of the primary somatosensory cortical neurons that are maximally excited at the first site would suppress the activity of neurons with partially overlapping receptive fields that are less effectively excited at the first site than at the second site. In contrast, for alternating stimulation of the same sites, the two subsets of neurons with partially overlapping receptive fields would be activated to some extent at a rate of 0.33 Hz, which could produce some TS.

(d) Spatial summation

Spatial summation (SS) of pain refers to an increase in pain perception when larger areas of stimulation are used (Raja et al. 1999). A positive SS effect of non-painful thermal stimuli has been observed (Hardy & Oppel 1937; Kenshalo et al. 1967; Kandel et al. 2000). For example, it has been found that the spatial characteristics of thermal sensation maintained that warm sensation is subject to considerable SS (Stevens & Marks 1971; Marks & Stevens 1973; Marks 1974; Stevens et al. 1974; Dyck et al. 1993).

However, existing results regarding the existence of SS for pain perception are contradictory. Early studies reported little or no SS for painful cold and heat stimuli (Wolf & Hardy 1941; Hardy et al. 1952; Green & Hardy 1958; Hardy et al. 1959; Murgatroyd 1964; Kenshalo et al. 1967; Stevens & Marks 1971; Stevens et al. 1974), while the important role of SS for pain coding has been demonstrated in both psychophysical (Hardy et al. 1940; Skouby 1951; Green & Hardy 1958; Chery-Croze & Duclaux 1980; Kojo & Pertovaara 1987; Price et al. 1989; Douglass et al. 1992; Coghil et al. 1993a,b; Lautenbacher et al. 1995; Defrin & Urca 1996; Nielsen & Arendt-Nielsen 1997; Defrin et al. 2002; Marchand & Arsenault 2002) and clinical studies (Atchison et al. 1991; Stohler & Kowalski 1999).

Studies show that increasing the area of noxious stimulation results in a decrease in pain threshold (Skouby 1951; Machet-Pietropaoli & Chery-Croze 1979; Kojo & Pertovaara 1987; Defrin & Urca 1996; Greenspan et al. 1997; Nielsen & Arendt-Nielsen 1997; Lautenbacher et al. 2001; Defrin et al. 2003) or an increase in perceived pain intensity (Price et al. 1989; Douglass et al. 1992; Defrin & Urca 1996; Marchand & Arsenault 2002). In these studies, SS was examined by applying either a single stimulus with an increasing area

Phil. Trans. R. Soc. A (2010)
Review. Skin thermal-pain modelling

533

(Machet-Pietropaoli & Chery-Croze 1979; Kojo & Pertovaara 1987; Defrin & Urca 1996; Defrin et al. 2003), or an increasing number of stimuli (one to three) of a fixed size (Price et al. 1989; Douglass et al. 1992; Nielsen & Arendt-Nielsen 1997).

The discharge from a single unit is not perceived as noxious, and many units need to be recruited over a period of time for ‘pain’ to be experienced, and actual pain thresholds are higher in man than the thresholds for activation of individual nociceptors (Millan 1999).

Dipping the entire hand in 18°C water for 1 min induced a transient faint pain, while decreasing cutaneous temperature at the rate of 1.3°C s⁻¹ with a 6.5 cm² area provokes a pricking pain only at about 10°C (Croze & Duclaux 1978). Gronroos et al. (1996) found that the minimal energy per surface area needed to produce a pain sensation was lower with a larger stimulus surface. Nielsen & Arendt-Nielsen (1997) found that the mean heat pain threshold decreased significantly from 45.6 to 43.5°C, as the stimulus dermatome area was increased from minimum (3.14 cm²) to maximum (15.70 cm²). Staud (2004) examined the characteristics of SS by progressive immersion of the fingers, hand and forearm in a heated waterbath, similar to previous spatial summation of pain studies (Coghill et al. 1993a, b; Marchand & Arsenault 2002), taking into account the contribution of pain-inhibitory mechanisms such as diffusion noxious inhibitory controls (Price 1972). There is a significant increase in pain ratings when the stimulus areas are increased from 0.21 to 2.10 cm² or from 1 to 3 cm² (Price et al. 1989; Douglass et al. 1992).

Experiments using multiple stimuli report that SS exists both within and between dermatomes, although the largest separation distance between stimuli tested was 10 cm (Price et al. 1989). Defrin et al. (2006) demonstrated that when stimulus separation exceeds a given distance (10 cm), SS is no longer evident, even if the stimuli are applied within the same dermatome. To complicate the matter further, Lautenbacher et al. (2001) found no significant effect of area for ratings of the suprathreshold stimuli.

c) Hyperalgesia and tissue damage

Thermal injury influenced the heat pain sensation (Stoll & Greene 1959; Meyer & Campbell 1981; LaMotte et al. 1982, 1992; Robinson et al. 1983; Torebjörk et al. 1984). Heat injury produced an immediate fall in heat pain threshold (Lewis & Hess 1933; Lynn 1980; Pedersen & Kehlet 1998) and increase in pain sensitivity (Pedersen & Kehlet 1998; Andrew & Greenspan 1999). Damage to tissue causes cell necrosis and releases a number of byproducts and mediators. Some of these substances activate nociceptors, but most of them sensitize nociceptors (hyperalgesia). Bleehen & Keele (1977) proposed that ATP released from damaged cells contributes to pain caused by tissue damage. It has been found that ATP applied to blisters causes pain (Bleehen & Keele 1977), and fractions of cytosol causing pain when applied to blisters are mostly composed of ATP (Bleehen et al. 1976). There have also been reports demonstrating ATP-evoked pain in whole animals (Bland-Ward & Humphrey 1997; Sawynok & Reid 1997).

