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MATHEMATICAL MODELING FOR THE PREDICTION AND IMPROVEMENT OF TOOTH THERMAL PAIN: A REVIEW

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Tooth pain, especially tooth thermal pain, is one of the most important symptoms and signs in dental clinic and daily life. As a special sensation, pain has been studied extensively in both clinic and experimental research aimed at reducing or eliminating the possible negative effects of pain. Unfortunately, the full underlying mechanism of pain is still unclear, because the pain could be influenced by many factors, including physiological, psychological, physical, chemical, and biological factors and so on. Besides, most studies on pain mechanisms in the literature are based on skin pain sensation and only few are based on tooth pain. In this paper, we present a comprehensive review on both neurophysiology of tooth pain mechanism, and corresponding thermal, mechanical, and thermomechanical behaviors of teeth. We also describe a multiscale modeling approach for quantifying tooth thermal pain by integrating the mathematic methods of engineering into the neuroscience. The mathematical model of tooth thermal pain will

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enable better understanding of thermal pain mechanism and optimization of existing diagnosis and treatment in dental clinic.

Keywords: Tooth; thermal pain sensation; thermal stress; mathematical model.

1. Introduction

The teeth are very important organs for human being and involved in chewing and grinding food, assisting to digest, and absorb the nutrition. The teeth are composed by enamel, the hardest tissue of the body, dentin and pulp chamber, the pulp located in chamber is soft tissue that contains sensory nerve endings, blood capillaries, and connective tissues. The teeth receive different kinds of stimuli in both people's daily life and medical treatments, such as mechanical (orthodontics, drilling, etc.[1,2]), thermal (temperature of food or material, laser and bleach, drilling,[3,4]) biological (microbes on the tooth surface, caries.[5,6]), and chemical (acid and alkali[7,8]) factors. In normal condition, the pulp is effectively prevented from noxious stimuli by the shelter composed of hard tissue (i.e., enamel and dentin) and no pain or unpleasant experience was produced. However, in some extreme circumstances, when the intensity of stimuli is out of normal range (such as contacting hard, supercooling, eating overheated foods; contacting noxious substance released by microbes; being treated by etch, laser, bleaching agent, and ultraviolet radiation during dental clinical treatment), dental tissue would be damaged gradually, nerve fibers in pulp would be activated, and the tooth pain sensation would be evoked.

In all above stimulus, thermal stimulation is often described as the most common and severe way that could evoke tooth pain sensation. Especially in recent years, the technical methods applied to diagnosis and treatment in dental clinic, including thermal tests for assessing pulp vitality,[9,10] light-activated resin composites,[11,12] cutting, bleaching and whitening tooth with different laser,[13,14] drilling, burnishing, and cutting tooth with high-speed drill,[15,16] etc., always generate lots of heat and induce thermal stress on dental tissue.[17,18] For example, the dental temperature can increase 16.1°C and 26.6°C at 10 and 60 minutes after Nd:YAG laser treatment respectively, and the temperature after application of Er:YAG laser even increased 24.7°C.[19] The temperature of hard tissue in 0.5 mm under drill bit rise to 40°C, 56°C, and 89°C after 5, 15, and 18 s respectively after high-speed drilling.[20] Another study[21] shows when the dental temperature increased to 16.7°C, the pulp will be damaged. Therefore, the heat generated by clinic operation may cause tooth damage, and when the heat transferred into pulp, the sharp tooth pain will be evoked.[22]

Pain sensation has been studied extensively, but the full underlying mechanism of pain is still unclear. All advances on pain mechanism studies will be the foundation-stone for revealing the complexity and variety of the tooth pain evoked by thermal stimulation. Further studies should focus on solving how to relieve the pain induced by thermal stimulation. Thermally induced physical, biological, chemical changes or damage of teeth also play an important role in generation of pain;

therefore, a valid mathematical modeling will greatly contribute not only to the study of pain mechanism but also to the countermeasure of pain.

Tooth thermal pain is a multidiscipline field which involves neurobiology, neurophysiology and biomechanics. In the present paper, we will review the neurophysiology, neurobiology of tooth pain mechanism, heat transfer, and thermal properties of teeth, with focus on the theoretical modeling approach of the process of thermal pain. The modeling approach can enhance the understanding of thermal pain phenomena and the refinement of thermal therapeutic methods. The review is divided into three parts: the physiology of tooth pain, tooth pain under thermal stimulation, and mathematic modeling of thermal tooth pain. Related issues, such as previous experiments and further studies are also mentioned.

2. The Physiology of Tooth Pain

2.1. *Pathways of tooth pain*

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" by the International Association for the Study of Pain (IASP).[23] In essence, pain phenomenon is advanced bioelectrical activity of nerve system, including the generation, transmission, and recognition of the electrical signal/action potential (AP),[24] a brief, regenerative, all-or-nothing electrical potential that propagates along an axon) along specific pathways.

The conduction and production pathway of tooth pain is simplified as the following: nociceptors in pulp tissue receive nociceptive stimuli (thermal, mechanical, and chemical) and transfer energy forms of stimuli into AP, which would be carried by sensory nerve fibers in the form of different frequency impulse (firing or trains) and conveyed from the nociceptor to the trigeminal (semilunar) ganglion; and then, AP from peripheral nerve would be integrated in thalamencephalon and continue being transmitted to superior structure, cerebral cortex, by specific projection pattern. Finally, the pain sensation generates in special area of cerebral cortex after nociceptive information carried by frequency of AP regulated by descending inhibitory and facilitory networks located in the brainstem. The integrated conduction tract of pain pathway is the precondition for pain sensation; we will make introduction of details in order.

2.1.1. *Nociceptor*

Free nerve ending distributed in superficial or deep layer of pulpal tissue is receptor of tooth pain, also called nociceptor.[25] Nociceptor can be classified into 3 groups (A, B, and C) according to the conduction velocity (CV)[26] of AP. The conduction velocities can be calculated as the length between the stimulating electrode and the recording electrode inserted into or placed on nerve fiber, divided by the time to onset of the AP (Table 1).

Table 1. Diameter, CV, and function in different type of never fibers.

Type	Diameter	CV	Function
A$-\alpha$	$12-22\,\mu$m	$70-120$ m/s	Motor: proprioception
$-\beta$	$5-12\,\mu$m	$30-70$ m/s	Sensory: touch pressure
$-\gamma$	$3-6\,\mu$m	$15-30$ m/s	Motor: muscle spindles
$-\delta$	$2-5\,\mu$m	$12-30$ m/s	Sensory: sharp pain
B	$< 3\,\mu$m	$3-15$ m/s	Preganglionic autonomic
C	$< 2\,\mu$m	$0.5-2$ m/s	Sensory: dull pain Postganglionic autonomic

The process of conduction is very different in nonmyelinated (C) and myelinated axons (A and B).[27] The electrical signals propagate along the nonmyelinated axons in a continuous pattern, but in myelinated fibers the signals are transferred as noncontinuous way in which the action potentials jump between consecutive node of Ranvier. The conduction velocity in myelinated fibers increases in direct proportion to the axonal diameter, but in nonmyelinated fibers, CV is proportional to the square root of the diameter of the fibers.[28]

It was found that only C fibers and A fibers (mostly A-δ and few A-β) innervated human teeth.[29] The distribution of nerve fibers is shown in Fig. 1.[30] The

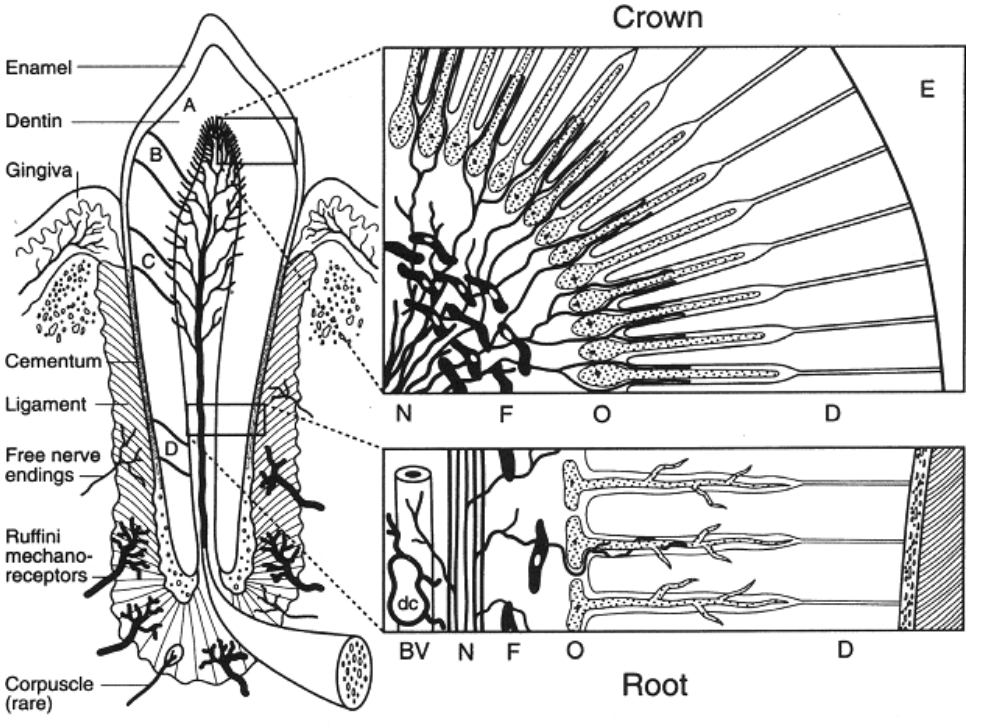


Fig. 1. The schematic diagram of innervation of tooth.[30]

enamel of the teeth is composed of dry hydroxyapatite crystals and is completely insensitive to any kinds of stimulation due to the noninnervated structure. Now the opinion that only the dentin was innervated is accepted generally.[31] The dentin and pulp contain body fluids and identifiable nerve endings and can be excited by thermal, mechanical and chemical stimulations.[32−35] Some researchers suggested that nerve fibers not only distribute in predentine, mineralized dentin, and tubulus but also extend up to enamelo-dentinal junction. Byers[36] showed that 50% of sensory nerve fibers innervate into the dentinal tubules in coronal pulp, only 0.2–1.0% and 0.02–0.2% of sensory nerve fibers innervate enamelo-cemental junction and dentinal tubules in central region of root, respectively. The innervation of sensory fibers can explain the phenomenon why hypersensitivity to pain in enamelo-dentinal junction.

