NMDA Receptors, Wind-Up and the Gate Control Theory of Pain - a Mathematical Model

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Abstract

We present a mathematical model which is an extension of that of Britton and Skevington (1989) for the gate control theory of pain (Melzack and Wall, 1965, 1982). The variables of the model are the electric potentials of various cells in the midbrain and the spinal cord, such as T-cells and inhibitory and excitatory cells of the substantia gelatinosa (SG). The original model simulated many of the phenomena observed in acute pain in humans, but not that of wind-up (Mendell, 1966). In retrospect this is not surprising, as it did not include the NMDA receptors that are now recognised to be crucial to the phenomenon. Here we rectify this omission, and obtain good agreement of the model with experimental data on wind-up. The positive feedback that NMDA receptors exhibit is shown to be the essential feature in producing wind-up. As an independent test of the model we simulate a completely different experimental set-up, and obtain good qualitative agreement with data there. Finally, we present a prediction of the model that is yet to be tested experimentally.

1. Introduction

We begin with a brief description of the neurophysiological mechanisms which cause pain to be experienced and inhibited. In the skin, muscles, joints and some viscera are certain receptors attached to nerve fibres. Following Britton & Skevington (1989), we shall concentrate on cutaneous sensation. When the receptors are stimulated nerve impulses travel along the nerve fibres to various systems in the spinal cord of which we shall concentrate on two. The first of these systems is the substantia gelatinosa (SG) which is situated in lamina II of the dorsal horns. The nerve cells here are small and are connected to one another by short fibres and also to other cells situated deeper in the dorsal horn. The second is composed of cells in lamina I and also deep in the dorsal horn which are stimulated directly by nerve impulses from the receptor fibre units of the skin; there are cells in this region whose axons form part of ascending tracts which connect with lower centres in the brain and which are also an integral part of the action system designed to deal with pain.

We are concerned with three types of nerve fibres from the skin to the spinal cord. The first type are known as C fibres, which are unmyelinated (i.e. without a covering of a fatty sheet of myelin) and hence conduct impulses relatively slowly, at around $0.25 - 1.25$m/sec. The second type are known as Aδ fibres and these are thinly myelinated, conducting impulses rather more quickly at approximately $6-30$m/sec. Finally there are the Aβ fibres which are heavily myelinated and conduct even more quickly, at around $30 - 100$m/sec. C and Aδ are of small diameter ($0.25 - 1.5$ and

$1-5\mu$ respectively) whereas the Aβ fibres are of large diameter ($5-15\mu$). The small fibres (i.e. the C and Aδ fibres) connect with the SG and cells deeper in the dorsal horns whereas the large (i.e. Aβ) fibres connect with these and the dorsal column as well. Each of these fibres is attached to a receptor in the skin which may be a Meissner's corpuscle, a Pacinian corpuscle, a Ruffini or Krause end-organ or, for the great majority ($60-70\%$), and most important for the study of pain, a free nerve ending.

Thus there are cells in the dorsal horns of the spinal cord which receive input from the SG, cells which receive input directly from the skin and cells which transmit output to the action system. The gate control theory of pain proposes that cells in this region which transmit to the action system are the same as cells which receive input from the skin and the SG - the so-called central transmission (T) cells. The gate control system is composed of these cells and the cells of the SG (see diagram, figure 1). The output from the system is via the T-cells and hence it is this, modified by the action of the brain, which determines the degree of pain felt. The inputs to the system come from large and small afferent fibres (e.g. from the skin) and from the brain.