Peripheral sensitization amplifies signal transmission, which contributes to central sensitization and clinical pain states. Hyperalgesia to cold as well as to heat and mechanical stimuli occurs following a mild freeze injury to the skin (Lewis & Love 1926; Kilo et al. 1994; Beise et al. 1998). Generally, it is believed

Phil. Trans. R. Soc. A (2010)
that secondary hyperalgesia in man is restricted to mechanical stimuli (Raja et al. 1984; Ali et al. 1996). However, some studies found no change in heat pain threshold in the zone of secondary hyperalgesia (Hardy et al. 1950; Dahl et al. 1993; Warncke et al. 1997), while other studies demonstrated lowered heat pain thresholds in the normal skin adjacent to burn and freeze injuries (Thalhammer & LaMotte 1982; Kilo et al. 1994), and in skin adjacent to capsaicin injections (Wallace et al. 1997).

However, unchanged pain thresholds do not imply unchanged suprathreshold pain responses (Hardy et al. 1950; Arendt-Nielsen et al. 1996). Hardy et al. (1950) demonstrated that heat pain was more than doubled in the zone with secondary hyperalgesia compared with normal skin on the control arm. Increased pain ratings to contact heat stimuli were reported by Thalhammer & LaMotte (1982) in skin adjacent to burn injuries (56°C, 7 s) delivered to the volar forearm.

Secondary hyperalgesia to heat has been demonstrated in animal studies (Lawand et al. 1997). Pedersen & Kehlet (1998) found significant hyperalgesia to heat within the zone of secondary hyperalgesia to punctate mechanical stimuli after a burn injury in hairy skin.

(f) Adaptation

Although much attention has been directed at nociceptor sensitization, relatively little attention has been devoted to the reciprocal property, i.e. adaptation. Nociceptive primary afferents act as proportional and differential sensors, exhibiting pronounced slow adaptation ($\tau \approx 2.5$ s) when stimulated with mechanical or heat stimuli (Meyer & Campbell 1981; Handwerker et al. 1987; Schneider et al. 1995; Treede et al. 1995).

The mean response of C-fibre nociceptors to 3s heat stimuli applied to the hand with an interstimulus interval of 25 s declines by 60 per cent from the first to the second stimulus (LaMotte & Campbell 1978). When a similar stimulus paradigm was applied to human subjects, a similar decline in the magnitude of pain (LaMotte & Campbell 1978) and nociceptor response (Torebjoyrk et al. 1984) was observed. Recovery from this adapted state took 10 min or longer (LaMotte & Campbell 1978; Treede et al. 1998) and affected the dynamic response more than the static response (Treede et al. 1995). This long-lasting reduction of nociceptor discharge is also called ‘suppression’.

The adaptation or suppression of nociceptive afferent action potential discharges may occur at two stages of the neural-encoding process: (i) transduction of physical stimuli into generator potentials and (ii) transformation of generator potentials into trains of action potentials. Although adaptation in the transformation process is supported by decreased CV (Thalhammer et al. 1994; Schmelz et al. 1995; Serra et al. 1999) and reduced kinetics of sensory neuron-specific sodium channels (Waxman et al. 1999), there is no evidence for adaptation in the transduction process so far.

The transduction process for noxious heat stimuli has been studied using dissociated neurons from dorsal root ganglia (DRG) as models of their own terminals (Cesare & McNaughton 1996; Kirschstein et al. 1997, 1999; Nagy & Rang 1999a, b; Vyklicky et al. 1999). Brief heat stimuli (<1 s) were found to

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6 Adaptation refers to a decrement in response to stimuli applied to the receptive field of sensory cells.
elicit inward currents ($I_{\text{heat}}$) in DRG neurons that did not adapt (Cesare & McNaughton 1996), and were reproducible with stimulus repetition at short intervals (Kirschstein et al. 1997, 1999; Guenther et al. 1999). Heat stimuli with slowly increasing temperatures revealed a threshold temperature of about 43°C to evoke $I_{\text{heat}}$ in DRG neurons (Vyklicky et al. 1999). The correlate of adaptation in the transduction process would be the inactivation of $I_{\text{heat}}$ upon constant stimulation; suppression would be visible as tachyphylaxis upon repeated stimulation.

