Thermo-mechanical pain: a hidden role for heat dissipation in biological tissues

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Mechanical pain is an important process for the preservation of living organisms, allowing potentially life-saving reflexes or decisions when given body parts are stressed. Its underlying mechanisms are believed to be various and to involve many neuronal transducers, whose individual actions remain to be fully unravelled. Here, we quantitatively discuss how the detection of painful mechanical stimuli by the human central nervous system may partly rely on thermal measurements. Indeed, most fractures in a body, including microscopic ones, release some heat, which diffuses in the surrounding tissues. Through this physical process, the thermo-sensitive TRP proteins, that are believed to translate abnormal temperatures into action potentials, shall be somewhat sensitive to damaging mechanical inputs. Such an implication of these polymodal receptors in mechanical algesia has been regularly suspected, for which we here propose a likely physical explanation.

On rupture and energy dissipation

The growth of mechanical damages through a body is an irreversible thermodynamic process [1]. Indeed, when a fracture progresses by a given surface unit, it dissipates a specific amount of energy, that is referred to, by rupture physicists, as the energy release rate (in J m⁻²). In most engineering materials (e.g., [2]), this quantity, denoted \( G \), is well studied, since it characterizes the loading necessary for a crack to propagate [3]. For instance, it is in the order of 10 J m⁻² in weak glasses [4] and can reach 100 kJ m⁻² in the strongest media, as titanium [5] or steel [6].

When it comes to biological tissues, this energy release rate can also be estimated, and was notably measured to be about \( G \sim 2000 \text{ J m}^{-2} \) in the human hand skin [7]. An important question, then, is how is this dissipated mechanical energy received and felt by the human body?

Most generally, there are many possible ways for it to be transformed, ranging from its storage as surface potential energy on the walls of the new fractures [8] or its emission to the far field as mechanical [9] (i.e., sound) or electromagnetic [10] (i.e., luminescence) waves. It was, in particular, shown that a significant part of the mechanical input is converted into heat close to the damage [11–14], as the rupture of stretched atomic and molecular bonds is prone to generate a local and incoherent (thermal) atomic motion.

The related elevations in temperature have been measured in various synthetic solids (e.g., [12, 13, 15]), and are believed to be more than only a side effect of the fracturing process. Indeed, from its positive feedback on the dynamics of rupture, it was pointed out as a likely cause for the brittleness of matter [16, 17] and for the instability of some seismic faults [18–20].

We here propose that, in the human body, this damage-induced heat may be sensed by the neural network, and may hence explain a degree of coupling between the thermal and mechanical pain, which has been regularly suspected [21–23].

Thermo-mechanical nociception

The perception of pain (i.e., nociception or algesia) arises from the bio-electrical signals (referred to as action potentials) that sensory neurons send from the aggressed body part to the nervous system (e.g., [24]). To initiate such messages, the dolorous inputs, being mechanical, thermal or chemical, need to be converted accordingly, at the surface of neurites (i.e., the extensions of neurons cell bodies).

We will here focus, as an example, on nociception in the human skin. As for other body parts, the TRPs proteins (Transient Receptor Potential cation channels) are notably believed to be responsible for the reporting of its temperature to the brain [21, 25]. For instance, TRPV3 sends action potentials between 30 and 40°C, with an activation intensity that is gradual with temperature [26, 27], leading to a harmless perception of warmth. The feel of a more intense, potentially more noxious, heat occurs when TRPV1 is activated, at higher skin temperatures above 43°C. The physico-chemical mechanism to translate heat into current is, in all cases, believed to be a temperature dependant shifts in the TRPs voltage-dependent activation curves [28].

