Towards Optimal Pain Relief: Acupuncture and Spinal Cord Stimulation

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Abstract

One of the important potential areas of application of intelligent virtual environment is to training medical doctors. One of the main problems in designing the corresponding intelligent system is the computational complexity of the corresponding computational problems. This computational complexity is especially high when the corresponding optimization is a discrete optimization problem, e.g., for pain relief methodologies such as acupuncture and spinal cord stimulation. In this paper, we show how to efficiently solve the corresponding discrete optimization problems. As a result, we get, e.g., a theoretical justification for the heuristic method of "guarded cathode".

Formulation of the problem. One of the prospective applications of intelligent virtual environments is to training medical doctors. For this application, it is desirable to design an intelligent system which would:

- simulate a patient, and
- recommend, to a doctor, the optimal way of curing the given patient.

Main difficulty in solving this problem. One of the main difficulties in undertaking this project is that realistic simulations (and the corresponding optimization) require a large amount of computations, i.e., in theory-of-computing language, have a large *computational complexity.*

From the viewpoint of computational complexity, we can divide the corresponding optimization problems into two classes:

- *continuous* optimization problems, i.e., problems in which the optimized parameters change *continually*; and

- *discrete* optimization problems, i.e., problems in which the optimized parameters can only take values from a *discrete* set.

Continuous optimization problems can require intensive computations, but in general, there are many efficient techniques for solving such problems. In contrast, discrete optimization problems are, in general, computationally intractable (see, e.g., [2]). This means that if we face a discrete optimization problem, we cannot simply apply an efficient *general* method; instead, we need to find an efficient method for *this particular* problem (or at least for a class of problems).

In this paper, we will describe an efficient algorithm for solving a certain class of medicine-related discrete optimization problems.

Two medical examples of discrete optimization problems. In this paper, we will consider two discrete optimization problems related to *pain relief*:

- problems of *acupuncture*, and

- problems related to *spinal cord stimulation*.

Acupuncture-related discrete optimization problems: informal description. In *acupuncture*, the pain relief (and possible cure) is achieved by applying special needles to certain "active" points on a patient's body (for problems related to the design of intelligent systems in acupuncture, see, e.g., [3, 4, 6], and reference therein). When we activate a point, we thus activate a certain area in the patient's body. If this area A exactly coincides with the area P in which the patient feels pain, then this pain is relieved.

The main problem with this activation is that the body area A activated by an acupuncture point is often larger than the targeted pain area P. As a result, in addition to diminishing pain in the targeted area (i.e., in the points $p \in P$), we may also have unpleasant undesired effects in other points $p \in A \setminus P$. To alleviate these effects, we need to "de-activate" these points. In principle, such a "de-activation" is possible because usually, to each body area, there correspond *two* acupuncture points:

- a point on a so-called *Yan meridian*, and

- a point on a so-called *Ying meridian*.

The activations of these two acupuncture points lead to opposite effect. Thus, to compensate for the unnecessary effect caused by one acupuncture point, we can activate an opposite-effect acupuncture point corresponding to a close body area. The importance of combining *several* acupuncture points is well-known in Oriental medicine (see, e.g., [5]).

The problem is: how to choose the *optimal* combination of acupuncture points, i.e., a combination which would target the desired point, and at the same time, affect as few un-desired points as possible.

Discrete optimization problems related to spinal cord stimulation: informal description. Similar discrete optimization problems occur in spinal cord stimulation SCS (for problems related to the design of intelligent systems in SCS, see, e.g., [1] and reference therein). In this technique, electrodes are surgically inserted into the vicinity of different points on the patient's spine, and then pain is alleviated by applying electric current to these electrodes.

Similarly to acupuncture, applying current to each point affects a certain area in the patient's body. If this area A exactly coincides with the area P in which the patient feels pain, then this pain is relieved. In reality, however, the body area A affected by a single electrode is often larger than the targeted pain area P. As a result, in addition to diminishing pain in the targeted area (i.e., in the points $p \in P$), we may also have unpleasant undesired effects in other points $p \in A \setminus P$. To alleviate these effects, we need to "de-affect" these points. In principle, such a "de-affectation" is possible because the application of currents of opposite *polarity* (+ and $-$) leads to opposite effects. Thus, to compensate for the unnecessary effects caused by activating one electrode, we may apply the current of opposite polarity to other electrodes which correspond to close body areas. The importance of simultaneously activating several electrodes is well-known in spinal cord stimulation.