Slugg et al. (2000) found that the C-fibres demonstrated a significant adaptation in response to mechanical stimuli when the interstimulus interval between the paired stimuli was $\leq 150\text{s}$, whereas the A-fibres did not demonstrate a significant adaptation until the interstimulus interval was $\leq 30\text{s}$. This phenomenon could result from changes in stimulus transmission, stimulus transduction, spike initiation and spike propagation (Slugg et al. 2000). It should be noted that, however, Garell et al. (1996), in their study of feline nociceptors, did not observe a similar adapting response.

4. Skin thermal-pain modelling

(a) Introduction

Mathematical modelling of skin thermal pain offers several benefits (Britton & Skevington 1996; Picton et al. 2001), including capability of handling extremely complex theories and predicting behaviours invasively that had perhaps previously gone unnoticed. However, there are limited studies on the utilization of computational models in the field of pain. The currently available models cover only the molecular/cellular level (Fors et al. 1984, 1986, 1988, 1989; Britton & Skevington 1989; Britton et al. 1995, 1996; Britton & Skevington 1996) or the level of the network of neurons (Minamitani & Hagita 1981; Haeri et al. 2003), without treating skin thermal-pain sensation from a multi-scale view, e.g. considering morphological plausibility, the thermomechanical response of skin tissue and transmission process, or correlating the external stimulus parameters directly with the pain sensation level. To address all these issues, we summarize below a multi-scale model of skin thermal pain that we have developed (Xu et al. 2008a,b,c).

(b) A multi-scale skin thermal-pain model

The developed multi-scale model has only attempted to model superficial nociceptive acute pain. Built upon the modelling of nociceptor transduction in skin thermal-pain sensation (Xu et al. 2008a,b,c), the holistic model of skin thermal pain combines the biothermomechanical response of skin (Xu et al. 2008a,b,c) with the biophysical and neurological mechanisms of pain sensation. In view of the pain pathway illustrated in figure 1, the holistic model is composed of three sub-models: transduction, transmission and perception and modulation.

7Tachyphylaxis refers to the decrement in response to repeated chemical stimuli.

Phil. Trans. R. Soc. A (2010)
Figure 4. Idealized skin model. \( H \) is the distance from the skin surface to the nociceptor located in the subcutaneous tissue and \( \sigma \) is the thermal stress in the skin, which is perpendicular to the skin surface.

(i) Model of transduction

According to the mechanism of nociceptor transduction, the proposed model of transduction is further divided into three sub-models: a biothermomechanical model of skin tissue, a model of current generation and a model of frequency modulation. Each of these models is presented in detail below.

(1) Biothermomechanical model of skin tissue. Thermal pain is governed by temperature at the location of the nociceptor, not at the skin surface (Tillman et al. 1995a,b), and thermal damage may cause the cells to break down and to release a number of tissue byproducts and mediators, which will activate and sensitize nociceptors (Junger et al. 2002). Furthermore, thermally induced stresses owing to non-uniform (both spatial and temporal) temperature distributions may also lead to the sensation of thermal pain (Xu et al. 2008a,b,c).

In the thermomechanical model of skin tissue, the skin is treated as a layered—laminated—material according to its histological structure, and its overall properties are assembled in a composite manner, as shown in figure 4. The skin is assumed to behave as a thermo-elastic material. Upon being subjected to thermal stimulations, the temperature of skin can be obtained by solving the bioheat transfer model of skin tissue (Pennes 1948), given as

\[
\rho c \frac{\partial T}{\partial t} = k \frac{\partial^2 T}{\partial z^2} + \omega_b \rho_b c_b (T_a - T) + q_{\text{met}} + q_{\text{ext}}, \quad (4.1)
\]

where \( \rho, c \) and \( k \) are the density, specific heat and thermal conductivity of skin tissue, respectively; \( \rho_b \) and \( c_b \) are the density and specific heat of blood, \( \omega_b \) is the blood perfusion rate; \( T_a \) and \( T \) are the temperatures of the blood and skin tissue, respectively; \( q_{\text{met}} \) is the metabolic heat generation in skin tissue; and \( q_{\text{ext}} \) is the heat source owing to other heating.
When the skin temperature rises above a critical value (approx. 43°C), thermal damage will be induced. The Arrhenius integration proposed by Henriques & Moritz (Henriques & Moritz 1947; Moritz & Henriques 1947) can be used to quantify the thermal damage. The dimensionless measure of thermal damage, $\Omega$, is introduced as

$$\Omega = \int_0^t A \exp\left(-\frac{E_a}{RT}\right) dt, \quad (4.2)$$

where $A$ is a material parameter equivalent to a frequency factor,$^8$ $E_a$ is the activation energy and $R = 8.314\,\text{J}\,\text{mol}^{-1}\,\text{K}$ is the universal gas constant.

The degree of thermal damage, defined as the fraction of denatured collagen and denoted by $\text{Deg}(t)$, can be calculated by

$$\text{Deg}(t) = \frac{C(0) - C(t)}{C(0)} = 1 - \exp[-\Omega(t)], \quad (4.3)$$

where $C(0)$ and $C(t)$ are the initial concentration and the concentration remaining at time $t$ of undenatured collagen, respectively. $\text{Deg} = 0$ denotes no damage, while $\text{Deg} = 1$ implies complete damage.