The role of A-δ and C fibers in dental pain perception has been studied through sudden cold stimuli applied to the human teeth.[37] The pain sensation was found to be correlated with electrical activity of the A-δ fibers. The frequency of firing from C fiber was slower and uncorrelated with the pain induced by cool stimulation. This indicates A-δ fibers is involved in the transmission of cold pain. The C fibers are typically polymodal nociceptive as shown by their response to all thermal, mechanical, and chemical stimulations.[38] The difference in perception of pain between C and A type nerve fibers is shown in Table 2. C fibers locate in deep layer of pulpal tissue and mediate the transduction of pulp pain; C fibers could be excited by multiple stimuli, such as mechanic, thermal, and inflammatory factors. Generally, A-δ fibers react to hydrodynamic stimuli in dentin and mechanical stimuli applied to pulp directly. Nonpain perception (prepain)[39] evoked by low-intensity electric stimulus is the activity of low-threshold A-δ and A-β fibers.[40−42] In addition, pulp pain responses are not due to the spatial and temporal summation of local potential in A-δ fibers.[43]

2.1.2. *Trigeminal system*

Nucleus sensorius nervi trigemini locate in mesencephalon, which are consisted of four parts, including mesencephalic nucleus, superior nucleus, main sensory nucleus,

Table 2. The different characters between A-δ and C fibers in tooth.

	A$-\delta$	C
Diameter	$2-5\,\mu$m	$0.3-3\,\mu$m
CV	$5-30$ m/s	$0.5-2$ m/s
myelinated	yes	no
location	Peri-pulp	Deep in pulp
Adequate stimuli	Fluid shift in dentinal tubule	Direct stimuli applied to pulp
reactiveness	Low threshold to electrical, thermal, and mechanics stimuli non-sensitivity to mediators of inflammation	High threshold to electrical, thermal, and mechanics stimuli sensitivity to mediators of inflammation
discharge	High frequency firing at once	Firing after long latent period
Pain character	Fast pain (first pain), sharp and clear	Slow pain (second pain), dull and obscure

and nucleus of spinal tract. In addition, the nucleus of spinal tract was proven to receive the project of nociceptive afferents from maxillofacial region, tooth, temporomandibular joint (TMJ) and facial skins,[44] and the nucleus of spinal tract were divided into three subnuclei, including rostralis subnucleus, interpolaris subnucleus, caudal subnucleus. Takemura[45–47] observed that afferent neurofibers originated from pulp and ended in Layers I and II of bilateral caudal subnucleus, which was the area nociceptive neurons.

2.1.3. *Reticular formation of brain stem*

Reticular formation of brain stem contains many parts in structure, including superior part of spinal cord and hypothalamus, such as solitary tract nucleus, locus ceruleus, nucleus parabrachialis, nuclei periventriculares, medioamygdaloid nucleus, and gray matter periaqueduct of mesencephalon.[48] Brain stem reticular formation modulates the activity of neurons involved in pain-transmitting.[49–51]

The brain stem reticular formation has inhibitory regulation on the pain. The excited neurons in PAG (periaqueductal gray matter) of the midbrain can activate the neurons located in the rostral medulla. The inhibitory interneurons in medullary inhibit the activity of trigeminal neurons involved in pain-transmission by projection fibers. Being a part of the negative feedback loop, pain as output of the neurons involved in pain transmission has an important role in activation of anti-pain system.[52,53]

2.1.4. *The cluster of thalamic nuclei*

Nucleus ventralis posteromedialis thalami (VPM) is involved in the conduction of pain from trigeminal nerve system.[54,55] In addition, some investigations point out that nucleus submedius (Sm) not only is a nucleus receiving pain but also modulate the pain by Sm — ventrolateral orbital cortex (VLO) — periaqueductal gray matter (PAG) system.[56,57]

2.1.5. *Cerebral cortex*

Cerebral cortex is the highest level in conduction pathway of tooth pain.[58] The cortical areas including I and II sensory cortices,[59] anterior cingulate and lobus insularis, parts of lobus frontalis have been proven involving the pain[60] and premotor cortex, auxiliary motor cortex, lobulus parietalis inferior, and frontal cortex are correlated with pain sensation.[46] Somatosensory cortex (SI) discriminates the temporal and spatial properties and intensity of nociceptive stimuli, which were encoded in frequency of AP released by neurons. In rats, 32% touch-sensitive neurons of facial sensory representative area in SI responded to stimuli applied to dental pulp; therefore, those cells called tooth pulp-driven neurons (TPD); TPD functional units are perpendicular columnar arrangement, every TPD neuron have identical peripheral and dental pulp receptive field.[61]

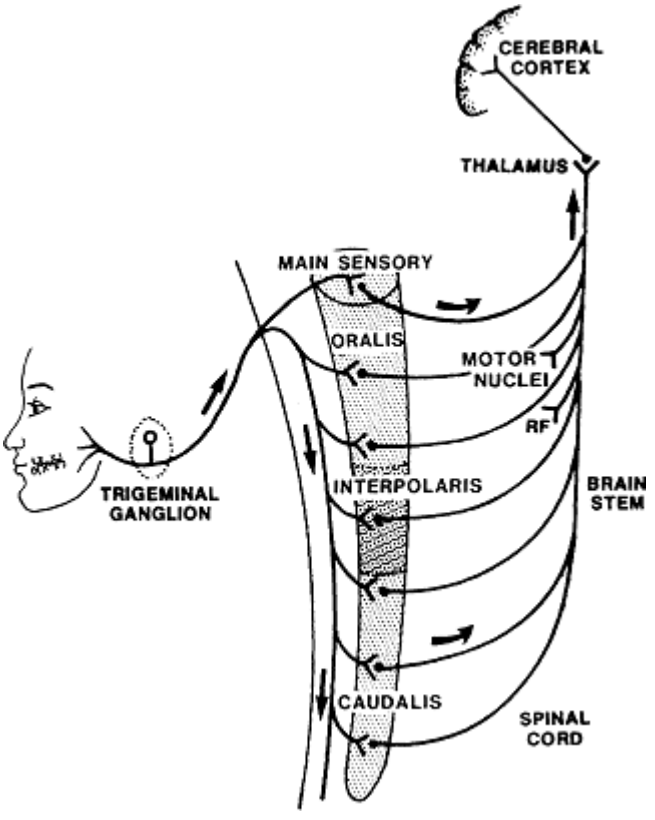


Fig. 2. The schematic diagram of conduction tract of pain perception.[106]

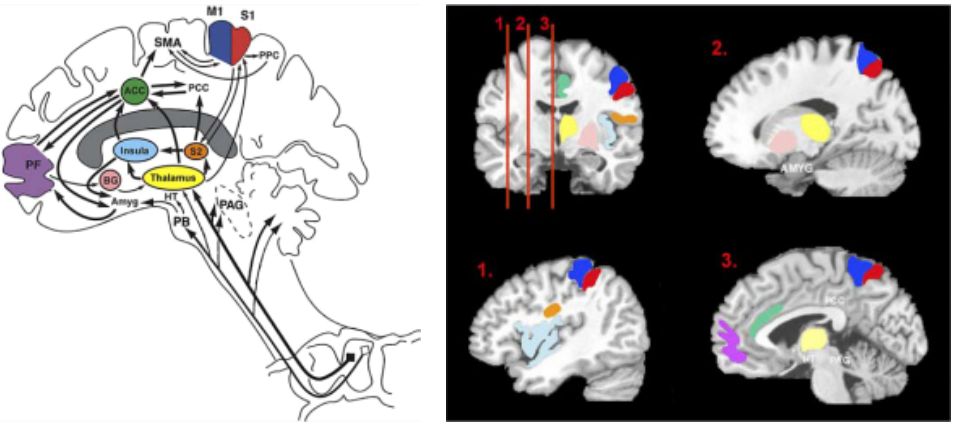
The pathway for dental pain perception is indicated in Fig. 2. Afferents from the mandibular and maxillary divisions relay to the spinal sensory nucleus in trigeminal nerve system. In this location, many fibers relay to the pontine reticular formation and cross the pons; ultimately, all fibers project to the cortex diffusely through the intralaminar and ventroposterior thalamic nuclei[62] (Fig. 3).

2.2. *Influence factors of tooth pain*

Generation and transmission of AP on the intradental nerve fibers are essential preconditions in the nature of pain sensation; therefore, intradental nerve activity (INA) is a key elements involved in occurrence of pain. In addition, many factors could affect the activity of intradental nerve.