Both kinds of small afferent fibres have similar qualitative effect and hence we shall ignore their differences (Melzack & Wall, 1965, 1982). They excite the T-cells directly (i.e. raising their potential towards the threshold at which they fire) and also excite cells in the SG which excite the T-cells. This part of the system accounts for the observation that increased stimulation of the small fibres in the skin increases pain. We assume that the phenomenon of wind-up (Mendell, 1966) - a progressive increase in the number of action potentials elicited per stimulus when the C afferent fibres are repetitively stimulated at frequencies greater than 0.2Hz - is generated in this part of the system. It is known (Shaw *et al.*, 1991; Arancio *et al.*, 1993; Henley *et al.*, 1993) that in the dorsal horn there exists a type of excitatory amino acid receptor - the N-methyl-D-aspartate receptor (NMDA receptor) - that potentiates postsynaptic potentials. Normally, the NMDA ion channels are blocked by Mg^{++} ions (Lodge & Johnson, 1990) and as such any excitatory compound will have no effect on the receptor. However, if the membrane becomes depolarized, the blockage disappears and Na^{+} and Ca^{++} ions can enter the cell, leading to further depolarization. This effect operates on a slow time scale compared to an action potential and hence superposition of the effects of many action potentials may lead to a cumulative effect over time (Mendell, 1966; Davies & Lodge, 1987; Dickinson & Sullivan, 1987, 1990; Thompson *et al.*, 1990; Sivilotti *et al.* 1993).

The large afferent nerve fibres excite the T-cells directly but also excite cells in the SG which inhibit the T-cells (i.e. lowering their potential from their firing threshold). If there is a delay in the second of these effects then the stimulation of the large afferent nerve fibres first causes an increase in the rate of firing of the T-cells (due to the direct excitation) and then a decrease (due to the inhibitive effect from the SG). Thus pain would increase transitorily and then decrease, but in the longer term it may be relieved, in accordance with experimental observations (Wall & Sweet, 1967; Chapman *et al.*, 1976). This is the basis for rubbing injured skin in order to relieve pain.

According to the gate control theory, the output from the gate control system via the T-cells stimulates nerve cells in a centre in the (mid-)brain which automatically activates a descending inhibitory control. This is assumed to act through the T-cells and the inhibitory SG cells, although it may act through only one of these. There are candidates for the relevant brain centre in the midbrain and reticular formation (Willis, 1989). Artificial stimulation of the relevant areas of the midbrain would have a similar inhibitory effect and this may explain the observation that pain relief may be achieved by electrical stimulation of the periaqueductal gray and the nucleus raphe magnus (NRM). The work of Reynolds (1969) (on rats) and Hosobuchi *et al.* (1977) (on humans) in this area was later confirmed by many other workers. In the present model the potential in the relevant part of the midbrain is considered to satisfy a differential equation, whereas in previous versions (Britton & Skevington, 1989; Britton *et. al*, 1995) it was assumed to depend algebraically on the T-cell output. This makes no significant difference to the results but is more biologically realistic. Higher centres in the brain which also have an effect on pain are not considered in this paper.

2. The Mathematical Model

The main variables in the model are the electric potentials of the various cells and their firing rates. The time scale that we work on is one of a few seconds and hence we neglect any very short term effects such as action potentials. The cell potentials that we work with are the **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. For effects on such a time scale, this is a good approximation. Thus the slow potential is defined as

$$\overline{V}(t) = \frac{1}{s}\int_{t-s}^{t} V(\tau)d\tau$$

where s is some appropriately chosen interval of time. Thus the effect of this time-averaging is to average out rapid temporal variations which take place on a time scale shorter than s, e.g. action potentials. Any long term effects such as plasticity are neglected. Following Britton & Skevington (1989), we shall consider inputs and outputs to one particular T-cell only and assume that all neighbouring T-cells behave in a similar manner. We shall also assume, for simplicity, that each T-cell is stimulated by one C or Aδ and one Aβ nerve fibre from the skin (with frequencies x_s and x_l respectively) and one inhibitory and one excitatory SG cell. Our calculations show that allowing more than one of any of these would not change the results. The slow potentials we shall work with are defined to be V_i, of the inhibitory SG cell, V_e of the excitatory SG cell, V_t of the T-cell and V_m of the relevant area of the midbrain.

