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Artificial Intelligence in Medicine 6 (1994) 83-102

Artificial Intelligence in Medicine

Fundamentals of clinical methodology: 1. Differential indication

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Abstract

Progress in the theory and practice of artificial intelligence in medicine requires awareness of basic issues in medical problem solving. To stimulate discussion and research on this subject, in a series of articles some logical, methodological and metatheoretical problems of clinical practice will be studied. The present paper reconstructs clinical decision-making as a computable process of action planning.

Key words: Diagnosis; Therapy; Indication; Contra-indication; Differential indication; Clinical decision-making; Clinical judgment; Medical knowledge engineering; Knowledge-based systems; Methodology of medicine; Deontic logic

1. Introduction

In spite of all progress in biomedical sciences and technology there are up to 40% misdiagnoses [7]. This implies that about the same amount of treatments might be wrong decisions. The main reason of this underdevelopment of physician performance lies in medicine's failure to recognize the need for, and to establish, a *Methodology of Clinical Practice* as a research and training branch [3]. Medical students are not taught any algorithm or logic for their clinical problem-solving. Every physician is thus left alone to re-discover the wheel of proficient practicing. And she carries it with herself into her grave. This is the entire (hi)story of clinical thinking. We can only hope that AIM research will be able to ameliorate the situation. But this would require AIM research to devote special attention to methodological problems of clinical practice because these problems underlie, complicate and bias most of the work in AIM research. Examples are inquiry into the methodology of forming and testing diagnostic hypotheses, understanding the structure and logic of medical language and knowledge, searching for appropriate

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SSDI 0933-3657(93)E0023-7

techniques of analyzing and representing nosological and diagnostic-therapeutic knowledge, clarifying the nature of temporal-causal systems and of etiology, uncertainty management in clinical knowledge engineering, etc. To enhance interest in and sensitivity to this kind of foundational issues, I would like to present in a series of articles some thoughts on selected topics which I deem relevant to AIM research. This opening paper of the series is dealing with the concept and computability of differential indication in diagnosis and therapy [11–14].

2. The problem

Although most physicians are aware of the 60% reliability limit of their clinical judgment, they don't believe that expert systems will enhance their cognitive capacities. Their disbelief is reinforced by the practical insufficiency of current medical expert-systems techniques. This insufficiency is mainly due to the lack of a theory and methodology of medical expert systems research, on the one hand, and to the inadequate picture most medical expert-system researchers entertain of clinical judgment, on the other. [1,2]

The notions of indication and differential indication are crucial to an understanding of clinical judgment, so that in my opinion it will not be possible to develop successful clinical knowledge-based systems without first constructing a logic and methodology of indication and differential indication. The present paper offers a framework for discussing basic problems in handling this task.

To begin with, it should be pointed out that the subjects the physician is dealing with are sick persons and not symptoms, findings, diseases and treatments. Since sick persons are bio-psycho-social agents governed by moral values and norms, different than physical devices, clinical judgment is not comparable to trouble-shooting in physical devices. Theories on trouble-shooting in physical devices therefore cannot provide appropriate foundations for AIM modelling of clinical reasoning. Raymond Reiter's celebrated "theory of diagnosis from first principles" [2,1] is no exception.

The starting-point of clinical judgment is a particular person, p, who is ill or believes herself to be ill, and thus presents a non-empty set of initial data consisting of complaints, symptoms or signs. Let us call this initial data about the patient the physician receives, patient data set D_1, where $D_1 = \{\delta_1, \ldots, \delta_m\}$ with

[1] These reasons may be added to those Ted Shortliffe has recently identified for understanding medicine's resistance to the adoption and use of expert-systems techniques ([18], pp. 97 ff.).

[2] The management of a patient's health affairs comprising history taking, diagnosis, prognosis, therapy, advice, and prevention will be termed clinical practice. The mental part of this practice, i.e. the reasoning tasks and strategies followed by the doctor when practicing, will be referred to as clinical judgment, clinical reasoning, clinical problem-solving, or clinical decision-making. These four terms will be considered synonyms.

$m \geq 1$, and each δ_i is a statement providing any information on the patient p. For instance, D_1 may be one of the following sets:

{p is a female of about 40, p is complaining of severe cough};
{p is a 12 year old boy, p is bleeding at the nose};
{p has just been involved in a car accident, p is unconscious, p's heart rate is 124 per minute, p's blood pressure is 80/60 Torr};
{p has undergone gastrectomy last year, p is complaining of acute pain in the upper left abdomen}.