The role of these proteins is, however, not limited to thermal sensing, and some TRPs are known to be sensitive to chemical aggression, responding for instance to capsaïcine (i.e., the component of chilli pepper that is felt as hot), menthol (that is felt as cold), or arachnid acids [21, 22]. They are hence often referred to as polymodal nociceptors. Similarly, a growing suspicion seems to have risen that they could also be involved in the feel-
As per the energy release rate $G$ of skin [7], the rupture of this fiber shall dissipate an energy $\pi R^2 G \sim 25 \text{nJ}$, that is here assumed to be mainly converted into heat on the atomic scale, which then diffuses [39] to the surrounding skin molecules. For simplicity, we suppose that the collagen fiber break is brutal, that is, with a rupture velocity comparable to that of sound in skin [40, 41], $V_0 \sim 1500 \text{m s}^{-1}$. We can then, for various times $\tau$ after the fracture that are superior enough to $2R/V_0 = 2.5 \text{ns}$, compute the temperature rise $\Delta T$ around the damage, by integrating the heat diffusion kernel [39] over the broken surface $S$:

$$\Delta T = \int_S \mathrm{d}s \frac{G\sqrt{C}}{(4\pi\lambda\tau)^{3/2}} \exp \left( -\frac{C\tau^2}{4\lambda\tau} \right).$$

(1)

In this equation, $r$ is the integration distance between a given point where the temperature is computed, and the various infinitesimal heat sources of $S$, that have an elementary surface $\mathrm{d}s$. In addition, the heat conductivity and volumetric heat capacity of skin are respectively denoted $\lambda$ and $C$, whose values [42] are about $\lambda \sim 0.4 \text{J m}^{-1} \text{s}^{-1} \text{K}^{-1}$ and $C \sim 4 \text{MJ K}^{-1} \text{m}^{-3}$. If the rise in temperature described by Eq. (1) can be captured by the human neural system, it could then be treated as mechanical pain. In a healthy skin, the density of neurites was estimated [36] to be about $\rho_n \sim 2000 \text{mm}^{-2}$, a quantity from which we derive an order of magnitude for the maximum distance between the surface of a broken collagen bundle and that of a neural receptor: $1/(2\sqrt{\rho_n}) - R \sim 9 \mu\text{m}$. We have here assumed very thin, evenly distributed, neurites, that are all thermo-sensitive. This might of course be rather simplified, considering the various types of cutaneous neurons (e.g., [29]) and their respective densities in different body parts [24]. In addition, the expression of the TRPs in the skin (and their role in thermo-sensing) is not limited to its sensory neurons, as they also appear, notably, in keratinocyte cells [21, 43]. Interestingly, however, such an approximate maximum distance (9 µm) is similar to the typical gap between the surfaces of two collagen fibers, which was measured [35] in average to be about 8 µm. Thus, if only two contiguous fibers were to break in response to a mechanical stimuli, one of it would, probably, be rather close (that is, in the micrometer range) to a neurite. We therefore show, in Fig. 2, the evolution of the temperature $T_0 + \Delta T$ predicted by Eq. (1), at various distances $x$ up to 9 µm perpendicularly to the broken fiber surface, $T_0$ being the normal internal skin temperature [44, 45] $\sim 35^\circ\text{C}$. We also show, in Fig. 3, the related spatial temperature maps at three given times $\tau$ after the fracture.

Close to the rupture plane, that is, for $x < 2 \mu\text{m}$, modelled temperatures superior to that of the activation of TRPV1 ($\sim 43^\circ\text{C}$) are quickly reached, in about 10 µs. A painful message can thus be triggered. More con-
FIG. 2. (a): Temperature elevation $\Delta T$ close to a fractured collagen fiber, as a function of the distances in space and time to the rupture event, as predicted by Eq. (1). (b): Local skin temperature felt at various distances and times from the fractured fiber. Each plots corresponds to a horizontal section of inset (a), to which an ambient skin temperature $T_0 = 35^\circ C$ was added. For readability, two graphs with different temperature scales are shown. (Top): temperature at a distance $x = 1, 2$ and $3 \mu m$ from the fracture. (Bottom): temperature at $x = 4, 6$ and $8 \mu m$. An approximate maximal distance between a neurite and the surface of a collagen fiber is about $9 \mu m$, as we developed in the core text. The vertical arrows show the domains of increasing activation of the TRPV1 [22] (strong heat) and TRPV3 [26] (warm feeling) protein channels at the surface of neurites.