The frequencies x_i, x_e, x_t, x_m at which these cells fire are therefore functions of the slow potentials

$$x_i = f_i(V_i), x_e = f_e(V_e), x_t = f_t(V_t), x_m = f_m(V_m) \ .$$

Following Britton & Skevington (1989) we assume that the potentials V_k depend on the frequencies of impulses arriving at their dendrites from various sources, and on the dendrites and synaptic junctions themselves, whose properties we shall assume to be constant over the time scales which we are considering. The effect of an input frequency x_j to an excitatory or inhibitory synapse of a cell of potential V_k will be to raise it by Φ_{jk}, where

$$\Phi_{jk} = \alpha_{jk} \int_{-\infty}^{t} h_{jk}(t-\tau) g_{jk}[x_j(\tau)] d\tau \ , \tag{2.1}$$

(an der Heiden, 1980). $\alpha_{jk} = 1$ for an excitatory and -1 for an inhibitory synapse, h_{jk} is a positive monotone decreasing function and g_{jk} is a bounded strictly monotone increasing function satisfying $g_{jk}(0) = 0$. We take the simplest form for h_{jk} ,

$$h_{jk}(t) = \frac{1}{\tau_k} \exp\left(-\frac{t}{\tau_k}\right) \tag{2.2}$$

which represents a simple RC-network with τ_k the time constant of the membrane. The total effect of all inputs on the potential of cell k gives

$$V_k = V_{k0} + \sum_j \Phi_{jk} \quad , \tag{2.3}$$

where V_{k0} is the resting potential of the cell. This assumes that the system is linear and is a good approximation at least for small variations in the variables. This assumption may be relaxed without qualitatively affecting the results. Differentiating (2.3) and using (2.1) and (2.2) yields

$$\tau_k \dot{V}_k = -(V_k - V_{k0}) + \sum_j \alpha_{jk} g_{jk}(x_j) \ , \tag{2.4}$$

where the sum is over all inputs j to the cell k. The system we study is illustrated schematically in figure 1 which shows the inputs from the large (x_l) and small (x_s) fibres to appropriate sites and the appropriate connections between the inhibitory (I) and excitatory (E) SG cells, the T-cell (T) and the midbrain (B). The model equations for the system are therefore

$$\tau_i \dot{V}_i = -(V_i - V_{i0}) + g_{li}(x_l) + g_{mi}(x_m) \tag{2.5}$$

$$\tau_e \dot{V}_e = -(V_e - V_{e0}) + g_{se}(x_s, V_e) \tag{2.6}$$

$$\tau_t \dot{V}_t = -(V_t - V_{t0}) + g_{st}(x_s) + g_{lt}(x_l) + g_{et}(x_e) - g_{it}(x_i) - g_{mt}(x_m) \tag{2.7}$$

$$\tau_m \dot{V}_m = -(V_m - V_{m0}) + g_{tm}(x_t) \tag{2.8}$$

The functions f, g are functions whose qualitative features are assumed known and whose parameters are in principle measurable. However, in most cases, direct measurements are unavailable and the parameters are chosen to fit the data. The functions f give a cell's firing frequency in terms of its slow potential. We shall assume that cells do not fire until their potential reaches some threshold, and that above this threshold the firing frequency is an increasing function of slow potential. Since the firing rate cannot increase indefinitely, the function must eventually saturate. In fact the functions f always occur composed with a function g, and the essence is to ensure that $g \circ f$ is a saturating function.

The functions g represent the effects of the inputs to a cell on its steady state slow potential. For example, g_{li} represents the effect of the input from the large fibres to the inhibitory cell, with similar interpretations holding for all other g_{jk}. If the input is excitatory, then increasing the input will tend to increase the slow potential, whereas if it is inhibitory it will tend to decrease it. The functions g must saturate since there is a limit beyond which no increase in slow potential is possible. We shall usually take them to be hyperbolic tangents, since these are among the simplest increasing, saturating functions, but the functional form is not crucial. This is a good model as long as the receptors on the cell are not of NMDA-type. However, as we have seen in the previous section, NMDA receptors do occur and seem to be important in certain aspects of the pain system, such as in the phenomenon of wind-up. In this case, the function g is no longer simply a function of the firing frequency of the postsynaptic cells but depends on the postsynaptic potential as well.