It is commonly assumed that in the first place clinical judgment aims at finding a diagnosis which will explain why D_1 occurred. For various reasons, however, this widespread opinion must be considered a metapractical misconception [5]. A more realistic and fruitful view is provided by treating D_1 as a clinical problem that evokes a problem-solving process, where the solution aimed at is not a diagnosis but a remedial action, including advice and 'wait and watch', which is meant to ameliorate the patient's present suffering and make her problem disappear. That the search for and the optimization of this remedial action often requires additional information on the patient, part of which may be termed diagnosis, is an accidental feature of the problem-solving process due to the particular course the history of medicine has taken in the past. It could have been otherwise.

If there were only one unique remedial action for all kinds of patients, no problem-solving, and thus no diagnosis, would be necessary. But unfortunately, the therapeutic inventory of medicine offers $n > 1$ different therapeutic measures $T_1, \ldots, T_n$, including the empty action 'doing nothing'. And each of these therapies may be viewed as a potential remedy for every patient with the initial data set D_1. The problem-solving task is to select from among the therapeutic inventory $\{T_1, \ldots, T_n\}$ a minimum subset $\{T'_1, \ldots, T'_m\}$ that is considered the best solution to the problem D_1 (see Fig. 1).

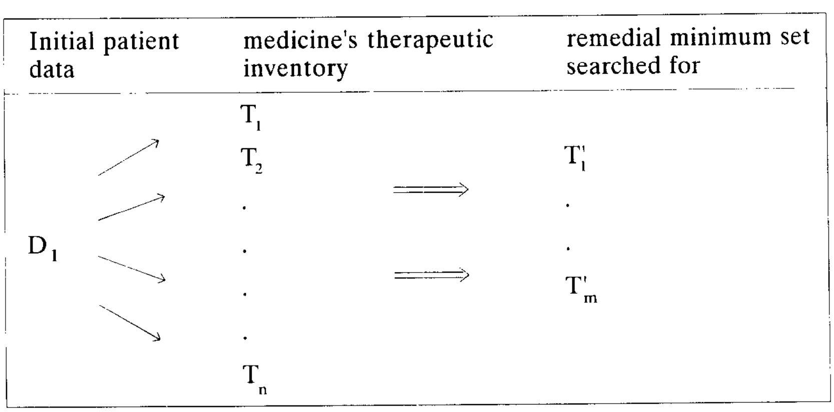

Fig. 1. The initial patient data set D_1 points to a large subset of the total set $\{T_1, \ldots, T_n\}$ of available treatments. Each element of this set is a potential remedy for the patient. The nontrivial problem to be solved is to find out which one of the trivial paths $\rightarrow$ is a solution path $\Rightarrow$ leading to the appropriate, minimum, remedial action set $\{T'_1, \ldots, T'_m\} \subseteq \{T_1, \ldots, T_n\}$. The diagnosis is only part of the solution path.

The initial patient data set D_1 provides us with a root problem, and the appropriate, minimum therapy set $\{T'_1, \ldots, T'_m\} \subseteq \{T_1, \ldots, T_n\}$ we are searching for, is the solution goal of the problem-solving process evoked by D_1. The entirety of paths between the root problem and the unknown solution goal $\{T'_1, \ldots, T'_m\}$ may be conceived of as a black box the patient and her pathogenetically relevant environment are placed in. We have the opportunity of administering to the box any stimuli, e.g. any questions we can ask, physical examinations and laboratory tests we are allowed to perform, x-ray photographs and NMR images we can take, etc. Through its/their responses to the stimuli the organism(s) in the black box guide(s) us through the labyrinth of the candidate paths to the desired solution goal.