The problem is: how to choose the *optimal* combination of stimulated electrodes so as to target the desired point, and at the same time, affect as few un-desired points as possible.

Towards the formulation of the pain relief optimization problem in precise mathematical terms: general case. In both cases, our goal is to relieve the pain in a given area P. It is sufficient to learn how to relieve the pain in a single point p; then, if we have pain in *several* points, we can combine the activations which relieve the pain in each of these points, and thus alleviate all the pain.

In both techniques, we have a finite set of possible *activation points* $a_1, \ldots, a_n$:

- in *acupuncture*, we have acupuncture points;
- in *SCS*, we have electrodes.

Each activation point a_i corresponds to a certain body area (set) $A_i \subseteq R^3$. For each body area A_i, we can also achieve the *opposite* effect:

- in *acupuncture*, by activating the acupuncture point which is dual (opposite-reaction) to a_i, and
- in *spinal cord stimulation*, by applying the current of opposite polarity to the same electrode a_i.

In both cases, we will say that we *de-activate* the activation point a_i.

Each treatment consists of activating some activation points and de-activating some other points. In other words, to describe a treatment, we must describe two subsets of the set $\{a_1, \ldots, a_n\}$ of activation points:

- the set A^+ of all points which are activated, and
- the set A^- of all points which are de-activated.

We want to choose a treatment which covers the desired body point p, and at the same time, which covers as few un-desired body points as possible.

Every activation or de-activation can cause side effects. Therefore, if several possible treatments cover the exact same body area, we would like to choose the treatment that activates and de-activates the smallest possible set of activation points.

How can we describe the set of all body points affected by a given treatment $\langle A^+, A^- \rangle$?

- If we only activate a single activation point a_i, then we affect the body area A_i.
- If we activate several activation points, then we affect the *union* of the body areas affected by each of these points:
$$\bigcup_{a_i \in A^+} A_i.$$
- Similarly:
  - if we de-activate a single activation point a_i, then we affect a body area A_i;
  - if we de-activate several activation points, then we affect the *union* of the body areas affected by each of these points:
$$\bigcup_{a_i \in A^-} A_i.$$
- Finally, if we both *activate* several activation points (which form the set A^+), and *de-activate* several other activation points (which form the set A^-), then we can describe the set of all affected body points as the set of all body points which are activated (by activation points $a_i \in A^+$) but not de-activated (by activation points $a_i \in A^-$), i.e., as a set
$$\bigcup_{a_i \in A^+} A_i \setminus \bigcup_{a_i \in A^-} A_i. \tag{1}$$

We are now ready for precise definitions:

Definition 1.

- *Let a set B be fixed. This set will be called a body.*
- *By a pain relief technique, we mean a pair consisting of a finite sequence $a_1, \ldots, a_n$, and a sequence of (pairwise different) sets $A_1, \ldots, A_n \subseteq B$, $A_i \neq A_j$.*
- *Let a pain relief technique be fixed. By a treatment, we mean a pair $t = \langle A^+, A^- \rangle$, where $A^+, A^- \subseteq \{a_1, \ldots, a_n\}$.*
- *By a body area $B(t)$ corresponding to the treatment $t = \langle A^+, A^- \rangle$, we mean a set (1).*
- *We say that a treatment t is better than a treatment $\widetilde{t} \neq t$ (and denote it by $t > \widetilde{t}$) if one of the following two conditions is satisfied:*
  - *either the treatment t covers fewer points than $\widetilde{t}$, i.e., $B(t) \subset B(\widetilde{t})$ and $B(t) \neq B(\widetilde{t})$,*
  - *or the treatments $t = \langle A^+, A^- \rangle$ and $\widetilde{t} = \langle \widetilde{A}^+, \widetilde{A}^- \rangle$ cover the same body area (i.e., $B(t) = B(\widetilde{t})$), but t uses the smaller set of activation points, i.e., $A^+ \subseteq \widetilde{A}^+$ and $A^- \subseteq \widetilde{A}^-$.*
- *By a body point, we mean a point $p \in B$.*
- *We say that a body point is covered by a treatment t if $p \in B(t)$.*
- *We say that for a body point, the treatment t is optimal if the following two conditions hold:*
  - *the point p is covered by the treatment t; and*
  - *no other treatment covering p is better than t.*

From this definition, we can make the following conclusion:

Proposition 1. *For every body point p, every treatment $t = \langle A^+, A^- \rangle$ which is optimal for this body point, activates exactly one point.*

Comments.