servatively, if the thermal transducers are further away from the rupture point ($x = 2$ to $9 \mu m$), it undergoes a temperature elevation of half a degree to a few degrees, about $0.1$ ms after the damage. While this quantity is not enough to trigger TRPV1, and not vastly outside the range of the normal temperature oscillations of the human skin [46], it could still be perceived as some abnormally sudden and localised heat by the brain. TRPV3 was indeed shown to be rather sensitive to small temperature changes around the normal body temperature [26, 27], and with a more intense response the faster these changes are [27]. Here, as shown in Fig. 2, we expect very high heating rates ranging from $10^5 \circ C s^{-1}$ to $1 M \circ C s^{-1}$.

The temperature bursts reaching the neurons in less than a millisecond, they could in theory trigger pain reflexes, whose characteristic delays are an order of magnitude bigger, and mainly arise from the two-way travel time of the bio-electrical signals from the neurites to the central nervous system (e.g., [24]). However, the time interval during which the temperature elevation holds is also of importance. In our case, it is of the order of $0.1$ ms and less (see Fig. 2), and a question stands on the response time of in situ TRPs proteins. Recent studies [47, 48] indeed suggest that the TRPs reach a steady current emission in times as large as a few milliseconds. While it could imply that some of the temperature signal we have described may, in practice, be low-pass filtered, an early (transient) response from the proteins channels may also be enough information to be interpreted as pain by the central nervous system.

Concluding remarks

Note that only a part, rather than the whole, of the released energy $G$ could be transformed into heat, leading to an equivalent reduction in our computed temperatures. And, if collagen fibers were to slowly creep rather than brutally snap, more time would be given to the thermal diffusion to evacuate the thus progressively generated heat, so that $\Delta T$ would also be significantly smaller [17]. Still, by considering only a microscopic lesion, we have here illustrated how the actual coupling between mechanical damages and the dissipation of heat may play some role in the nervous response to mechanical stimuli. While the rupture of a single fiber is likely representative of the orders of magnitude at stake in this very local phenomena, larger traumas, in particular if not limited to collagen bundles, could be accompanied with stronger thermal anomalies. There, the spatial extent of the warmed-up neurites may also play some role in the nociception [24]. Furthermore, other and similar phenomena could also be at play in thermo-mechanical sensing. For instance, the
FIG. 3. Modelled temperature anomaly ($\Delta T$) around a brutally broken collagen fiber, as per Eq. (1). Three times $\tau$ after the rupture are shown in chronological order. The color scale is saturated at 10°C for readability. In each frame, the volume integral $\int\int\int C\Delta T \, dv = \pi R^2 G$ is conserved. The white vertical lines mark the border of the broken fiber and of its closest neighbours [35]. Each map is a cross-section cutting though the central fiber center and has an area of about $1/\rho_n$, where $\rho_n$ is the typical neurite density in the human skin [36]. Thus, at least one neurite is likely to be present on the displayed surface. The two arrows below the color bar represents the domains of activation of the TRPV3 and TRPV1 channels, when assuming a background temperature of 35°C.

friction between different collagen units (that is, without an actual rupture) of a compressed or stretched skin is also to generate some heat bursts. By contrast, the vasocstriction in such a deformed body is prone to induce a local cooling [49], which could also be sensed. Note also that, while we have focused on the example of skin, the main concepts we have here discussed are general enough to stand for both somatic (that is, related to the skin, tissues and muscles) and visceral (i.e., related to internal organs) pain, in which the TRPs are also likely involved [50]. Let us conclude by amusingly pointing out that temperature monitoring has regularly been used by material scientists, including the authors of the present manuscript, to monitor the ongoing damage of engineered solids (e.g., [10, 13, 15]). In these experiments, we might have unknowingly mimicked our own biology.

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