Non-NMDA receptors are either open, allowing depolarization of the postsynaptic or target cell, or closed, preventing such depolarization. The more the target cell is depolarized, the faster it fires. The incoming signal itself opens the receptors, so that the steady state firing rate of the postsynaptic cell is a monotonic function of the firing rate of the presynaptic cell i.e. the frequency of the input. It follows that it is impossible to obtain two different firing rates for the same input frequency, as occurs in wind-up experiments.

NMDA receptors, on the other hand, we know to occur in three states (at least), open, closed and blocked (Jahr & Stevens, 1990). Depolarization of the postsynaptic cell, via the receptor, occurs only in the open state. The open-closed transition works in the same way as for non-NMDA receptors, and therefore depends only on the presynaptic cell, but the open-blocked transition is more complex. The blockage is caused by a magnesium ion, and can only be removed when the postsynaptic cell becomes sufficiently depolarized. There is therefore a positive feedback or autocatalytic effect - input leads to depolarization which leads to unblocking which leads to further depolarization. We have included this effect in our model in the excitatory interneurons, as the cells with the highest number of NMDA receptors appear to be concentrated in the substantia gelatinosa (Jansen *et al.*, 1990). This is the reason for the V_e dependence in g_{se} in equation (0.2). The function g_{se} must have the following properties. First, for any V_e it is an increasing saturating function of x_s, just as for the other functions g. Second, for any V_e we have $g_{se}(0, V_e) = 0$, since if there is no input we expect no corresponding change in potential. Third, for any $x_s > 0$ then g_{se} must be an increasing saturating function of V_e, since the higher V_e is, the more NMDA receptors will be unblocked, and the more effect the input will have on the potential. We choose one of the simplest functions with these properties, by taking the saturating functions to be hyperbolic tangents.

Suitable initial conditions for the above system are imposed together with known inputs for x_s and x_l. The precise forms of all functions f, g chosen together with the inputs for x_s and x_l along with the prescribed initial conditions are given in the appendix.

3. Results

We performed numerical simulations of the model corresponding to various experimental scenarios such as the effect of stimulation of large cutaneous nerve fibres, the effect of stimulation of small cutaneous nerve fibres and a so-called "ramping-off" of a pain stimulus according to an experiment of Humphries *et al.* (1993). The results presented below (figs. 2-5) show the T-cell potential in each of the above scenarios, since these cells are most often used to obtain the experimental data.

Qualitatively similar output to the T-cell potential is obtained for the potential in the inhibitory and excitatory cells and the midbrain.

There is a lot of evidence about the effect of large fibre stimulation on pain sensation, but much of it is anecdotal. It dates back to Roman times, when Scribonius Largus recommended the use of a live electric fish, the black torpedo, to relieve the pain of gout (Ottoson, 1983). Electric machines were used in the nineteenth century in pain relief, and transcutaneous electrical nerve stimulation (TENS) is used as a therapy today. A more familiar example is that of rubbing the skin to obtain relief after a painful knock. The available scientific data is equivocal, perhaps because of the complexity of the processes involved. One difficulty is that small fibres alone must be stimulated first, using one stimulus, and then the large fibres in addition, using an additional stimulus. However, most natural stimuli that stimulate small fibres also stimulate large ones, so the first stimulus is often unnatural and its choice varies between studies. Furthermore, it may be that the effect is small and depends upon the magnitude of the stimulation. In summary, however, we can say that there is evidence that stimulation of large fibres can relieve pain in certain circumstances (see Price, 1988, for a review of the experimental data). The model results for large fibre stimulation are shown in figure 2 and clearly show that after a small initial increase in pain, as the inhibitory interneurons are brought up to threshold, large fibre stimulation does reduce pain. A further increase in stimulation is predicted to increase pain again, a result of the model which has yet to be tested experimentally.