2.2.1. *Mechanical stimulus*

Most of A fibers respond to mechanical stimuli, such as probe, blow, and drill on surface or deep in dentin, von Frey hairs applied to pulp directly. However, the



(a) (b)

Fig. 3. The projection of pain in different areas of nerve system.[62]

response of C fibers to mechanical stimulus are different with A fibers, only parts of C fibers react to the stimuli applied to deeper dentin and pulp.[63]

2.2.2. *Thermal stimulus*

The response of pulp nerve to thermal stimuli was biphase: the A fiber could be activated immediately by heat stimuli, but only when the temperature of pulp increased to 43.8°C by continuous heat, the C fibers could be excited. The experimental results were coincided with the clinic observation. Stimulations applied to the exposed dentin, such as blowing with hot air, drilling or probing, hyperosmotic solution, and thermal stimulation, would result in a pain sensation. In common, the acute sharp pain was evoked by the stimulation associated with movement of tubular fluid in dentin, obscure and dull pain was usually evoked by thermal stimulation (especially by heating).[37,64–67]

2.2.3. *Electrical stimulus*

In animal experiments,[68] electrical stimulus is often used widely in evoking the acute pain sensation. The CV can be calculated by 1-ms (duration) square wave, and the pain threshold can determine by 10-ms (duration) square wave. The threshold of A and C fibers in pulp of feline was $8.4-13.5\,\mu$A and $37.4-40.4\,\mu$A, respectively.

2.2.4. *Chemical stimulus*

The tooth pain induced by chemical stimulus was often happened associated with dental caries.[37,64,67] CARIES is a kind of localized damage in the surface of tooth induced by decalcification of the enamel due to enzymatic lysis of organic structures.

The caries can involve the enamel, dentin and even pulp, and some bioactive matters such as ammon, indole, and carbonylamines could excite the intradental nerve and induce tooth pain.[69]

2.2.5. *Drugs or medical treatment*

Fluoride usually was applied to relieve the pain induced by dental hypersensitivity in clinic; many studies[70−73] showed that the fluorion could decrease the diameter of dentine tubulus. Phenols[74−77] can denature and deposit the proteins in tubulus, block the tubular fluid movement, and attenuate the dental hypersensitivity. Potassium can reduce the pain induced by hypersensitivity through deactivating the excitability of sensory nerve ending; in some papers, it was observed that potassium blocked the tubulus in dentine.[78−80]

In clinic, the laser was also approved to deal with the dental hypersensitivity and relieve the pain of patients. There were five types lasers used widely, Nd:YAG,[81−83] CO_2-,[16] He-Ne,[84−86] CaAlAs semiconductor,[87−89] and Er:YAG.[90−93]

Nd:YAG, CO_2, and Er:YAG lasers have the same mechanism in the treatment of the pain or dentinal hypersensitivity. The laser denatured the organic substance, melted the mineral, sealed the tubulus, and desensitized the dentine. However, the mechanism of CaAlAs semiconductor[94−96] and He-Ne laser involved in the treatment were not clear; the possible explain was that the low-level laser could alter the ion permeability of neuron cell/fiber membrane to potassium and sodium and increase the threshold of excitation of nerve ending. Low-level laser also can improve the micro-circulation suggested in some studies.[97−100]

2.2.6. *The hypersensitivity of dentine*

The dentine hypersensitivity is a relatively common pathological condition due to tooth defect, which is characterized by short and sharp pain when thermal, tactile, osmotic, evaporative or chemical stimulus were applied to the exposed dentine.[101−104] In dentine hypersensitivity, appropriate stimuli can trigger pulpal nerves to generate a typically sharp, short pain response via special mechanisms, which include three major theories for pulp nerves activation[105,106] (see Fig. 4). In addition, Brannstrom's hydrodynamic theory was accepted widely,[107−110] in this theory, the pain is induced by the movement of fluid in dentinal tubules.

3. Tooth Pain Under Thermal Stimulation

3.1. *Dynamic temperature change in tooth*

Resting mouth temperature (intraoral temperature), with no mouth breathing and no thermal loading, has been measured at 35.2 ($\pm$2.1)°C,[111] and as "approximately" 35°C.[112] The temperature of outer surface of teeth have been measured

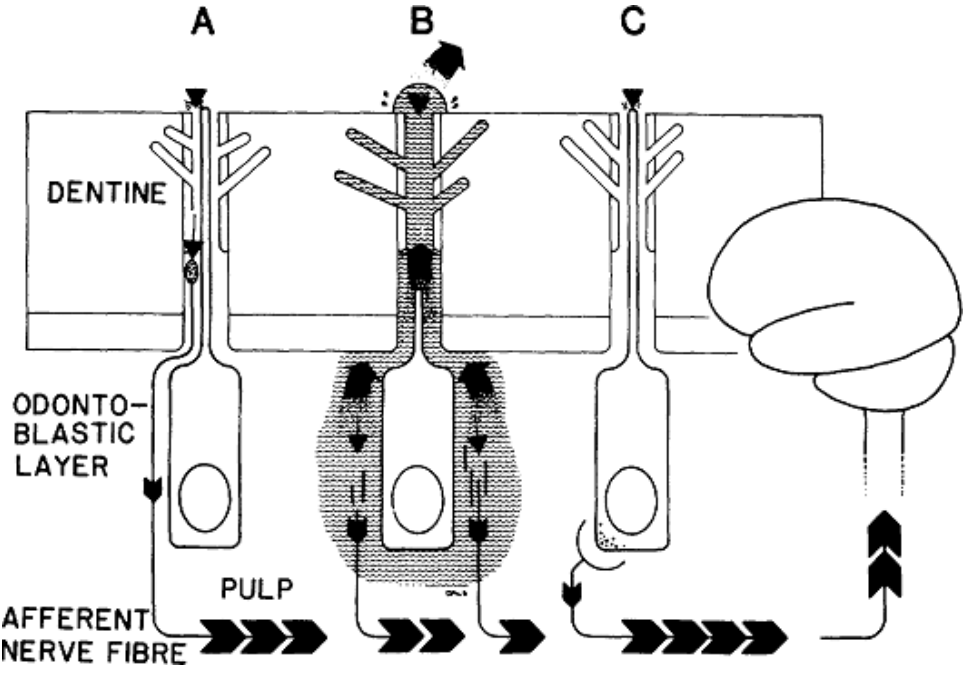


Fig. 4. The three major theories for activation of dental nerve fibers.[106] (A) the conduction theory, (B) the hydrodynamic theory, and (C) the transduction theory.

or thermocouples during by thermistors intake of hot and cold drink in previous research[112−117] (Table 3).

In early stage, temperature in pulp was not easy to measure until the equipments were designed by some researchers[118] (Fig. 5). In experiment on dog teeth, the pulp nerve had no response to thermal stimulus when temperature in oral cavity or enamel was lower than 15°C or higher than 50°C, in spite of pulp nerve was more sensitive to the temperature ranges. The temperature ranges that could evoke the pain sensation effectively and not occur irreversible tooth damage were

Table 3. Temperatures recorded at the tooth surface.[203]

Location	Volume drunk (ml)	Hot liquid temp. (°C)	Max. tooth temp. (°C)	Cold liquid temp. (°C)	Min. tooth temp. (°C)
Incisor labial	/	60	45	0	15
Incisor palatal	/	< 61	58.5	/	/
Molar occlusal	/	< 61	53.1	0	1.0
	/	63.5	53.5	/	/
	/	58	50	/	/
	/	55	47	/	/
Molar palatal	/	60	48.5	/	/
	30	60	44.86	0	21.63

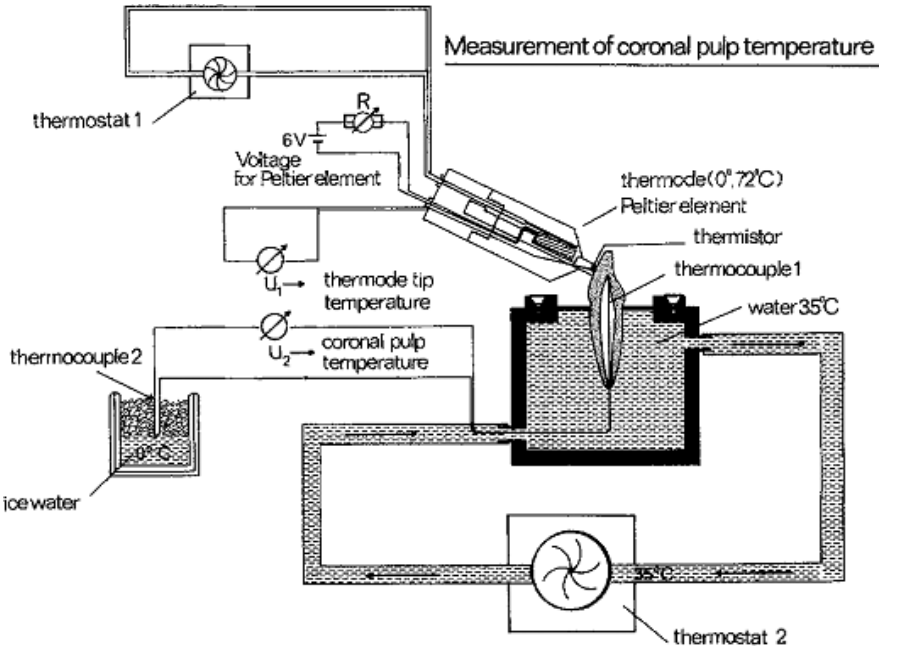


Fig. 5. Schematic diagram showing the setup for measuring the intrapulpal temperature changes in a freshly extracted human tooth.[118]

0 −5°C or over 50°C (lasting time < 15 s). When 55°C high temperature stimulation was applied to surface of tooth, the pulp temperature was 44°C in 3 s, 48°C in 5 s, 50°C in 7 s, and 52°C in 12 s. In addition, 0°C was given to surface of tooth, the pulp temperature was 22°C in 3 s, 14°C in 5 s, 10°C in 7 s, and 7°C in 12 s.