Thermally induced stresses owing to non-uniform temperature distributions may also lead to the sensation of thermal pain. For a given temperature history, obtained by solving equation (4.1), the corresponding stress distribution in skin can be calculated as (Xu et al. 2008a, b, c)

$$\sigma_k = \tilde{E}_k \begin{cases} 
- \tilde{\lambda}_k \delta T + \left[ C_1 (1 + \nu_k) \left( \sum_{i=1}^{M} \int_{z_{i-1}}^{z_i} \tilde{E}_i \tilde{\lambda}_i \delta T \, dz \right) 
\right. \\
+ C_2 (1 + \nu_k) \left( \sum_{i=1}^{M} \int_{z_{i-1}}^{z_i} \tilde{E}_i \tilde{\lambda}_i \delta T \, dz \right) \\
+ \left. z(1 + \nu_k) \left[ C_2 \left( \sum_{i=1}^{M} \int_{z_{i-1}}^{z_i} \tilde{E}_i \tilde{\lambda}_i \delta T \, dz \right) 
\right. \\
+ C_3 (1 + \nu_k) \left( \sum_{i=1}^{M} \int_{z_{i-1}}^{z_i} \tilde{E}_i \tilde{\lambda}_i \delta T \, dz \right) \right] 
\end{cases} \quad (4.4)$$

where $\tilde{E} = E/(1 - \nu^2)$, $\tilde{\lambda} = (1 + \nu)\lambda$, $E$ is Young’s modulus, $\nu$ is Poisson’s ratio, $\lambda$ is the thermal expansion coefficient and $C_1$, $C_2$ and $C_3$ are constants depending on the relative thickness of each layer of skin tissue.

(2) Model of current generation. The pain signal starts from the current induced by the opening of ion channels in nociceptors. Since ion channels are generally gated by three different stimuli (thermal, mechanical and chemical stimuli), there are correspondingly three different currents. The total current may be simply

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$^8$The units of $A$ are identical to those of the rate constant and vary depending on the order of the reaction. If the reaction is of first order, it has units $s^{-1}$, and for that reason, it is often called the frequency factor.
calculated as

\[ I_{st} = I_{\text{heat}} + I_{\text{chem}} + I_{\text{mech}}, \tag{4.5} \]

where \( I_{\text{heat}} = f_h(T_n, T_t) \), \( I_{\text{chem}} = f_c(Deg) \) and \( I_{\text{mech}} = f_m(\sigma_n, \sigma_t) \) are the currents due to the opening of thermally, chemically and mechanically gated ion channels, respectively. The heat current \( (I_{\text{heat}}) \) is assumed to be a function of nociceptor temperature \( (T_n) \) and thermal-pain threshold \( (T_t) \), where \( T_t \) is assumed to be 43°C (Cain et al. 2001; Patapoutian et al. 2003). The chemical current \( (I_{\text{chem}}) \) is assumed to depend on the thermal damage degree of skin tissue \( (Deg) \). The mechanical current \( (I_{\text{mech}}) \) is taken as a function of the stress at the location of nociceptor \( (\sigma_n) \) and mechanical-pain threshold \( (\sigma_t) \), where \( \sigma_t \) is assumed to be 0.2 MPa (James & Richard 1996).

(3) Model of frequency modulation. When the induced current surpasses the threshold, an action potential is generated, where the intensity of external stimulation is carried through the frequency of these impulses \( (f = f_m(I_{st})) \). Although there has been no relative analysis on nociceptor kinetics, all neurons have been found to behave qualitatively similar to that described by the Hodgkin–Huxley (H–H) model of nerve excitation (Hodgkin & Huxley 1952). The H–H model was originally developed for an unmyelinated nerve fibre. It is used here for skin nociceptors that are found to be both unmyelinated (C-fibre) and myelinated (A-fibre), in view that the H–H model has already been extended to myelinated axons (Frankenhaeuser & Huxley 1964) and muscle fibres (Noble 1966; Adrian et al. 1970).

In our previous study (Xu et al. 2008), we revised the original H–H model to match experimental observations of nociceptors in mouse glabrous skin by including a change of rates of existing channels, consideration of the temperature influence and the addition of transient K\(^+\) channels. The modified H–H model is schematically shown in figure 5 and can be mathematically described as

\[ C_m \frac{dV_m}{dt} = I_{st} + I_{Na} + I_K + I_L + I_{K2}, \tag{4.6} \]

where \( V_m \) is the membrane potential (depolarization positive; mV), \( t \) is the time (ms), \( C_m \) is the membrane capacity per unit area (\( \mu \)F cm\(^{-2}\)), \( I_{st} \) is the stimuli-induced current density (positive outward; \( \mu \)A cm\(^{-2}\)). \( I_{Na} = \bar{g}_{Na} m^3 h (E_K - V_m) \),