Clinical judgment thus presents itself as a path-searching endeavor based on an information producing stimulus-response process controlled by the physician. The process is initiated by the initial patient data set D_1 which evokes the first stimulus, i.e. the initial clinical action A_1 the physician takes, and is terminated by her final action A_n. To formulate my problem, I will now reconstruct the microstructure of this process [3]:

Any particular instance of clinical judgment is initiated at a particular instant of time, t_1, and is terminated at a later instant of time, t_n. A doctor d at t_1 starts inquiring into whether or not the patient p presenting the data set D_1 suffers from any disorder and needs any treatment. The total period of this inquiry, $[t_1, t_n]$, can be partitioned into a finite sequence of discrete sub-periods $t_1, t_2, t_3, \ldots, t_n$. Proceeding from the root data set D_1 at t_1, the physician chooses form among all possible actions she might consider, a particular set of actions, A_1, and performs it. This action set A_1 may be any questions she asks the patient, a diagnostic inference she makes, a particular physical examination, laboratory test, treatment or the like. For instance, A_1 may be one of the following action sets:

{since when do you suffer from cough?};
{is there any genetic disease in your family?};
{measure p's body temperature, determine her heart rate};
{an ECG should be recorded first, followed by postero-anterior chest radiography and Coomb's test};
{I believe that p suffers from systemic lupus erythematosus};
{give the patient a Nitroglycerin tablet of 0.3 mg}.

The outcome of the actions A_1 is some information on the patient the doctor obtains. This new information changes the original data set D_1 to the data set D_2 at t_2, e.g. to {p is a female of about 40, p is complaining of severe cough, p's body temperature is 39 Celsius, p's heart rate is 102 per minute}.

Proceeding from D_2 at t_2, a second set of actions, A_2, is chosen and performed whose result changes the data set D_2 to the data set D_3 at t_3, and so forth until a final action set A_n is performed at time t_n terminating the clinical practice.

We have thus partitioned the whole period $[t_1, t_n]$ of clinical decision-making into the discrete sub-periods $t_1, t_2, \ldots, t_n$ such that the sequence of patient data sets available in these temporal granules is $D_1, D_2, \ldots, D_n$, and the corresponding action sets performed are $A_1, A_2, \ldots, A_n$, respectively. Clinical judgment may now be viewed as a linear solution path of the form displayed in Fig. 2.

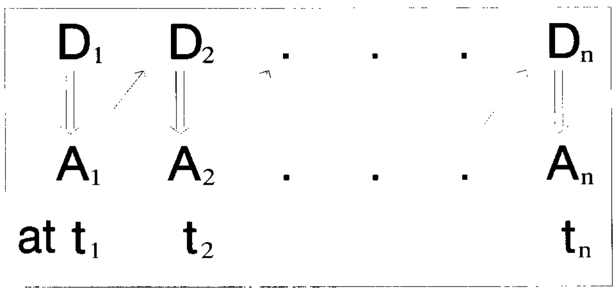

Fig. 2. The solution path.

The path consists of a finite sequence of (a) data-based selection of actions $A_1, A_2, \ldots, A_n$, and (b) successively building the patient data sets $D_1, D_2, \ldots, D_n$ that are used in identifying and selecting the corresponding actions. A double arrow in the figure says that the data set D_i leads the decision-maker to the action set A_i, whereas a simple arrow represents the A_i-mediated acquisition of the data set D_{i+1}.

Let us now formalize the above idea. We will assume that statements about the patient are ordered pairs of attribute-value type such as, for example:

$\langle$sex, female$\rangle$ $\equiv$ statement δ_1
$\langle$age, about 40$\rangle$ $\equiv$ statement δ_2
$\langle$cough, severe$\rangle$ $\equiv$ statement δ_3
$\langle$body temperature, high$\rangle$ $\equiv$ statement δ_4
$\langle$heart rate, 102 per minute$\rangle$ $\equiv$ statement δ_5.

In special analyses this core data structure may be supplemented by a variety of additional dimensions, e.g. by adding patient name and time period to yield temporal quadruples of object-time-attribute-value type such as, for instance, $\langle$Hilary Ciccione, February 20, cough, severe$\rangle$.

We will symbolize:

- statements describing singular data by $\delta, \delta_1, \delta_2, \ldots$ to connote *data*;
- sets of such data statements by $D, D_1, D_2, \ldots$ to connote *data set*;
- statements describing actions by $\alpha, \alpha_1, \alpha_2, \ldots$ to connote *action*;
- sets of such action statements by $A, A_1, A_2, \ldots$ to connote *action set*.