In Linsuwanont's[22] study, fine J-type thermocouples placed in different layers of tooth (the surface of enamel, the DEJ and pulpal wall) were used to detect the temperature change after thermal stimuli applied at surface of tooth, namely, hot water (80°C), cold water (2−8°C), and carbon dioxide dry ice (−72°C). From the results (Table 4), we can find temperature change at the DEJ was detected more quickly than at the pulpal wall (1.17–1.77 s vs. 4.15–5.81 s). In terms of response time, hot water tended to be the strongest stimulus, dry ice does not seem to be a stronger stimulus than iced water at the DEJ and pulpal wall, but dry ice changed the temperature greater than iced water in DEJ and pulpal wall.

3.2. *Dental fluid shift and pain response*

Dental fluid measurement was settled up by many investigators.[119−121] The Flodec device[22,121,122] was designed to observe the movement of fluid in dentinal tubules

Table 4. The temperature change at the DEJ and pulpal wall during thermal stimulation.[22]

Thermal stimuli	Dentino-enamel junction			Pulp wall		
	Initial response time (s)	Time to max. temp. (s)	Max. temp. change (°C)	Initial response time (s)	Time to max. temp. (s)	Max. temp. change (°C)
Hot water (80°C)	1.17 (0.19)	10.06 (2.41)	27.35 (6.34)	4.15 (1.16)	26.69 (3.74)	16.83 (1.69)
Dry ice (−72°C)	1.77 (0.64)	12.275 (2.04)	24.86 (8.54)	5.81 (1.10)	30.51 (4.45)	13.50 (2.16)
Iced water (2°C)	1.57 (0.32)	11.75 (3.05)	8.41 (1.75)	5.51 (1.17)	30.6 (5.27)	5.53 (1.15)

and was an effective tool to detect fluid flow in extracted human teeth and dentine (Figs. 6 and 7). In Linsuwanont's investigation, the movement of fluid were two patterns:

(1) In the first second after the heat stimulation, the direction of fluid flow was in same with the hydrodynamic theory, heat causing inward movement and cold provoking outward movement (toward the pulp).
(2) The bidirectional movement of fluid flow were observed in almost 60 percent of the teeth. Hot stimulation induced a small outward fluid movement firstly (after approximately 0.6 s), and then a large inward flow (approximately 1.0 s)

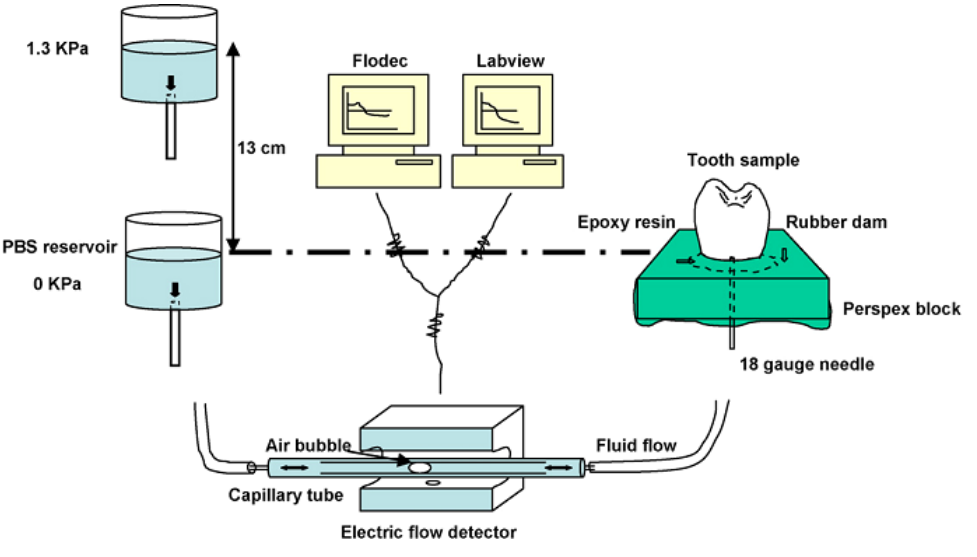
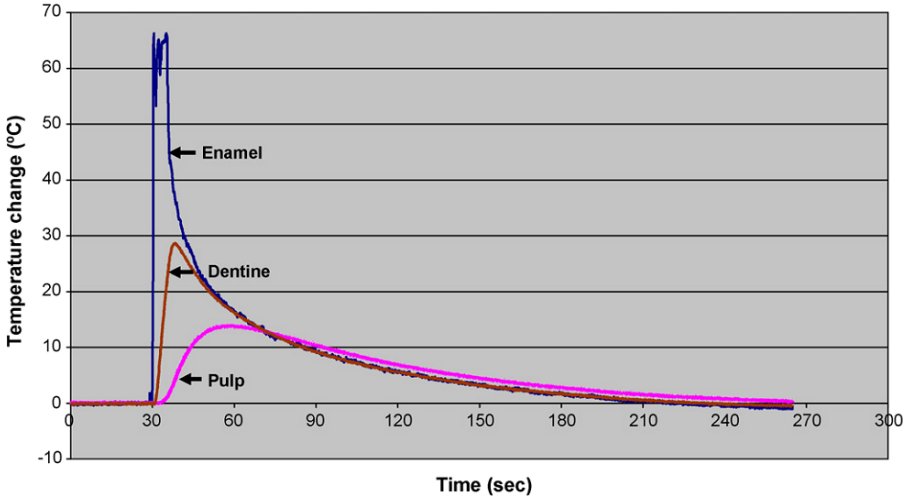


Fig. 6. Diagram showing the experimental setup for dentinal fluid movement measurement during and after thermal stimulation, using the Flodec device.[22]



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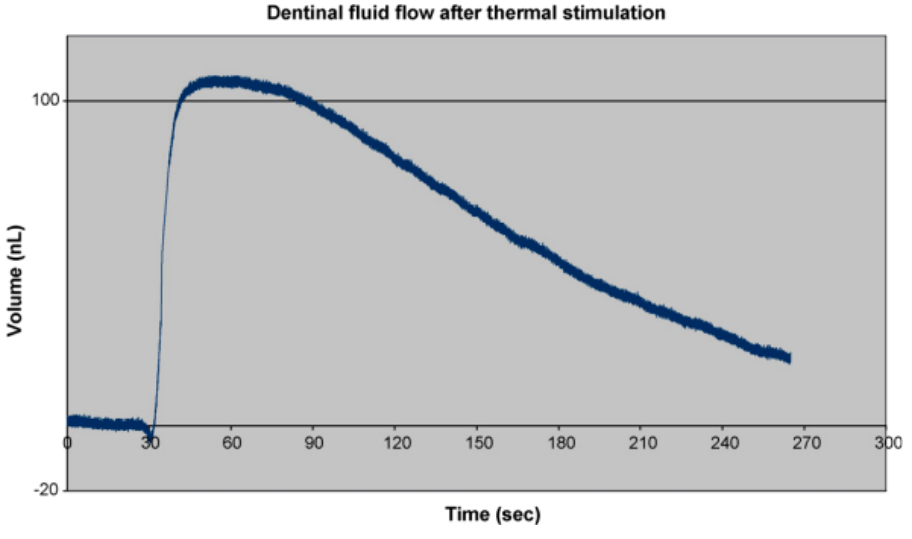
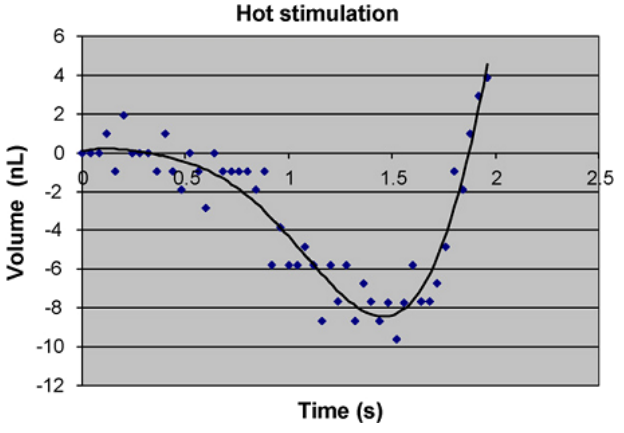


(b)

Fig. 7. Temperature change at enamel, dentino-enamel junction, and pulpal wall after hot stimulation (temperature = 80° C, duration = 5 s). (b) Dentinal fluid flow after hot stimulation.[22]

(Fig. 8(a)). And the cold stimulation induced a small inward fluid movement preceded the main outward flow (Fig. 8(b)).