The effect for steady stimulation of small cutaneous nerve fibres, under most circumstances, is an increase in pain (or output from the T-cells) with input, at a rate slightly faster than linear (cf. Price, 1988). Figure 3 shows that the model is in good qualitative agreement with this. However, for periodic stimulation the phenomenon of wind-up arises. There are some neurons in the spinal cord that respond in an unexpected way when small fibres are stimulated repeatedly at low frequencies ranging from 0.2 - 2.0 Hz over a period of approximately 20 seconds (Thompson & Woolf , 1991). The average frequency of their output starts at a low level, and remains at that level for a time of the order of 10 seconds. It then jumps to a higher level, where it remains for as long as the stimulation is continued, and for as much as several tens of seconds longer than this. The connection with pain in human subjects was demonstrated by Price *et al.* (1977). The results of the wind-up simulations are shown in figure 4 and are seen to be in excellent agreement with the experiments carried out on rats reported by Thompson & Woolf (1991).

We have already seen that a constant peripheral stimulus that activated both the large and small afferent fibres would be likely to be perceived as painful, but there would be some reduction in the intensity of the pain due to the inhibitory action of the large fibre activity. If the peripheral stimulus was then ramped-off, the large fibre activity at the spinal level would fall away more quickly due to the different conduction velocities of the large and small fibres. The gate control theory predicts that as the pain stimulus is being ramped-off there will be a transient increase in pain above that of the background level i.e. a pulse of pain. Humphries *et al.* (1993) recently devised such an experiment. Potassium iontophoresis was used as an experimental pain stimulus at an upper and lower site on a subject's dominant arm. A stimulus trial consisting of four seconds of constant pain followed by a stimulus ramp-off phase was carried out. The rate of ramp-off was varied and subjects were asked to indicate if they could detect a brief pulse of additional pain during this ramp-off phase i.e. a threshold detection task. The results showed that subjects were indeed clearly able to detect a pulse of pain. Figure 5 shows the model simulation of the above experiment and once again excellent qualitative agreement is observed with a pulse of pain clearly visible.

4. Conclusions

We have presented a mathematical model for the gate control theory of pain which is an extension of that of Britton & Skevington (1989). One modification is the inclusion of NMDA receptors in the model. The second is the introduction of an explicit equation for the potential in an area of the midbrain. The model is derived from a theory (the gate control theory) based on the available biological evidence, although it does not (and indeed cannot, without becoming horrifically complex) include all that evidence. It is a testable model in that it makes concrete predictions of neuronal behaviour in certain situations. The simulations of the model show that, once again, many of the phenomena observed in acute pain in humans can be captured and in addition the model is in very good qualitative agreement in demonstrating the phenomenon of wind-up, where two output frequencies occur successively at one input frequency. As in the experimental situation, the phenomenon is observed only for a small range of input frequency. At input frequencies which are too low the higher output frequency is never achieved, as the effect dies down too much between stimuli. At input frequencies which are too high the higher output frequency is attained almost immediately. The mathematical model has also predicted a result which has yet to be tested experimentally concerning the stimulus of the large fibres after the small fibres have been stimulated. Anecdotal evidence of a reduction in pain for moderate levels of large fibre stimulation is supported but an increase in pain at higher levels of large fibre stimulation is predicted. Finally, we note that although the principal aim of the modified model was to simulate the phenomenon of wind-up, we have been able to reproduce qualitatively the results of a completely independent experiment (Humphries *et al.*, 1993) concerning the ramping-off of a pain stimulus. This strengthens our confidence that the model is a good one. It has passed the tests so far required of it and we put forward in this paper a further prediction that is so far untested.