The set of all data patients may present in the course of clinical decision-making, the *data space*, will be denoted by $\mathscr{D}$. The physician's *action space* comprising all possible and clinically relevant actions she may consider, will be termed $\mathscr{A}$. 'Clinically relevant actions' means methods of clinical inquiry in history taking, diagnosis, prognosis, therapy, and prevention. Note that the omission of an action is also an action, and is thus included in the action space $\mathscr{A}$. The powerset of a set X is written power(X). Thus we have:

$$\mathscr{D} = \{\delta \mid \delta \text{ is an attribute-value statement about the patient}\}$$

$$\mathscr{A} = \{\alpha \mid \alpha \text{ is a statement describing an action the physician may consider}\}$$

$$\text{power}(\mathscr{D}) = \{D \mid D \subseteq \mathscr{D}\}$$

$$\text{power}(\mathscr{A}) = \{A \mid A \subseteq \mathscr{A}\}.$$

Succinctly stated, the basic problem in the methodology of clinical reasoning is this [3]: assuming the temporal sequence of the decision-making process is $t_1, t_2, \ldots, t_n$ with $n \geq 1$, is it possible to construct an effective procedure which can be initiated at t_1 such that given the patient data set $D_i \subseteq \mathscr{D}$ with $1 \leq i \leq n$, the optimal action set $A_i \subseteq \mathscr{A}$ can be selected unambiguously from among the action space $\mathscr{A}$, the next data set $D_{i+1} \subseteq \mathscr{D}$ can be built as objectively as possible, and the particular doctor d is in principle exchangeable by any doctor x? Put another way, is there a mapping

$$f\colon \text{power}(\mathscr{D}) \rightarrow \text{power}(\mathscr{A})$$

$$f\colon \text{power}(\mathscr{A}) \rightarrow \text{power}(\mathscr{D})$$

such that f is a computable function so as to render the process of clinical judgment sketched in Fig. 2 above a computable path-searching with

$$f(D_i) = A_i$$

$$f(A_i) = D_{i+1}$$

and to unambiguously provide the physician in all possible clinical situations with an optimal guide for her decisions? A computable function of this type will be referred to as a computable clinical decision function, *ccdf* for short.

In what follows, the conceptual apparatus needed for constructing a ccdf is analyzed. To prevent misunderstandings, however, note that the chronologically ordered patient data sets $D_1, D_2, \ldots, D_n$ above are not supposed to display a monotonic relationship of the type $D_1 \subseteq D_2 \subseteq D_3 \subseteq \ldots \subseteq D_n$. Such monotonicity is never found in clinical practice. Otherwise, neither healing nor recovery could exist.

Note, secondly, that no distinction has been made between patient data and diagnosis. What is usually called diagnosis may be part of any of the patient data sets $D_1, D_2, \ldots, D_n$. We will in this way be able to avoid both the impracticable partition of clinical decision-making into diagnostic and therapeutic phases, and the old-fashioned differentiation between diagnostic and therapeutic actions.

3. Multiple modal structures in medical knowledge

It is desirable in AIM research to be aware of all kinds of intensional structures appearing in clinical knowledge, data and reasoning. Besides the ubiquitous extensional operators such as the usual propositional connectives ('not', 'or', 'and', etc.), there are several sets of non-extensional (= intensional) operators dealt with in modal logics, all of which are also ingredients of medical language and knowledge. They include the following, familiar ones, which show why the logic of clinical reasoning must be something beyond predicate logic, probability calculus and fuzzy logic [9,11,12]:

Intensional operators of

- temporal logic = {always, sometimes, never, future, past, before, after, while}

- epistemic logic = {to consider it possible that, to conjecture that, to believe that, to be convinced that, to know that}
- alethic modal logic = {it is possible that, it is necessary that}
- deontic logic = {it is permitted that, it is obligatory that, it is forbidden that}.

The latter three operators will be used below. They represent three classes of natural language deontic operators such as, for example:

- may, is allowed, optional = permission operator ('it is permitted that...')
- must, should, ought, is required = obligation operator ('it is obligatory that...')
- omit, don't do, avoid, must not = prohibition operator ('it is forbidden that...').

Let α be any first-order sentence. By prefixing the operators we will write $O\alpha$, $F\alpha$, and $P\alpha$ to express, respectively, it is obligatory that α, it is forbidden that α, it is permitted that α. For instance, let α be the atomic proposition 'the doctor records an ECG'. $O\alpha$ means, it is obligatory that the doctor records an ECG. $F\alpha$ means, it is forbidden that the doctor records an ECG. And $P\alpha$ says, it is permitted that the doctor records an ECG.