- In precise terms, for every body point p and for every treatment $t = \langle A^+, A^- \rangle$ which is optimal for this body point, the set A^+ consists of exactly one element: $|A^+| = 1$.
- For readers' convenience, all the proofs are placed at the end of the paper.

Pain relief optimization problem as a linear problem. In both of our medical problems (acupuncture and spinal cord stimulation), the activation points are located in one or several vertical *lines*. Each point corresponds to a certain body area. Normally, higher activation points correspond to higher body areas, and lower activation points correspond to lower body areas. This remark enables us to simplify the corresponding optimization problem:

- In general, a body is a 3D set, and we need three coordinates to specify a body point: a vertical coordinate z and two horizontal coordinates x and y.
- However, due to the above remark, to check whether a body point is covered by a activation point, we do not need to know x and y, it is sufficient to know the vertical coordinate z.

Thus, in a reasonable first approximation, we can neglect the two horizontal coordinates and only consider the vertical coordinates of different points. In other words, in this approximation, each body point can be characterized by the value of a single coordinate z. In this representation, a body B is a (closed) 1D interval. Correspondingly, for each activation point a_i, the corresponding set A_i is also a (closed) interval $A_i = [a_i^-, a_i^+] \subset B$.

Since activation points are located on a line, we can assume (without losing generality) that they are ordered from the lowest to the highest. Correspondingly, the affected body areas $A_1, \ldots, A_n$ will also become "ordered" from the lowest to the highest in the sense that both their lower bounds and their upper bounds are increasing with i: $a_1^- < a_2^- < \ldots < a_n^-$ and $a_1^+ < a_2^+ < \ldots < a_n^+$.

Definition 2. *By a linear pain relief technique, we mean a pain relief technique in which the body B is a closed interval, the body areas $A_i = [a^-, a_i^+]$ are closed intervals, and both sequences a_i^- are strictly increasing: $a_1^- < a_2^- < \ldots < a_n^-$ and $a_1^+ < a_2^+ < \ldots < a_n^+$.*

Optimal choice of activation points. In the previous text, we assumed that the activation points (and the corresponding body areas) are given. This is true in acupuncture, but in spinal cord stimulation, we can *choose* these points.

The more activation points we choose, the more complicated the corresponding surgical procedure. Therefore, it is desirable to use as few activation points as possible, as long as they cover the entire body B. Let us formulate this problem in precise terms.

Definition 3. *Let a body B be fixed. We say that a pain relief technique $\langle\{a_1, \ldots, a_n\}, \{A_1, \ldots, A_n\}\rangle$ is optimal if the following two conditions are satisfied:*

- *every body point is covered by one of the areas A_i, i.e., $B \subseteq \cup A_i$; and*
- *if we delete one of the activation points (i.e., one of the sets A_i), then the remaining body areas A_j no longer cover the entire body, i.e., for every i, there exists a point $p \in B$ for which*

$$p \notin \bigcup_{j \neq i} A_j.$$

For linear pain relief techniques, we can explicitly describe when a technique is optimal:

Definition 4. *Let A_i be a pain relief technique;*

- *we say that body areas A_i and A_j are neighboring if $|i - j| = 1$.*
- *we say that body areas A_i and A_j intersect if $A_i \cap A_j \neq \emptyset$.*

Proposition 2. *If a linear pain relief technique is optimal, then the following two conditions hold:*

- *all neighboring body areas intersect, and*
- *all non-neighboring body areas do not intersect.*

Comments.