In Matthews's[123] research, thermal stimulation (55°C and $0-5$°C, 15 s) was applied to the lower canine tooth in dogs. In 117 pulp fibers of 17 dogs, only 43 units responded to cooling but not to heating and nine units responded to heating



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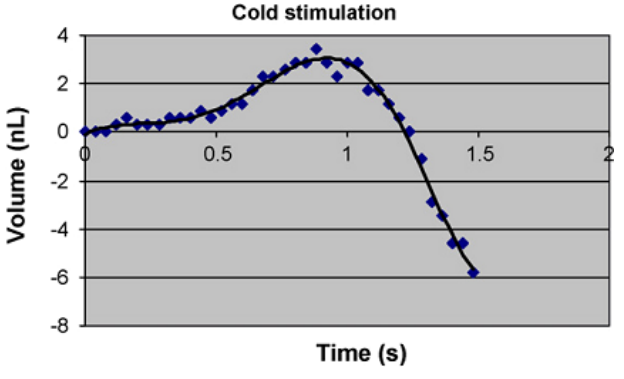
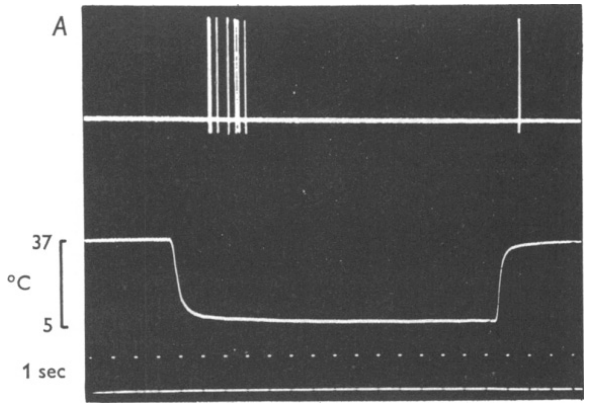


(b)

Fig. 8. The initial movement of fluid was studied by a fine capillary tube during heat and cold stimulation (80 and −72 degree). In 0.5 s after heat stimulation, outward fluid movement followed with inward fluid was observed. On the contrary, cold stimulation induced inward fluid movement before the outward fluid flow.[22]

but not to cooling (Fig. 9). Some studies[37,124] carried on mechanisms involved in pain induced by cold stimulation applied to dentine shown, individual pain VAS was increased obviously after exposed dentine was stimulated by lower temperature, but on the contrary, the rates of fluid movement in tubulus was decreased.

Other researchers[122,125,126] compared the direction, rate of fluid movement in dentinal tubule, and discharges from intradental afferent fibers under different pressures applied (positive pressure vs. negative pressure, different directions) (Figs. 10 and 11). They found that the outward fluid flow (equal to negative pressure) triggered intradental afferents more easily than inward fluid flow (equal to positive pressure) through the dentinal tubules (Fig. 12).



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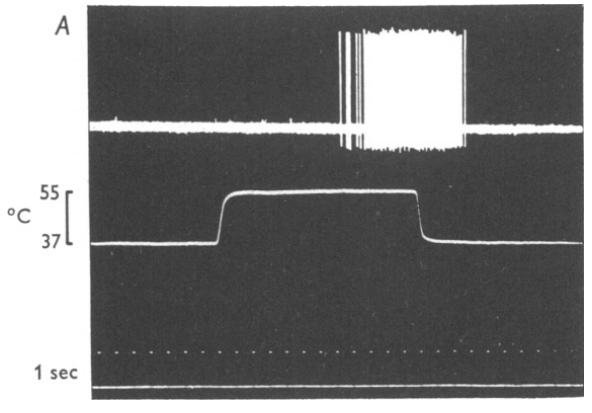


(b)

Fig. 9. (a) Response of a single pulpal fiber to a 15-s cold stimulus. (b) Response of a single fiber to a 12-s hot stimulus.[123]

3.3. *Thermal stress of tooth*

The thermal stimulation applied to tooth not only evoked the pain sensation, but also induced enamel damage by extreme hot (cold) food or fluids. The destruction of tooth would weaken the capability of anti-external force and elicit pain response easier than normal condition.

Previous experimental studies *in vitro*[127−129] demonstrated that crack initiation and growth occur in the enamel when teeth are subjected to sudden and repeated fluid temperature changes. The extent of the damage is correlated with the environment temperature and the thermal resistance between the medium and the tooth.[128] In addition, geometry of tooth, age, material properties of the tooth, the thermal conductivity coefficient, and thermal resistance (Table 5) between the tooth and

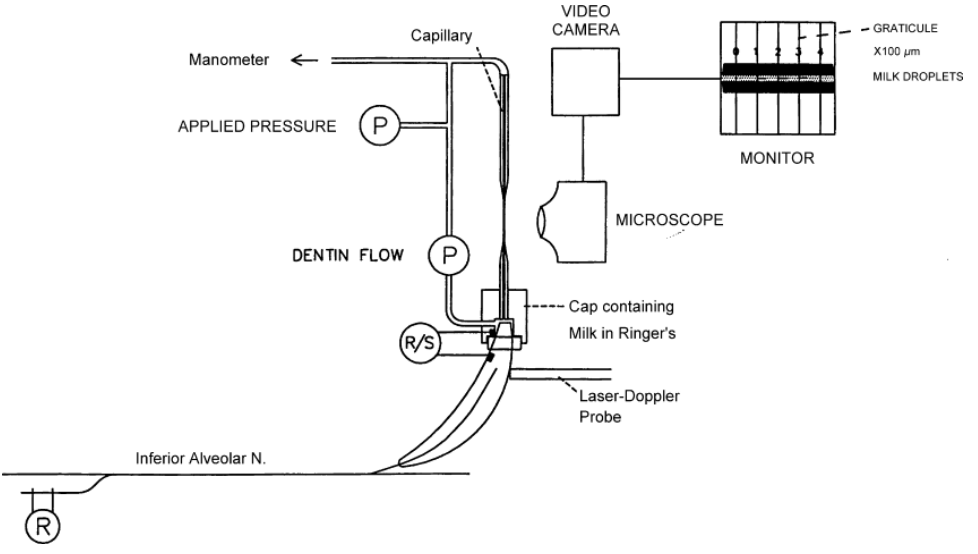
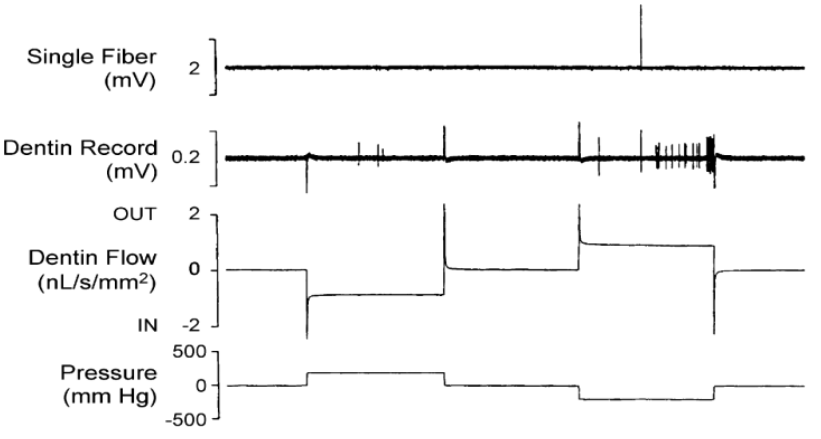
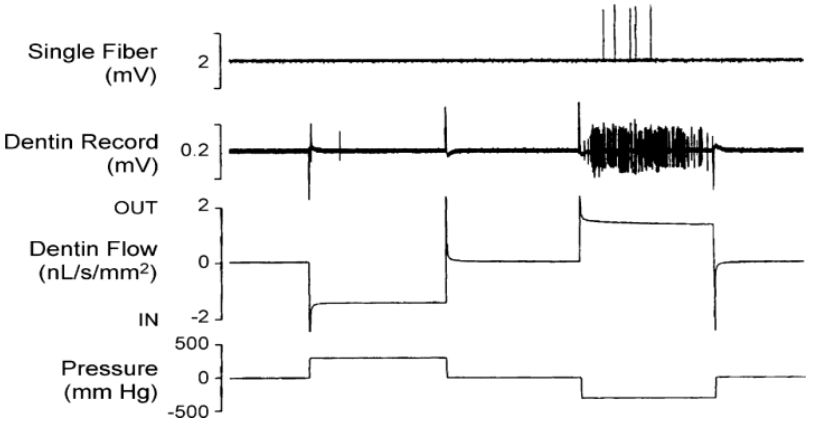


Fig. 10. Diagram of the preparation. The transducers (P) were used to record the pressure change and the electrodes (R/S) were used to record the activity from intradental nerves and to stimulate the intradental nerves.[122]

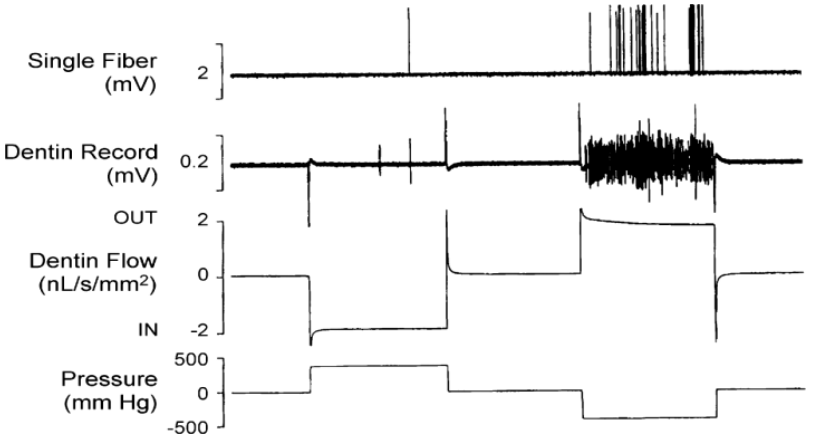


(a)

Fig. 11. The responses of intradental nerves were evoked by fluid flow through dentine when negative and positive pressures were applied to exposed dentine.[204]



(b)



(c)

Fig. 11. (*Continued*)

the medium surrounding the tooth[22,118,127,130] would contribute the thermal stress in teeth. Average crack growth is shown in (Fig. 13).