\[ I_{Na} = \bar{g}_{Na} m^3 h (E_K - V_m), \]

\[ I_{K} = \bar{g}_K n^4 (E_K - V_m), \]

\[ I_{L} = \bar{g}_L h (E_L - V_m), \]

\[ I_{st} = I_{\text{heat}} + I_{\text{chem}} + I_{\text{mech}}, \]

\[ f_h(T_n, T_t) = f_h(T_n), \]

\[ f_c(Deg) = f_c(Deg), \]

\[ f_m(\sigma_n, \sigma_t) = f_m(\sigma_n, \sigma_t). \]
I_K = \bar{g}_K n^4 (E_K - V_m), I_L = g_L (E_L - V_m) and I_{K2} = \bar{g}_A A^3 B (V_A - V_m) are sodium, potassium, leakage and the second potassium current components (\mu A cm^{-2}), respectively, while I_{K2} is an additional current for the second potassium channel. \( E_{Na}, E_K \) and \( E_L \) are the corresponding reversal potentials for sodium, potassium and leakage current components, given by the Nernst equation (all in mV), respectively; \( \bar{g}_{Na}, \bar{g}_K \) and \( g_L \) are the maximal ionic conductance through sodium, potassium and leakage current components (all in mS cm^{-2}), respectively; and \( m, n, h \) are gating variables. \( \bar{g}_A = 47.7 \) mS cm^{-2} and \( A \) and \( B \) are factors having the same functional significance as factors \( m \) and \( h \) of the sodium conductance system (Connor et al. 1977). These conductances are regulated by voltage-dependent activation and inactivation variables (gating variables), which are given as

\[
\frac{dx}{dt} = C_{Tx} \frac{x_{\infty}(V_m) - x}{\tau_x(V_m)},
\]

where \( x \) can be either of the gating variables, \( m, n \) and \( h \), \( x_{\infty}(V_m) \) is a steady-state voltage-dependent (in)activation function of \( x \) and \( \tau_x(V_m) \) is a voltage-dependent time constant. The temperature coefficient \( C_{Tx} \) depends on the difference of actual temperature \( T \) and laboratory temperature \( T_0 \), defined as

\[
C_{Tx} = (Q_x)^{(T-T_0)/10},
\]

where \( T_0 = 32^\circ C \) and \( Q_x \) is a special constant that gives the acceleration in membrane behaviour when the temperature is increased by 10\(^\circ C\).

The predicted membrane potential and frequency responses under stimulus of different nociceptor temperatures \( (T_n) \) are presented in figure 6b. Compared with experimental observations of nociceptors (Cain et al. 2001) shown in figure 6a, a good agreement has been achieved for the intensity-response relationship although, because of the simplifications in the analytical model, higher temperatures are required to mirror the corresponding intensities. In particular, with the revised model, the predicted neural impulse rate is comparable with that of the actual nociceptors.

In summary, by considering the temperature effect and adding transient K\(^+\) channels to the original H–H model, a frequency response behaving in a manner consistent with the experimental observation has been achieved. It should be noted here that, in developing the revised model, given the limited knowledge about noxious stimuli-sensitive ion channels and one’s desire for simplicity, an approximation between noxious stimuli applied to nociceptors and generator current has been assumed. Ideally, it would be desirable to incorporate the actual noxious stimuli-sensitive ion channels into the model for compatibility with other models of excitable membranes. However, the addition of actual ion channels cannot be achieved until more is known about these channels.

(ii) Model of transmission

The time for transmission \( (t_t) \) of noxious stimulus-triggered neural signals (impulses) from the skin along the respective fibres to the spinal cord and brain can be obtained according to the CV \( (v_c) \) and the corresponding nerve length \( (L_n) \). Here, a fibre length of 1 m is chosen, which is about the same distance as
that between a finger and the spinal cord (de Medinaceli et al. 1997)

\[ L_n = 1 \text{ m}. \quad (4.9) \]

CV \( v_c \) is found to be directly related to fibre diameter \( D \) (Julius & Basbaum 2001) and temperature (Paintal 1965, 1966). A linear relationship has been assumed between \( v_c \) and \( D \), given as

\[ v_c = v_{cT} = c_T v_{cN} = c_T c_d D; \quad (4.10) \]
where $v_{cN}$ is the CV under normal conditions, $c_d$ is the coefficient between diameter and velocity, $v_{cT}$ is the velocity when the fibre rests in an environment of temperature, $T$, and $c_T$ is the influence factor of temperature on CV. When both the nerve length and CV are known, the time latency, i.e. the period between stimulation and sensation, can be calculated as

$$t_l = \frac{L_n}{v_{c}}. \quad (4.11)$$

(iii) Model of modulation and perception

The signal from skin under localized heat stimuli is finally transmitted via the dorsal horn ganglion to the cerebral cortex, where it is modulated and perceived as pain sensation. The popular GCT (Melzack & Wall 1965) can be employed to describe the modulation and perception process of skin thermal pain.