- Thus, for spinal cord stimulation, if we choose the optimal linear pain techniques, then we can be sure that the two conditions from Proposition 2 are satisfied.
- For acupuncture, we do not have the choice of activation points, so we cannot make a similar claim; however, it turns out that in most cases, these two conditions are satisfied for acupuncture as well. A probable explanation may be that the choice of biologically active acupuncture points was also restricted by the requirements of optimality: redundant resources such as un-necessary activation points, can be redirected into some other biological functions.
- For optimal linear pain relief techniques, optimal treatments can be explicitly described:

Proposition 3. *Let B be a body, let $p \in B$ be a body point, and let $\langle\{a_1, \ldots, a_n\}, \{A_1, \ldots, A_n\}\rangle$ be an optimal linear pain relief technique. Then, every treatment $t = \langle A^+, A^-\rangle$ which is optimal for p has one of the following forms:*

$$t = \langle\{a_i\}, \{a_{i+1}\}\rangle, \quad t = \langle\{a_i\}, \{a_{i-1}\}\rangle, \quad t = \langle\{a_i\}, \{a_{i-1}, a_{i+1}\}\rangle,$$

$$t = \langle\{a_1\}, \emptyset\rangle, \quad \text{and} \quad t = \langle\{a_n\}, \emptyset\rangle.$$

Comments.

- In the linear case, we can describe each treatment as a sequence of n 0's, $+$'s and $-$'s, where:
  - $+$ on i-th place means that $a_i \in A^+$ (i.e., that the activation point a_i is activated);
  - $-$ on i-th place means that $a_i \in A^-$ (i.e., that the activation point a_i is de-activated); and
  - 0 on i-th place means that $a_i \notin A^+$ and $a_i \notin A^-$ (i.e., that the activation point a_i is neither activated nor de-activated).

  In these notations, every optimal treatment has one of the following five forms:

  - $0 \ldots 0 + -0 \ldots 0$,
  - $0 \ldots 0 - +0 \ldots 0$,
  - $0 \ldots 0 - + - 0 \ldots 0$,
  - $+0 \ldots 0$, and
  - $0 \ldots 0+$.

- In spinal cord stimulation, it has been *empirically* noticed that these (and similar) treatments (called "guarded cathode") are indeed optimal. Thus, our Proposition 3 *justifies* this *empirical* fact.

- The reader should be warned that there is a minor difference in notations between our paper and literature on spinal cord stimulation:
  - we denote the activation of an activation point by $+$, because it is *activation* and not *de-activation* (de-activation is, correspondingly, denoted by $-$);
  - however, since this activation is done by sending a *negative* current, it is often denoted by $-$ (and de-activation, correspondingly, by a $+$).

- According to Proposition 2, the values a_i^- and a_i^+ are ordered as follows: $a_1^- < a_2^- \le a_1^+ \le a_3^- \le a_2^+ \le \ldots a_i^- \le a_{i-1}^+ \le a_{i+1}^- \le \ldots \le a_{n-1}^+ < a_n^+$. Depending on where the point p is, different treatments are optimal:
  - when $p \in [a_1^-, a_2^-]$, then the optimal treatment is $+ - 0 \ldots 0$;
  - when $p \in [a_2^-, a_1^+]$, then the optimal treatment is either $+0 \ldots 0$, or $0 + -0 \ldots 0$;
  - when $p \in [a_1^+, a_3^-]$, then the optimal treatment is $- + -0 \ldots 0$;
  - when $p \in [a_3^-, a_2^+]$, then the optimal treatment is either $- + 0 \ldots 0$, or $00 + -0 \ldots 0$;
  - $\ldots$;
  - when $p \in [a_i^-, a_{i-1}^+]$, then the optimal treatment is either $0 \ldots 0 - +0 \ldots 0$ or $0 \ldots 0 + -0 \ldots 0$;
  - when $p \in [a_{i-1}^+, a_{i+1}^-]$, then the optimal treatment is $0 \ldots 0 - + - 0 \ldots 0$;
  - $\ldots$
  - when $p \in [a_n^-, a_{n-1}^+]$, then the optimal treatment is $0 \ldots 0+$;
  - finally, when $p \in [a_{n-1}^+, a^+n]$, then the optimal treatment is $0 \ldots 0 - +$.