APPENDIX

The precise system of equations solved numerically is given here below together with initial conditions. We took all time constants τ_k to be 0.7 and assumed all resting potentials V_{k0} to be -70 (millivolts). Equations (2.5) - (2.8) then become

$$0.7\dot{V}_i = -(V_i + 70) + 60\tanh(\theta_{li}x_l) + 40\tanh(f_m(V_m)) \tag{A1}$$

$$0.7\dot{V}_e = -(V_e + 70) + 40\tanh(\theta_{se}x_s)[1 + 3\tanh(4f_e(V_e))] \tag{A2}$$

$$0.7\dot{V}_t = -(V_t + 70) + 40\tanh((1-\theta_{se})x_s) + 40\tanh((1-\theta_{li})x_l) +$$

$$40\tanh(f_e(V_e)) - 40\tanh(f_i(V_i)) - 40\tanh(f_m(V_m)) \tag{A3}$$

$$0.7\dot{V}_m = -(V_m + 70) + 40\tanh(f_t(V_t)) \tag{A4}$$

where θ_{li} , θ_{se} are the proportions of the inputs that pass through interneurons in the SG and correspondingly $(1-\theta_{li})$, $(1-\theta_{se})$ are the proportions passing through to the T-cell.

Since the neurons we are considering usually operate far from their limiting firing rate we take as the form of the functions f

$$f(V_k) = [K(V_k - V_{thr})/(-V_{k0})]H(V_k - V_{thr}) \ , \tag{A5}$$

where H is the usual Heaviside function, K is a constant and V_{thr} is the firing threshold potential which we take in all cases to be -55 (millivolts).

As initial conditions in each simulation we assume each cell to be at its resting potential of -70 (millivolts) i.e. $V_i(0) = V_e(0) = V_t(0) = V_m(0) = -70$.

The functional form of the inputs used for x_s and x_l depends upon the particular experiment being simulated as detailed in the results section.

- *Constant small fibre input, variable large fibre input*

$$x_s = \text{constant} = 2.0, \quad 0.0 \leq x_l \leq 3.0 \tag{A6}$$

- *Small fibre input only, no large fibre input*

$$x_s = 2\tanh t, \quad x_l = 0.0 \tag{A7}$$

- *Wind-up simulation*

$$x_s = 2.5\cos^8(2\pi t), \quad x_l = 0.1x_s \tag{A8}$$

- *"Ramp-off" simulation*

$$x_s = \begin{cases} 2 & 0 \leq t \leq 7 \\ 10(7.2 - t) & 7 < t < 7.2 \\ 0 & t \geq 7.2 \end{cases} \tag{A9}$$

$$x_l = \begin{cases} 1 & 0 \leq t \leq 6 \\ 5(6.2 - t) & 6 < t < 6.2 \\ 0 & t \geq 6.2 \end{cases} \tag{A10}$$

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Figure Legends

Figure 1: Schematic diagram of the tenets of the gate control theory. The cells labelled T, I and E are the central transmission cells and inhibitory and excitatory neurons respectively, all in the dorsal horn of the spinal cord. B represents certain important areas of the midbrain. Higher centres in the brain are also important but are not modelled here.

Figure 2: Theoretical response of T-cell potential to large fibre stimulation with small fibre stimulation being held constant. $\theta_{li} = \theta_{se} = 0.8$

Figure 3: Theoretical response of T-cell potential to small fibre stimulation alone (no large fibre stimulation). $\theta_{li} = \theta_{se} = 0.8$

Figure 4: Theoretical response of T-cell potential to small fibre stimulation at a frequency input of 2Hz illustrating the phenomenon of wind-up. $\theta_{li} = \theta_{se} = 0.8$

Figure 5: Theoretical response of T-cell potential to stimulation of small and large fibres representing the "ramp-off" experiment of Humphries *et al.* (1993). $\theta_{li} = \theta_{se} = 0.8$