GCT has been used to extrapolate the relevant features of pain and was translated into a mathematical model by Britton and co-workers (Britton & Skevington 1989, 1996; Britton et al. 1995, 1996), as shown in figure 7. The validity of the theory has been verified by four different simulations: (i) simulation consisting of a constant small fibre input with a variable large fibre input, which ascertained the inhibitory effect of the large fibre input, as evidence for this had been anecdotal owing to the difficulty in obtaining experimentally independent stimulation of large and small fibres, (ii) simulation involving small fibre input only, which aims to establish that, as the small fibre input is increased, the $T_{cell}$ output also increases at a rate ‘slightly greater than linear’, (iii) simulation involving the phenomenon of ‘wind-up’ (Mendell 1966), which occurs following repeated stimulation of C-fibres, resulting in a progressive increase in the $T_{cell}$ response, and (iv) simulation of ‘ramp-off’, which occurs when the peripheral stimulus is removed, causing a pulse of pain (Humphries et al. 1996). The mathematical description of GCT is given as

$$\tau_i \dot{V}_i = -(V_i - V_{i0}) + g_{hl}(x_l) + g_{mi}(x_m),$$

$$\tau_e \dot{V}_e = -(V_e - V_{e0}) + g_{se}(x_s, V_e),$$

Figure 7. Schematic of the GCT used in the mathematical model of pain. (Reproduced with permission from Xu et al. (2008a,b,c).)
\[
\tau_t \dot{V}_t = -(V_t - V_{t0}) + g_{se}(x_s) + g_{ht}(x_l) + g_{st}(x_e) - g_{ht}(x_l) - g_{mt}(x_m) \quad (4.14)
\]
and
\[
\tau_m \dot{V}_m = -(V_m - V_{m0}) + g_{tm}(x_l), \quad (4.15)
\]
where subscripts i, e, t and m stand for inhibitory SG cell, excitatory SG cell, T-cell and midbrain, respectively; \( \tau_j \) is the time constant, \( V_j \) the membrane potential; \( V_{j0} \) the initial membrane potential; \( x_j \) the firing frequency; \( x_l \) and \( x_s \) are signals (frequency) from large and small fibres, respectively; and function \( g_{jk} \) represents the effect of inputs (j) to a cell (k) on its steady-state slow potential.

The frequency \( x_j \) at which the cell fires is a function of its slow potential, so that \( x_j = f(V_j) \) and
\[
f(V_k) = \left[ \frac{K(V_k - V_{thr})}{(-V_{k0})} \right] H(V_k - V_{thr}), \quad (4.16)
\]
where \( H \) is the Heaviside function, \( K \) is a constant and \( V_{thr} \) is the firing threshold potential (taken as \(-55 \text{ mV}\)). The output from the T-cell is taken to be in direct relation to the pain experience, such that if the T-cell exceeds its firing threshold \( (V_t \geq -55 \text{ mV}) \), then the noxious signal is transmitted to the next relay point. If the noxious signals reach the cortex, then they are perceived as pain.

With the parameters given by Britton & Skevington, equations (4.12)–(4.15) can be recast into the following form:
\[
0.7 \dot{V}_i = -(V_i + 70) + 60 \tanh(\theta_i x_l) + 40 \tanh(f_m(V_m)), \quad (4.17)
\]
\[
0.7 \dot{V}_e = -(V_e + 70) + 40 \tanh(\theta_a x_s)[1 + 3 \tanh(4f_e(V_e))], \quad (4.18)
\]
\[
0.7 \dot{V}_t = -(V_t + 70) + 40 \tanh((1 - \theta_a)x_s) + 40 \tanh((1 - \theta_i)x_l) + 40 \tanh((1 - \theta_i)x_l)
\]
\[
\quad + 40 \tanh(f_e(V_e)) - 40 \tanh(f_l(V_l)) - 40 \tanh(f_m(V_m)) \quad (4.19)
\]
and
\[
0.7 \dot{V}_m = -(V_m + 70) + 40 \tanh(f_l(V_l)), \quad (4.20)
\]
where \( \tanh(4f_e(V_e)) \) is the NMDA component of the equation. It has been argued that the NMDA receptor is responsible for pain sensation phenomena such as wind-up, where the response of a neuron increases progressively as the neuron is repeatedly stimulated. \( \theta_i \) and \( \theta_a \) are the proportions of inputs that pass through interneurons in the SG and, correspondingly, \( (1 - \theta_i) \) and \( (1 - \theta_a) \) are the proportions passing through to the T-cell.