3.4. *Mechanism involved in thermal tooth pain*

The thermal stimuli could evoke tooth pain sensation effectively. However, there are still many unclear points are eager to be answered. For example, was the excitation of intradental nerve endings mediated by thermo-gated channel (CMR1, VR1,[131] VRL-1[132]) or mechano-gated channel (DEG/ENaC,[133] P_2X_3 and $P_2Y^{134-137}$) even or both during thermal stimulation? Were chemically gated channels involved in? Can we quantify the input (thermal stimulation) and output (the pain response)? And, how to do that? Obviously, the exploration of above should carry on

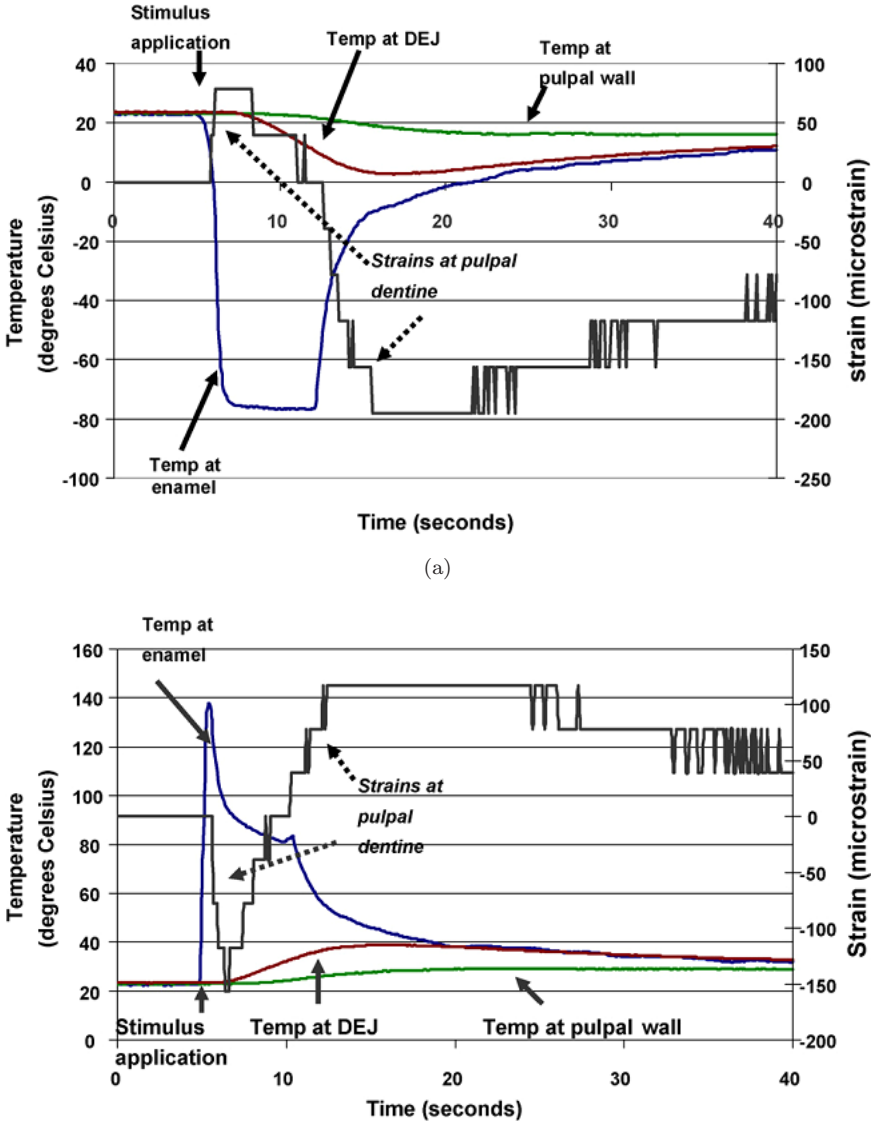


Fig. 12. Relationship between temperature changes in different layers (the enamel, dentinoenamel junction and pulpal dentine) and strain changes at pulpal dentine during and after the application of heat (a. heated gutta percha) and cold(b.carbon dioxide dry ice) stimulation. A positive value represents a tensile strain and a negative value represents a compressive strain.[139]

multi-discipline and inter-discipline research, neurobiology, thermal thermodynamics, hydrodynamics, mechanics, neurophysiology, etc. are involved in the future. We try to clarify and consummate the mechanism of tooth pain induced by thermal stimulus.

Table 5. Material properties of enamel and dentin.[125]

Material	Modulus of elasticity, "E" ($\times 10^6$ psi)			Poisson's ratio, "v"	Coefficient of thermal expansion, "α" ($\times 10^{-6}$/°C)		Thermal conductivity, "k" ($\times 10^{-3}$ cal/s cm°C)		Density, "p" (gm/cm^3)		Specific heat, "c" (cal/gm°C)		Thermal diffusivity, "k/pc" ($\times 10^{-3}$ cm^2/s)	
	Compressive	tensile												
Enamel	1.8−8.2						2.23		2.8		0.17		4.69	
	1.4−9.1		6.7	0.25	12.0	12.0	1.56	2.23	2.84−2.87	2.8	0.18	0.17	4.20	4.69
	11.3−12.2						2.2		2.96					
Dentin	2.2	2.8					1.36−1.39		1.96		0.38		1.83−1.87	
	2.4−2.7	0.55−3.15	1.7	0.25	7.5	7.5	0.96−1.07	1.36	2.11	1.96	0.28	0.38	2.60	1.83
	1.7 − 2.4						0.257							
							1.5							
							2.29							

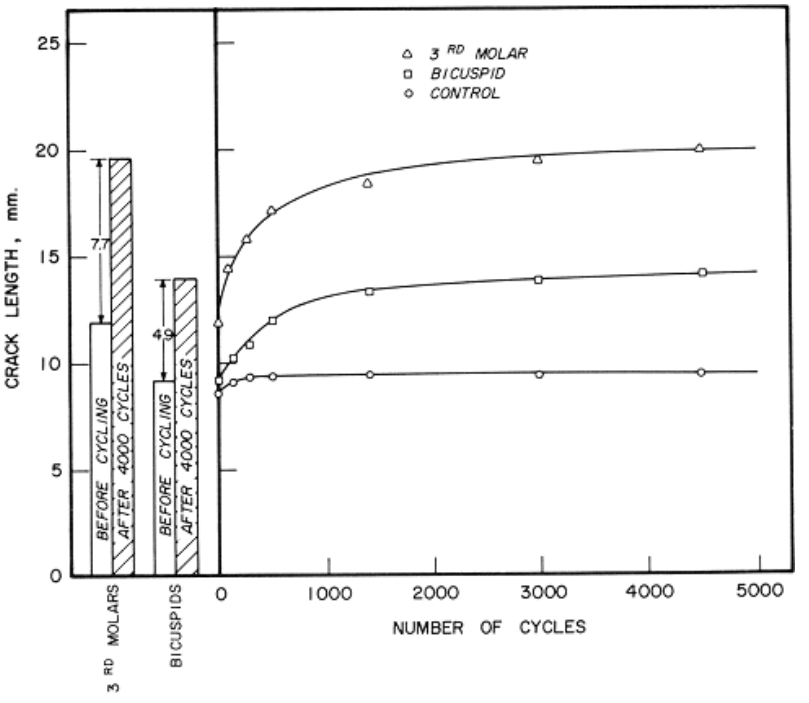


Fig. 13. Average crack growth in third molars (average age 20.4, 24 samples, △) and bicuspids (average age 13.2, 43 samples, □) subjected to thermal cycling with a temperature differential of 28°C (each cycle 30 s at 52°C and 30 s at 24°C).[125]

After a survey of the related literature, we review the whole course of thermal tooth pain which could be divided into four procedures as following:

(1) Thermal energy was transferred from enamel to dentine and induced the fluid movement in tubulus; the intradental nerve was excited by hydrodynamics.[112,113,136–138]
(2) The deformation[139–141] in structure (dentine) of tooth under thermal stress was equal to mechanical stimulation and the corresponding ion channels in pulp nerve fibers could be activated and pain response was evoked.[124,142,143]
(3) The temperature in pulp was changed out of normal range, the thermo-TRP channels (TRP, TRPM8, and TRPA1) were probably excited directly by thermal stimulation.[63,123,144,145]
(4) Inflammation[146] will initiate after the heat stimulation, which is characterized by pro-inflammatory cytokine or inflammatory factors released from cell or tissue, associated with algesic substance, such as H^+, histamine,[147] NOS/NO,[148] bradykinin,[149,150] serotonin, and prostaglandin E_2,[149,151] and Interleukins.