Let $\Box$ be any of the three deontic operators, O, F or P. We write $\Box\alpha$ to represent any of the propositions $O\alpha$, $F\alpha$, and $P\alpha$.

If $x_1, \ldots, x_m$ are the free variables of the proposition β, the universal statement $\forall x_1 \forall x_2 \cdots \forall x_m \beta$ says that for all $x_1, \ldots, x_m$, β holds. For the sake of convenience, however, a universal statement of the kind just mentioned will be abbreviated to β omitting the quantifier prefix $\forall x_1 \forall x_2 \cdots \forall x_m$.

4. Indications and contra-indications

Anatomical knowledge can be formalized and represented below the level of modal logics. Pathophysiological and nosological knowledge will at least require temporal predicate logic, probability theory and fuzzy set theory [11]. What kind of logic does the appropriate understanding, representation and management of diagnostic and therapeutic knowledge require?

A thorough, logical analysis reveals that the basic units of diagnostic and therapeutic knowledge are commitments stating that in a particular clinical circumstance δ a particular action α should be performed or omitted. They are therefore reconstructible as universal deontic conditionals of the form

$$\forall x_1 \forall x_2 \cdots \forall x_m \text{ If } \delta, \text{ then } \Box\alpha$$

which we will briefly formalize as

$$\delta \to \Box\alpha \tag{1}$$

omitting the quantifier prefix [6,10,14]. The antecedent δ is an atomic or compound sentence describing a pathological state or any other boundary condition such as patient sex, age, her social environment, etc. The consequent is a deontic statement, $\Box\alpha$, expressed by deontic phrases such as 'should be performed', 'is required', 'must be applied', 'is recommended', 'do!', 'omit!', 'may be used', and the like. Simple examples are the following diagnostic-therapeutic propositions:

(1) If a patient complains of angina pectoris and her ECG is unknown, then an ECG should be recorded.
(2) Given acute myocardial infarction, taking exercise ECG is forbidden.
(3) In acute myocardial infarction one may administer oxygen to the patient.

These examples demonstrate that depending on the nature of the operator $\Box$ in the consequent of formula (1), we have to distinguish between

- conditional obligation: $\delta \rightarrow O\alpha$
- conditional prohibition: $\delta \rightarrow F\alpha$
- conditional permission: $\delta \rightarrow P\alpha$.

Example 1 above is a conditional obligation, example 2 is a conditional prohibition, and example 3 is a conditional permission.

A clinical indication rule prescribing particular diagnostic or therapeutic measures may be construed as a conditional obligation, $\delta \rightarrow O\alpha$. A contra-indication rule, on the other hand, may be construed as a conditional prohibition, $\delta \rightarrow F\alpha$. The propositions δ and α may be of arbitrary complexity. [3]

Suppose a particular clinical knowledge contains, among other things, the following indication and contra-indication rules:

$$\delta_1 \rightarrow O\alpha_1$$

$$\delta_2 \rightarrow O\alpha_2$$

$$\vdots$$

$$\delta_m \rightarrow F\alpha_m.$$

Given a particular patient with the data set $\{\delta_1, \ldots, \delta_m\}$, a deontic-logical inference will yield the conclusion $\{O\alpha_1, O\alpha_2, \ldots, F\alpha_m\}$ which says that action α_1 is indicated and ... and action α_m is contra-indicated.

These brief remarks explain why clinical knowledge cannot be appropriately formalized and handled below the level of deontic predicate logic [11,12].

5. Differential indication

The preliminaries above enable us to reconstruct clinical judgment as a process of searching for differential indications. To enhance the expressive power of the framework, however, I will not confine myself to individual deontic conditionals. Given a patient with the data set D such that

$$D = \{\delta_1, \ldots, \delta_m\},$$

[3] For a detailed analysis of the structure and dynamics of indication systems, see [17].