It should be pointed out that, while the model shown above produced expected results in line with the literature, certain assumptions have been made in order to simplify the theory: (i) the cell potentials in the model are slow potentials, or moving time averages of membrane potentials at the soma, and the firing frequency of a particular cell is assumed to be a function of its slow potential, (ii) any long-term effects, such as plasticity, are neglected, (iii) each T-cell is simulated by one C- or Aδ-fibre and one Aβ nerve fibre from the skin (with frequencies \( x_s \) and \( x_l \), respectively), together with one inhibitory and one excitatory SG cell, (iv) the potentials \( V_k \) depend on the frequency of impulses arriving at their dendrites from various sources, and on the dendrites and synaptic junctions themselves, the properties of which are assumed constant over the time scales, (v) the system is linear, (vi) the cells do not fire until their potential reaches a certain threshold, and that above this threshold, the firing frequency is an increasing function of slow potential, and (vii) the function must also saturate.
(c) Case study

In this section, results from a case study of skin heating with constant surface temperature are presented to illustrate the applicability of the holistic thermal-pain model. The skin is initially kept at constant normal temperature. At $t = 0$, its surface is suddenly taken into contact with a hot source of constant temperature $T_s$ for 5s (i.e. the surface temperature is instantaneously raised to $T_s$). The location of nociceptors is assumed to vary in the depth range of $25 \mu m \leq z_n \leq 200 \mu m$; and the nociceptors are assumed to be C-fibres with a CV of $1\text{ms}^{-1}$. With the skin thermomechanical model, the temperature history of the nociceptor is obtained first, which is then used as an input for the neural model. The skin is divided into four layers with different properties: stratum corneum, epidermis, dermis and subcutaneous fat. Blood perfusion is only considered in the dermis layer, while metabolic heat generation is considered in all four layers. The details of relevant parameters can be found in Xu et al. (2008a, b, c).

(ii) Influence of nociceptor depth

Nociceptors located at four different depths ($z_n = 25, 50, 100, 200 \mu m$) have been considered with the surface heat stimulus fixed at $T_s = 55^\circ C$. The predicted temperature history of nociceptors is plotted as a function of its location in figure 8a, and the corresponding pain level is shown in figure 8b. From figure 8a, it can be seen that the nociceptor temperature increases nearly exponentially with heating, tending eventually to a constant value. As expected, at a given time, the temperature of a nociceptor located closer to the skin surface is much higher than that located further away, e.g. at $t = 5$ s, the temperature at $z_n = 25 \mu m$ is almost $5^\circ C$ higher than that at $z_n = 200 \mu m$. It has been established that the pain level is decided by signal frequency (Torebjörk et al. 1984). The pain level, as shown in figure 8b, is higher if the nociceptor is located closer to the surface of skin under the same stimulus intensity. This may be used to explain why different pain thresholds were obtained by different studies for the same stimulus (Tillman et al. 1995a, b). It should be noted here that there is a clear latency (about 1 s) because of transmission, as shown in figure 8b. Similar results have also been experimentally observed. For example, Campbell & LaMotte (1983) found that the median time to the detection of temperature stimuli ranging from 39 to $51^\circ C$ lies within the range of 0.7–1.1 s for the finger tip and 0.4–1.1 s for the arm.

(iii) Influence of stimulus intensity

Naturally, it is expected that the magnitude of skin surface temperature has a great effect on pain. The stimulus intensity–pain level relation is shown in figure 9. It is seen that there is a nearly linear relation in the temperature range of concern. Similar results have been observed by others. For example, LaMotte & Campbell (1978) found that heat pain increases monotonically with stimulus intensity between 40 and $50^\circ C$, while Torebjörk et al. (1984) observed a linear relationship between the mean responses of CMHs recorded in awake humans and the median ratings of pain over the temperature range of 39–51$^\circ C$. It was also shown that the intensity of cold pain is linearly correlated with that of a cold stimulus (Iggo 1959; Georgopoulos 1976, 1977; Chery-Croze 1983a, b).
For example, Georgopoulos (1976, 1977) found that the stimulus-response functions were approximately linear, with a mean slope of 1.15 for power functions, while Simone & Kajander (1997) obtained a slope of 1.07.

(iv) Role of thermal stress and thermal damage

To examine the roles played by thermal stress and thermal damage in the pain process, currents owing to the opening of chemical-gated ($I_{\text{chem}}$) and mechanical-gated ($I_{\text{mech}}$) ion channels are added to the stimulation current ($I_{\text{st}}$). The results

Phil. Trans. R. Soc. A (2010)
obtained with this current ($I_{st} = I_{heat} + I_{chem} + I_{mech}$) are then compared with that obtained by considering $I_{heat}$ alone. Since no experimental data are available, a simple linear relationship between the generated currents and stimuli has been assumed for both $I_{chem} = C_c(Deg)$ and $I_{mech} = C_m(\sigma_n - \sigma_t)/\sigma_t$, where $C_c = C_m = 20 \mu A cm^{-2}$ is assumed.

The skin is initially kept at a constant normal temperature. At $t = 0$, the skin surface is suddenly taken into contact with a hot source of constant temperature $T_s = 55^\circ C$; after contacting for 5s, the hot source is removed and the skin is cooled by natural convection of environmental air ($T_e = 25^\circ C$, $h = 7 W m^{-2}K$) for 5s. The nociceptors are assumed to be located at a depth of 50 $\mu m$.