  The corresponding optimal treatments can be ordered into the following sequence:

$$
\begin{array}{cccccc}
+ & - & 0 & 0 & \ldots & 0 \\
+ & 0 & 0 & 0 & \ldots & 0 \\
0 & + & - & 0 & \ldots & 0 \\
- & + & - & 0 & \ldots & 0 \\
- & + & 0 & 0 & \ldots & 0 \\
0 & 0 & + & - & \ldots & 0 \\
0 & - & + & - & \ldots & 0 \\
0 & - & + & 0 & \ldots & 0
\end{array}
$$

For every $i \neq 1, n$, there are three optimal treatments in which this particular activation point a_i is activated; these treatments cover three sub-intervals of the interval $A_i = [a_i^-, a_i^+]$:

- the treatment $0 \ldots 00 + -0 \ldots 0$ corresponds to the lowest sub-interval $[a_i^-, a_{i-1}^+]$;
- the treatment $0 \ldots 0 - + - 0 \ldots 0$ corresponds to the middle sub-interval $[a_{i-1}^+, a_{i+1}^-]$; and
- the treatment $0 \ldots 0 - +0 \ldots 0$ corresponds to the highest sub-interval $[a_{i+1}^-, a_i^+]$.

These three treatments are similar to three tones corresponding to a single note n: the lower tone $n^\flat$, the normal tone n, and the higher tone $n^\sharp$.

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Proof of Proposition 1. First, if no points are activated, i.e., if $A^+ = \emptyset$, then $B(t) = \emptyset$, and so, we cannot have p covered by the treatment t. So, the set A^+ must contain at least one activation point.

Let us prove, by reduction to a contradiction, that we cannot have more than one activation point in a set A^+ from an optimal treatment $t = \langle A^+, A^- \rangle$. Indeed, let us assume that we have several elements in A^+. From $p \in B(t)$ and the definition of $B(t)$ (formula (1)), we can conclude that $p \notin A_j$ for all $a_j \in A^-$, and that

$$p \in \bigcup_{a_i \in A^+} A_i,$$

i.e., that p belongs to one of the sets A_i, with $a_i \in A^+$. Then, one can easily check that a new treatment $\widetilde{t} = \langle \{a_i\}, A^- \rangle$ is better than t: indeed, it has fewer points activated and the same (or smaller) set of body points covered. So, $\widetilde{t} > t$ and thus, contrary to our assumption, t is not optimal. This contradiction proves that an optimal treatment can only activate one activation point. The proposition is proven.

Proof of Proposition 2. Let us first prove that neighboring areas must intersect. Indeed, suppose they do not intersect, i.e., $A_j \cap A_{j+1} = [a_j^-, a_j^+] \cap [a_{j+1}^-, a_{j+1}^+] = \emptyset$ for some j. In general, the fact that two intervals have an empty intersection means that one of them is located "to the left" of the other, i.e., in our case, that either $a_{j+1}^+ < a_j^-$, or $a_j^+ < a_{j+1}^-$.

The first case is impossible because in this case, due to monotonicity of sequences a_i^- and a_i^+, we have $a_j^- < a_{j+1}^-$, and hence, $a_{j+1}^+ < a_{j+1}^-$, which is impossible. Thus, $a_j^+ < a_{j+1}^-$. Therefore, any point p from the open interval (a_j^+, a_{j+1}^-) is neither covered by A_j (because all points from A_j are too small) nor by A_{j+1} (because all points from A_{j+1} are too large). Due to monotonicity, we can conclude that this point p cannot be covered by any of the body areas at all; indeed:

- if $i < j$, then A_i is even smaller than A_j, and thus, all points from A_i are smaller than p;
- if $i > j+1$, then A_i is even larger than A_{j+1}, and thus, all points from A_i are larger than p.

Hence, the point p is not covered by any of the body areas A_i, which contradicts to the definition of the optimal technique. This contradiction shows that our assumption was wrong, and that the optimal body areas do intersect.

Let us now show that non-neighboring body areas do not intersect. We will prove this statement also by reduction to a contradiction. Indeed, let us assume that $A_j \cap A_k = [a_j^-, a_j^+] \cap [a_k^-, a_k^+] \neq \emptyset$ for some non-neighboring and different j and k. Without losing generality, we can assume that $j < k$; in this case, "non-neighboring" means that $k > j+1$. Let us show that in this case, the optimality condition is violated for $i = j+1$, i.e., that if we delete A_i, we will still be able to cover all body points. To be more precise, we will show that every point $p \in A_i = [a_i^-, a_i^+]$ can be covered either by A_j, or by A_k.