Some studies[152,153] have found that inflammation could increase sodium currents and improve the excitability of sensory nerve fibers by decreasing tetrodotoxin

(TTX)-sensitive Na^+ conductance. The inflammation can increase the expression of calcitonin gene-related peptide (CGRP),[149,154] substance P,[155] *N*-methyl-*D*-aspartic acid (NMDA) or a-amino-3-hydroxy-5-methyl-4-isoxa-zolep-propionate (AMP) receptors,[156] neuropeptide Y,[157] which induced pain sensation by neurogenic inflammation. The neuroinflammatory interactions were very complex and involved in pain sensation.[30]

4. Mathematical Modeling of Tooth Thermal Pain

In clinical research, the pain sensation is always regarded as the most important symptom and sign. However, in animal experiments, the pain is a special response of nerve system to noxious stimulation, such as tail-flick and avoidance behavior. How can we handle or quantify the objective "sensation" in clinic treatment or research without harm or invasion to subjects? The answer is the utilization of computational models. In addition, several mathematical models based on the molecular level, cellular level, and network of neurons have been developed.[158−162] However, only in our previous papers,[163−169] a holistic pain model has been developed considering the microstructure and biothermomechanical response of biological tissue.[170−176] This holistic model also correlates the stimulus parameters with the pain sensation level (represented by frequency of AP),[177] and the transmission process has been considered.

The modeling of thermal tooth pain will be based on and followed the computational models of skin thermal pain from Xu *et al.*[163−165] For simplicity, Xu's study attempts to model acute pain evoked by superficial nociceptive stimulus (chronic and neuropathic pain are not considered). The holistic model proposed by Xu is composed of 3 submodels: transduction model, transmission model, perception and modulation model, as schematically shown in Fig. 14.

4.1. *Model of transduction*

The transduction model is composed of three sub-models according to the mechanism of nociceptor transduction: biothermomechanical model, current generation model, and frequency modulation model.

4.1.1. *Biothermomechanical model*

As we know that pain intensity induced by heat is decided by the temperature excited the nociceptor effectively not the temperature applied to the surface of tissue.[178,179] Besides, thermal damage and thermal stress can activate and sensitize nociceptors.[180] Therefore, more pain could be evoked by a heat stimulus than a mechanical stimulus, and the tissue deformation induced by heating or cooling may be involved in the generation of pain.[181,182] The thermal stress generated by heat stimulation may surpass the threshold of nociceptors excited only by mechanical stimulation.

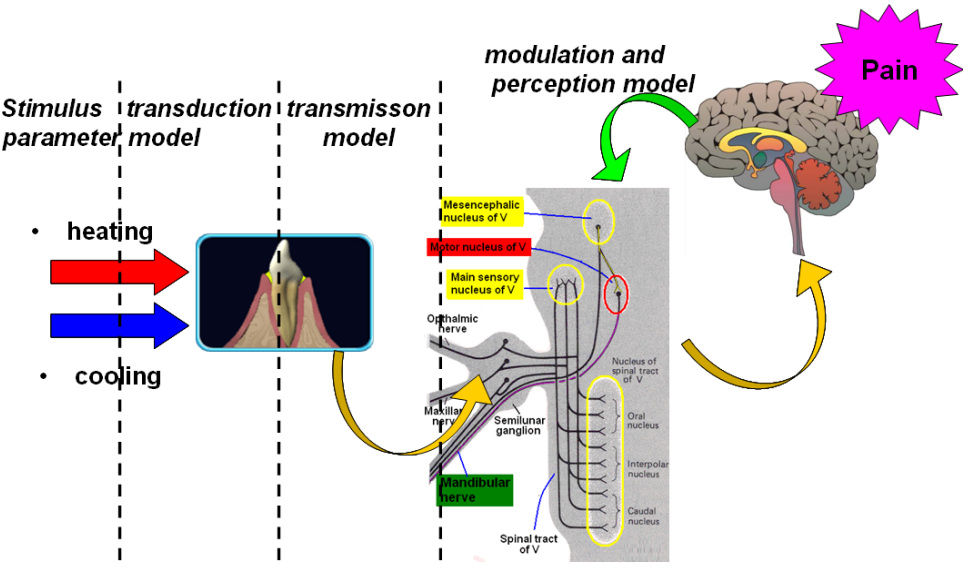


Fig. 14. The schematic diagram of tooth thermal pain pathway.[165]

As for multi-layered bio-tissue Pennes equation is often applied to represent the process of heat transfer given as:

$$\rho c\frac{\partial T}{\partial t} = k\frac{\partial^2 T}{\partial z^2} + \varpi_b \rho_b c_b (T_a - T) + q_{\text{met}} + q_{\text{ext}}, \tag{1}$$

where ρ, c, and k are the density, specific heat, and thermal conductivity of tooth, respectively; ρ_b and c_b are the density and specific heat of blood, ϖ_b is the blood perfusion rate of pulp; T_a and T are separately the temperatures of blood and tooth; q_{met} is the metabolic heat generation in tissue, and q_{ext} is the heat source due to other heating.

Then, if the temperature distributions have been obtained, the thermal stress (σ_k) and the thermal damage (Deg(t)) could be calculated by the following equation,[183,184]

$$\sigma_k = \overline{E}_k \left\{ \begin{array}{l} -\overline{\lambda}_k \Delta T + \left[\begin{array}{l} C_1(1+\nu_k)\left(\sum_{i=1}^{M}\int_{z_{i-1}}^{z_i} \overline{E}_i\overline{\lambda}_i \Delta T dz\right) \\ \quad + C_2(1+\nu_k)\left(\sum_{i=1}^{M}\int_{z_{i-1}}^{z_i} \overline{E}_i\overline{\lambda}_i \Delta T z dz\right) \end{array} \right] \\ + z(1+\nu_k)\left[\begin{array}{l} C_2\left(\sum_{i=1}^{M}\int_{z_{i-1}}^{z_i} \overline{E}_i\overline{\lambda}_i \Delta T dz\right) \\ \quad + C_3(1+\nu_k)\left(\sum_{i=1}^{M}\int_{z_{i-1}}^{z_i} \overline{E}_i\overline{\lambda}_i \Delta T z dz\right) \end{array} \right] \end{array} \right\}, \tag{2}$$

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

$$\mathrm{Deg}(t) = 1 - \exp(-\Omega(t)),$$

where, $\overline{E} = E/1 - \nu^2, \overline{\lambda} = \lambda(1 + \nu), E$ is the Young's modulus, ν is the Poisson ratio, λ is the thermal expansion coefficient and C_1, C_2, and C_3 are constants the thickness of decided by different layers of special of tissue, t is the heating time, A is a material parameter, E_a is the activation energy, and R is the universal gas constant.

However, tooth is small white hard tissue, with height about 23 mm and diameter about 11 mm (human molar).[185] Tooth has a composite structure of complex geometry containing enamel, dentine, cementum, and dental pulp,[186] (Fig. 1). Both the mechanical and thermal properties of teeth structures are different in each layer, and are anisotropic and nonhomogeneous.[187,188] Therefore, it is not proper to treat tooth as an infinite multi-layer plate and use Eqs. (1) and (2) to calculate the temperature and thermal stress distributions. In view of this point, 3D finite elementary methods (FEM) were employed to analyze the biomechanical behavior of tooth structure,[139,189–192] which make it more practical to achieve temperature and thermal stress distribution from engineering viewpoint.

4.1.2. *Model of current generation*

When different stimuli (thermal, mechanical, and chemical) were applied/transferred to nociceptors, the ion channels were opened and generated corresponding currents. The total current may be calculated as:

$$I_{\mathrm{st}} = I_{\mathrm{heat}} + I_{\mathrm{chem}} + I_{\mathrm{mech}}, \tag{3}$$

where $I_{\mathrm{heat}} = f_h(T_n, T_t), I_{\mathrm{chem}} = f_c(\mathrm{Deg})$ and $I_{\mathrm{mech}} = f_m(\sigma_n, \sigma_t)$ are the currents due to the opening of thermally, chemically, and mechanically gated ion channels,[163,184] respectively.

The heat current (I_{heat}) is a function of nociceptor temperature (T_n) and thermal pain threshold (T_t). The chemical current (I_{chem}) is assumed to depend on the thermal damage degree (Deg). The mechanical current (I_{mech}) is assumed to be a function of the stress at the location of nociceptor (σ_n) and mechanical pain threshold (σ_t).

4.1.3. *Model of frequency modulation*

AP is characterized by "all" or "none," and the frequency of these impulses (f_s) depends on the intensity of external stimulation. On the other hand, the frequency not the shape or magnitude of the signal represents the intensity the pain sensation, which can be calculated as:

$$f_s = f_{\mathrm{fm}}(I_{\mathrm{st}}). \tag{4}$$

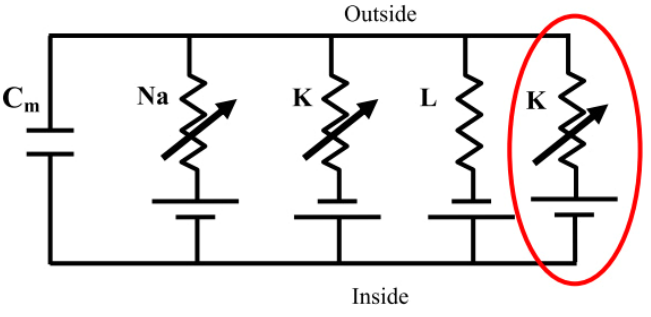


Fig. 15. Revised Hodgkin and Huxley model.[163]

In order to quantify the current–frequency relationship, Hodgkin-Huxley (H-H) model[193] was chosen. The original H-H model was developed based on data from squid axon, but many H-H models have been modified for modeling pain sensations, such as mechanical[194−198] and thermal pain sensations.[199,200] The H-H-form model is used here to model the frequency modulation of nociceptors. The membrane potential in the basic H-H model can be represented by the network shown in Fig. 15. Mathematically, the model can be described as:

$$C_m \frac{dV_m}{\mathrm{dt}} = I_{\mathrm{st}} + I_{\mathrm{Na}} + I_{\mathrm{K}} + I_{\mathrm{L}} + I_{\mathrm{K2}}, \tag{5}$$

where V_m is membrane potential (depolarization positive) (mV); t is time (ms); C_m is membrane capacity per unit area (μF/cm^2; I_{st} is stimuli-induced current density, positive outward (μA/cm^2; and I_{Na}, I_{K}, and I_{L} are sodium, potassium, and leakage current components (μA/cm^2, respectively. While I_{K2} is an additional current for the second potassium channel. The parameters of these current model can be found in our works.[163,165]

4.2. *Model of transmission*

The model of transmission is to simulate the transmission of bioelectric signals triggered by noxious stimulus from the primary sensory fibers to the spinal cord and brain. The time for this transmission (t_t) will be obtained according to the CV and corresponding nerve length. The same simplification process in papers[163−165] can be implemented here to calculate the transmission time.