and given a particular clinical knowledge, a set function f will identify from among this knowledge a bundle of $m \geq 1$ deontic rules whose antecedents match D:

$$\delta_1 \to \Box\, \alpha_1$$
$$\delta_2 \to \Box\, \alpha_2$$
$$\cdot$$
$$\cdot$$
$$\delta_m \to \Box\, \alpha_m$$

and will infer their consequents, $\{\Box\, \alpha_1, \ldots, \Box\, \alpha_m\}$. This concluded deontic set informs us about the actions $\alpha_1, \ldots, \alpha_m$ each of which, depending on the prefixed operator $\Box$, is obligatory, forbidden, or permitted in this situation. The whole procedure can thus be simply formalized as a set-functional relationship between input and output:

$$f(D) = \{\Box\, \alpha_1, \ldots, \Box\, \alpha_m\}.$$

If in the output $\{\Box\, \alpha_1, \ldots, \Box\, \alpha_m\}$ the operator $\Box$ is exclusively one of the three operators O, F, or P, one may also conveniently write $O\{\alpha_1, \ldots, \alpha_m\}$, $F\{\alpha_1, \ldots, \alpha_m\}$, or $P\{\alpha_1, \ldots, \alpha_m\}$ to express that the whole set $\{\alpha_1, \ldots, \alpha_m\}$ is obligatory, forbidden, or permitted, respectively. That means:

Definition 1. If A is a set of sentences, $A = \{\alpha_1, \ldots, \alpha_m\}$, we write

$O(A)$ instead of $\{O\alpha_1, \ldots, O\alpha_m\}$

$F(A)$ instead of $\{F\alpha_1, \ldots, F\alpha_m\}$

$P(A)$ instead of $\{P\alpha_1, \ldots, P\alpha_m\}$.

The set-function variable f used in the following framework may be supposed to be a pair of the type {knowledge K, methodology of applying K} consisting of a particular piece of knowledge and a particular set of methods how to apply this knowledge in the real world. The methodology component may also explicitly or implicitly include, or be based upon, any particular system of classical or non-classical logic.

Definition 2. x is a decision-making frame if there are c, d, t, $\mathscr{D}$, $\mathscr{A}$, D, A, f, and $\Box$ such that

(1) $x = \langle c, d, t, \mathscr{D}, \mathscr{A}, D, A, f, \Box \rangle$,
(2) c is a non-empty set of clients,
(3) d is a non-empty set of decision-makers, not necessarily distinct from c,
(4) t is a time period,
(5) $\mathscr{D}$ is the data space, i.e. a set of statements about c's possible states,
(6) $\mathscr{A}$ is d's action space at t,
(7) D is a subset of $\mathscr{D}$ accepted by d at t,
(8) A is a subset of $\mathscr{A}$,
(9) f is a function from power($\mathscr{D} \cup \mathscr{A}$) to power($\mathscr{D} \cup \mathscr{A}$),
(10) $\Box$ is a deontic operator.

This definition axiomatizes only the frame of a decision-making situation. The function f will be referred to as the decision function of the frame. In the following definitions, this decision function is characterized and specialized yielding indication, contra-indication and differential indication structures.

Definition 3. x is a permissive structure if there are c, d, t, $\mathscr{D}$, $\mathscr{A}$, D, A, f, and P such that
(1) $x = \langle c, d, t, \mathscr{D}, \mathscr{A}, D, A, f, P \rangle$,
(2) x is a decision-making frame,
(3) $f(D) = A$,
(4) $P(A)$.

Assume, for example, D is any of the patient data sets $D_1, D_2, \ldots, D_n$ the physician is faced with in the decision-making process $t_1, t_2, \ldots, t_n$. According to Axioms 3–4, the decision function f will identify the action set $A \subseteq \mathscr{A}$ which is permitted in this situation. A permissive structure may also be termed weak indication structure.

The following definitions in an analogous manner determine indication, contra-indication, and differential indication structures as deontic-logical models.

Definition 4. x is an indication structure if there are c, d, t, $\mathscr{D}$, $\mathscr{A}$, D, A, f, and O such that
(1) $x = \langle c, d, t, \mathscr{D}, \mathscr{A}, D, A, f, O \rangle$,
(2) x is a decision-making frame,
(3) $f(D) = A$,
(4) $O(A)$.

Definition 5. x is a contra-indication structure if there are c, d, t, $\mathscr{D}$, $\mathscr{A}$, D, A, f, and F such that
(1) $x = \langle c, d, t, \mathscr{D}, \mathscr{A}, D, A, f, F \rangle$,
(2) x is a decision-making frame,
(3) $f(D) = A$,
(4) $F(A)$.