Indeed, let $p \in A_i = [a_i^-, a_i^+]$, i.e., let $a_i^- \leq p \leq a_i^+$. Due to monotonicity, we have $a_j^- < a_i^- < a_k^-$ and $a_j^+ < a_i^+ < a_k^+$. From $p \geq a_i^-$ and $a_i^- > a_j^-$, we can conclude that $p > a_j^-$. Similarly, from $p \leq a_i^+$ and $a_i^+ < a_k^-$, we can conclude that $p < a_k^+$. We will consider two possible cases:

- $p \leq a_j^+$, and
- $p > a_j^+$.

In the first case, we have $p > a_j^-$ and $p \leq a_j^-$, i.e., we have $p \in [a_j^-, a_j^+] = A_j$.

Let us now analyze the second case. From the fact that the intervals $A_j = [a_j^-, a_j^+]$ and $A_k = [a_k^-, a_k^+]$ have a common point (let us denote it by x), we can conclude that $a_k^- \leq x \leq a_j^+$, and therefore, that $a_k^- \leq a_j^+$. Thus, from $p > a_j^+$, we conclude that $p > a_k^-$. We also know that $p < a_k^+$. Thus, $p \in [a_k^-, a_k^+] = A_k$.

Thus, every point $p \in A_i$ is indeed covered by either A_j or A_k, so the body area A_i is unnecessary, contrary to our assumption that the pain relief technique was optimal. This contradiction shows that our assumption was wrong, and non-neighboring body areas cannot intersect. The proposition is proven.

Proof of Proposition 3. Due to Proposition 1, the optimal treatment includes only one activated point a_i, for which $p \in A_i$. So, to prove Proposition 3, we must show that the only de-activated points are the activation points neighboring to a_i.

Indeed, if a point a_j is not neighboring for a_i, then, according to Proposition 2, the corresponding body areas A_i and A_j have no common points. Therefore, if the activation point a_j belongs to the set A^- of de-activated points, we can delete it from this set A^- without changing $B(t)$. After this change, we get a new treatment $\widetilde{t} = \langle \{a_i\}, A^- \setminus \{a_j\} \rangle$, which covers the same body area ($B(t) = B(\widetilde{t})$), but activates the smaller set of activation points. In other words, we have a new treatment $\widetilde{t}$ which still covers the same body point p, and which is better than the original treatment t. This conclusion contradicts to the assumption that the treatment t is optimal. Thus, the optimal treatment can only de-activate points which are neighboring to a_i.

Depending on how many neighboring points are de-activated, we get four possibilities: $A^- = \{a_{i-1}\}$, $A^- = \{a_{i+1}\}$, $A^- = \{a_{i-1}, a_{i+1}\}$, and $A^- = \emptyset$. To complete the proof, it is sufficient to show that the last case is only possible when $i = 1$ or $i = n$.

Indeed, let $1 < i < n$, $p \in A_i$, and let $t = \langle \{a_i\}, \emptyset \rangle$ be an optimal treatment for the body point p. Since the body areas A_{i-1} and A_{i+1} are not neighboring, they have no common points. Thus, the body point p cannot belong to both of these areas, so either we have $p \notin A_{i-1}$, or $p \notin A_{i+1}$.

- In the first case, a new treatment $\widetilde{t} = \langle\{a_i\}, \{a_{i-1}\}\rangle$ still covers p, and covers a smaller body area $B(\widetilde{t}) = A_i \setminus A_{i-1} \subset A_i = B(t)$. This area $B(\widetilde{t})$ is smaller because, due to Proposition 2, $A_i \cap A_{i-1} \neq \emptyset$, and all points from this intersection belong to $B(t)$ but not to $B(\widetilde{t})$. Thus, we get a better treatment $\widetilde{t} > t$, which contradicts to our assumption that t is the optimal treatment.

- In the second case, we can similarly prove that $\widetilde{t} = \langle\{a_i\}, \{a_{i+1}\}\rangle$ is a better treatment, so the second case is also impossible.

Since in both cases we get a contradiction, the treatment $t = \langle\{a_i\}, \emptyset\rangle$ can be optimal only for $i = 1$ or $i = n$. The proposition is proven.