4.3. *Model of modulation and perception*

The signal is modulated at spinal level before pain sensation is perceived, where gate control theory (GCT)[201] is used to describe the modulation and perception process of thermal pain.

4.3.1. *Gate control theory (GCT)*

GCT (Fig. 16(a)) was proposed by Melzack and Wall in 1965. The small (C, A-δ) fibers carry information about noxious stimuli and the large (A-β) fibers carry information about mechanical stimuli. As the signal from the (C, A-δ) fibers is routed through substantia gelatinosa (SG) to central transmission (T) cells and onwards, the double inhibition (indicated by the minus signs) actually strengthens the signal and pain sensation is more easier evoked. However, the signal from the

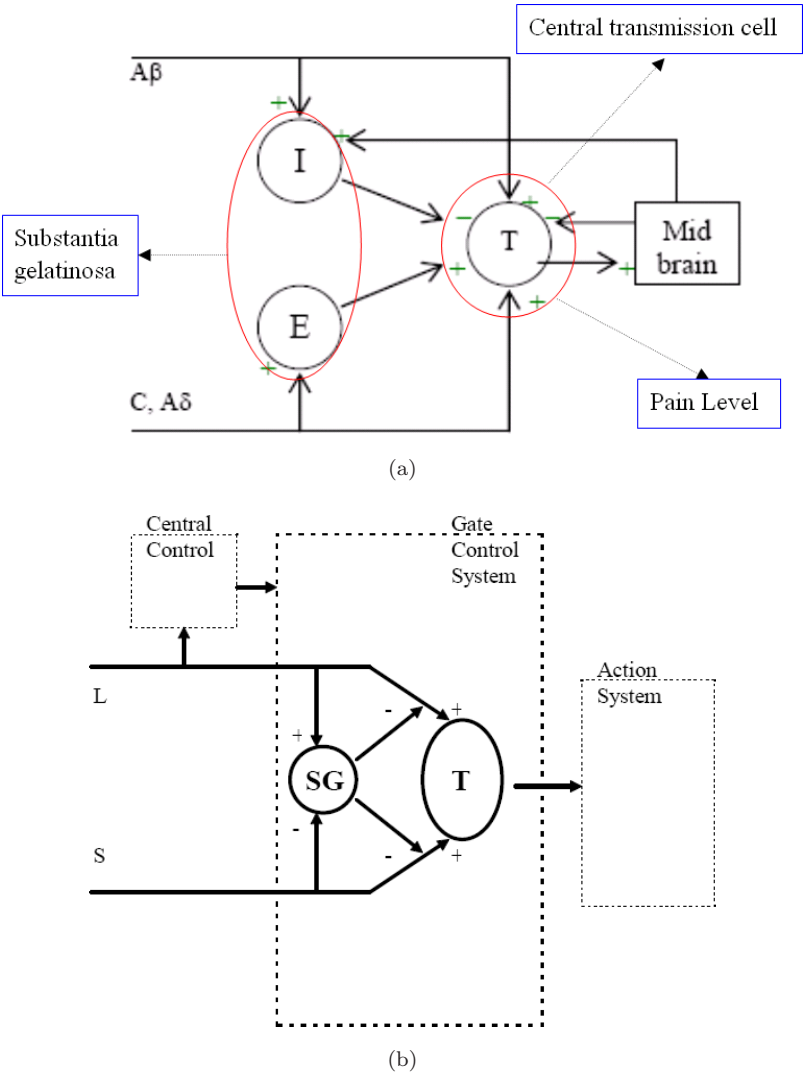


Fig. 16. The schematic of the GCT[163,164]: (a) basic schematic of the GCT and (b) that used in the mathematical model of pain.

A-β fibers activates the inhibitory function of SG, which will reduce the firing to transmission (T) cells and suppress the pain finally.

4.3.2. *Mathematical model*

The GCT (Fig. 16(b)) has been used to extrapolate the relevant features and translated into a mathematical model by Britton and Skevington.[159–161,189] The mathematical description of GCT is given as:

$$\tau_i \dot{V}_i = -(V_i - V_{i0}) + g_{li}(x_l) + g_{mi}(x_m), \tag{6}$$

$$\tau_e \dot{V}_e = -(V_e - V_{e0}) + g_{se}(x_s, V_e), \tag{7}$$

$$\tau_t \dot{V}_t = -(V_t - V_{t0}) + g_{st}(x_s) + g_{lt}(x_l) + g_{et}(x_e) - g_{it}(x_i) - g_{mt}(x_m), \tag{8}$$

$$\tau_m \dot{V}_m = -(V_m - V_{m0}) + g_{tm}(x_t), \tag{9}$$

where subscripts i, e, t, and m stand for inhibitory SG cell, excitory SG cell, T-cell, and midbrain, respectively; τ_j is the time constant, V_j is membrane potential; V_{j0} is initial membrane potential; x_j is the firing frequency; x_l and x_s are signals (frequency) from large and small fibers, respectively; the functions g_{jk} represent the effects of the inputs (j) to a cell (k) on its steady state slow potential.

The firing frequency x_j at which the cell fibers is a function of its slow potential, so that $x_j = f(V_j)$, given as:

$$f(V_k) = \left[\mathrm{K}\frac{(V_k - V_{\mathrm{thr}})}{(-V_{k0})}\right] H(V_k - V_{\mathrm{thr}}), \tag{10}$$

where H is the usual Heaviside function, K is a constant, and V_{thr} is the firing threshold potential (taken as $-55\,\mathrm{mV}$). All the parameters can be found in Britton and Skevington's work.[159–161,202]

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 ($V_t \geq -55\,\mathrm{mV}$) then the noxious signal is transmitted to the next relay point. If the noxious signals reach the cortex, then they are perceived as pain.

The mathematic model of tooth thermal pain is composed of three interconnected parts: (i) peripheral modulation of noxious stimuli, which converts the energy from a noxious thermal stimulus into electrical energy via nerve impulses; (ii) transmission, which transports these neural signals from the site of transduction in the nociceptor to the spinal cord and brain; and (iii) modulation and perception in the spinal cord and brain.

The model is vadilated in descripting the essential features of nerve discharges responsed to stimulation in experiments. Using the model, the levels of pain evoked by thermal stimulus can be predicted in terms of the properties of the noxious stimulation. So in clinical practice, a given thermal diagnosis or treatment can be determined how discomfortable or painful (or not) it will become. The mechanism

of tooth thermal pain can be better understood and some features of pain sensation can be explained.

5. Conclusions

In dental clinic, the operations during diagnose and treatment would generate lots of heat, such as laser, light-cure, and high-speed rotary instruments. When thermal loading is applied to the tooth, not only tooth states, including temperature, stress–strain distributions, etc. would change, but also subjects' pain sensation would be evoked through different mechanisms.

In this paper, we summarized the underlying mechanisms involved in thermal tooth pain from current literature, including neurobiological mechanism, such as activation of the related receptors or channels in neurons, biochemical mechanism, such as inflammation in pulp tissue, and physical mechanism, such as temperature change, hydrodynamics, and biothermomechanics under thermal stress.

And then, we try to describe the processes of tooth pain under thermal stimulation through mathematic modeling methods based on the neurophysiological mechanisms of pain after making full considerations of bioheat transfer, deformation, stress–strain distributions, and crack generation of tooth. Finally, we conclude that thermal is tooth pain is a multidisciplinary field which involves neurobiology, neurophysiology and biomechanics.

How to protect dental tissue and relieve thermal pain effectively become more serious for both physicians and patients, further refinement of current medical treatments and innovation in medical instruments require a comprehensive understanding of this interdisciplinary area. We hope to build a multiscale model for quantifying thermal tooth pain by coupling the concepts of engineering with the established methods in neuroscience. Not only the neurophysiological mechanisms of tooth pain, but also the corresponding thermal and thermomechanical behaviors of teeth were taken into consideration during the procedure of modeling. The mathematic model of tooth thermal pain can contribute to understanding and supplement of thermal pain mechanism and to refinement of diagnosis and treatment in dental clinic.

5.1. *Future work*

The primary objectives of current study are to understand and to couple the underlying mechanisms of tooth biothermomechanics and thermal pain. In order to obtain comprehensive information in this area, experiments, numerical simulations, and theoretical analysis have already been carried out. The detailed objectives for current research are:

- To design and build experimental systems for studying tooth thermomechanical behavior and to obtain suitable data to describe the tooth thermomechanical behavior.

- To develop a holistic model of tooth thermal pain based on neurophysiological experiments and to explain some physiological features of tooth thermal pain sensation according to the present understanding.

Acknowledgment

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