The thermomechanical responses of skin tissue are plotted as functions of time in figure 10a–c, while a comparison between the neural responses of nociceptor and the pain level with and without considering $I_{chem}$ and $I_{mech}$ is presented in figure 10d. It can be seen from these results that, during heating, the pain level increases continually, peaking at about $t = 5$ s. Although the heating is stopped at $t = 5$ s, there is still generation of action potential for both cases since temperature at the nociceptor location is still higher than the threshold (figure 10a). For the model without considering $I_{chem}$ and $I_{mech}$, after the peak, the pain level decreases quickly owing to the decrease of temperature and, at about $t = 7$ s, the generation of action potential stops because of the decrease of $T_n$ below the threshold. In comparison, the pain level obtained from the model with $I_{chem}$ and $I_{mech}$ included is still high after the heating has stopped; even during the heating process, the model predicts a higher frequency than that predicted from the model.

*Phil. Trans. R. Soc. A* (2010)
considering $I_{\text{heat}}$ alone. This is mainly attributed to the thermal damage ($I_{\text{chem}}$), since the thermally induced stress is smaller than the mechanical threshold of the nociceptor (figure 10c) so that $I_{\text{mech}} = 0$. Thermal damage has been accumulated in skin tissue during heating, which is an irreversible process, causing the cells to break down and release a number of tissue byproducts and mediators that keep the chemically gated ion channels fully opened. This explains why people still feel pain, even when a noxious heat source has been removed from skin, a common phenomenon called hyperpathia.\(^9\)

\(d\) Summary

A multi-scale model for quantifying skin thermal pain has been developed by using thermomechanical models of skin tissue and considering the biophysical and neurophysiological mechanisms of pain sensation. The concepts of bioengineering are coupled with established methods in neuroscience, and the biological behaviour of skin has been recast in engineering systems parlance.

\(^9\)Hyperpathia is a painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold (Loeser & Treede 2008).

\(\text{Phil. Trans. R. Soc. A}\) (2010)
The model is composed of three interconnected parts: peripheral modulation of noxious stimuli, which converts the energy from a noxious thermal stimulus into electrical energy via nerve impulses; transmission, which transports these neural signals from the site of transduction to the spinal cord and brain; and modulation and perception in the spinal cord and brain.

The mathematical model enriches the understanding of the transduction of temperature to action potentials. It has been demonstrated that the model is capable of capturing the essential properties of experimentally measured frequency responses. With this model, the intensity of thermal pain can be predicted directly in terms of the character of noxious stimuli, as a corollary, for a given thermal treatment profile, one can predict how painful a thermal medical treatment will evoke. The mechanism of skin thermal pain can be better understood and some important features of pain sensation can be explained, such as hyperpathia.

5. Further research

The focus of this review has been placed on the biological and physiological features of skin thermal-pain sensation and their theoretical modelling, in order to provide a predictive analytical and computational framework for the coupled thermomechanical behaviour of skin and pain sensation in extreme thermal environments (figure 1). By grouping together various solution tools, it is hoped that these can lead to more effective thermal-treatment therapies. An engineering approach has been taken, which is mainly concerned with the biothermomechanics of skin and the prediction of thermal pain using a multi-scale model. With this approach, the concepts in engineering are coupled to established methods from neuroscience, biological behaviours are recast in engineering systems parlance, and known but essentially disparate models of tissue behaviour are assembled for a complete description of skin thermal pain.

Schematically, the framework can be described as follows: (i) thermal loading applied to skin leads to changes in the thermomechanical states of skin, such as temperature, thermal stress and thermal damage-induced inflammation distributions, (ii) these skin states will work as stimuli (input) for skin nociceptors, and (iii) when the stimuli are sufficiently high (larger than the pain threshold), electrical signals (action potential) will be induced and transmitted to the brain, where the signals are perceived as pain. To the best of our knowledge, the proposed approach is applied for the first time to this specific area of research. Despite the promising results obtained for selected case studies, the multi-scale skin thermal-pain model has crucial limitations that one needs to explore further on both the peripheral and central transmission parts. For engineers, however, attention should be directed at the peripheral transmission part, focusing on skin thermomechanical and nociception response. Accordingly, the improvement of the model can be achieved by considering several acquainted effects. For example, most thermal medical treatments work by further damaging the diseased tissue, resulting in its destruction as well as variations in skin properties (thermal, mechanical, optical, etc.). However, there is relatively few published data on the relationship between skin properties and thermal injury (damage) effects (Xu et al. 2009a, b), while their incorporation into the...
current analytical and computational framework demands greater sophistication. This issue should be carefully investigated and addressed in future studies. In addition, experimental studies of pain sensation under different medical treatment conditions are needed to validate the proposed mathematical model for skin thermal pain. The aim is to explore the effects of different treatment parameters on the degree of pain felt by patients.

The full suite of models and experimental results could be used for the characterization of existing strategies for delivering thermal therapies, optimization of thermal treatments by maximizing the therapeutic effect while minimizing unwanted side effects, such as pain sensation, and design of new and better treatment strategies in order to assert novel heat treatments in view of productive commercial exploitation.

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Review. Skin thermal-pain modelling


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