By interpreting the set D as patient data, and the action set A as a set of diagnostic or therapeutic measures, diagnostic and therapeutic reasoning will become a model of these definitions. We may therefore term the decision function f a *clinical* decision function. What is particularly important in understanding the deontic nature, and in representing the methodology, of clinical reasoning is this clinical decision function f installed in the axiomatizations above. It assigns to a given patient data set a particular set of actions which is permitted, obligatory or forbidden in this situation. Informally, the physician's knowledge, experience and ethic act as a function of this type, though not as a very good one.

There is an inverse relationship between obligation and prohibition expressed by the following deontic-logical theorem, where α is any sentence and $\neg\alpha$ is its negation to be read 'not α':

$$F\alpha \text{ iff } O\neg\alpha.$$

That is to say that a particular action is forbidden if and only if it is obligatory to omit this action. Thanks to this theorem, every contra-indication turns out to be the indication of the omission of the contra-indicated action as expressed in the following theorem:

Theorem 1. *$\delta \rightarrow O\neg\alpha$ is equivalent to $\delta \rightarrow F\alpha$. That means that the omission of a contra-indicated action is indicated.*

In this way, a contra-indication structure

$$\langle c, d, t, \mathscr{D}, \mathscr{A}, D, \{\alpha_1, \ldots, \alpha_m\}, f, F\rangle$$

may be viewed as an indication structure of the form

$$\langle c, d, t, \mathscr{D}, \mathscr{A}, D, \{\neg\alpha_1, \ldots, \neg\alpha_m\}, f, O\rangle$$

where the action set $\{\neg\alpha_1, \ldots, \neg\alpha_m\}$ is the omission of the actions $\{\alpha_1, \ldots, \alpha_m\}$. This view is based on the following theorem that follows from Definitions 4–5 and Theorem 1.

Theorem 2. *$\langle c, d, t, \mathscr{D}, \mathscr{A}, D, \{\neg\alpha_1, \ldots, \neg\alpha_m\}, f, O\rangle$ is an indication structure if $\langle c, d, t, \mathscr{D}, \mathscr{A}, D, \{\alpha_1, \ldots, \alpha_m\}, f, F\rangle$ is a contra-indication structure.*

In what follows, we can therefore integrate contra-indications as obligatory omissions into indication structures, and thus omit the term 'contra-indication'.

When a particular set $A = \{\alpha_1, \ldots, \alpha_m\}$ of clinical actions is indicated, it is natural to assume that there is a clinical priority ordering $\succ$ which determines the temporal sequence of performing the elements or subsets of A, say in the order $\alpha_1 \succ \cdots \succ \alpha_m$. A performance order of this kind will be written $\langle A, \succ\rangle$.

Definition 6. x is a well-ordered indication structure if there are c, d, t, $\mathscr{D}$, $\mathscr{A}$, D, A, f, O, and $\succ$ such that
(1) $x = \langle c, d, t, \mathscr{D}, \mathscr{A}, D, A, f, O, \succ\rangle$,
(2) $\langle c, d, t, \mathscr{D}, \mathscr{A}, D, A, f, O\rangle$ is an indication structure,
(3) $\succ$ is a binary relation on power(A),
(4) $\langle A, \succ\rangle$ is the performance order induced by f over A.

Taking account of the circumstance that in clinical settings individual clinical actions may be more or less urgent, more or less invasive, more or less productive of information, more or less valuable, and more or less expensive, one will appreciate the advantages of a performance ordering $\succ$ of the type above which, depending on the degree of its sophistication, may contribute to a more or less ideal, well-ordered indication structure.

Well-ordered indication structures are necessary, but not sufficient for optimal patient management. There are clinical situations where a patient presents various data sets $D_1, \ldots, D_m$ at the same time, e.g. multiple disorders to be treated or multiple groups of coherent symptoms and signs to be interpreted. Each of these data sets, considered separately, necessitates a particular diagnostic or therapeutic indication set A_i such that an array $A_1, \ldots, A_m$ of action sets appears to be indicated. In these cases the physician is faced with the problem of whether or not there is any conflict of action among the indication set $\{A_1, \ldots, A_m\}$, and of how to resolve this conflict and to minimize the union $A_1 \cup \cdots \cup A_m$. The solution aimed at is a minimum set $B \subset A_1 \cup \cdots \cup A_m$ such that B is indicated due to the present data set $D_1 \cup \cdots \cup D_m$. A conflict analysis, optimization and resolution of this type is referred to as making a *differential indication* decision.

Considering the fact that every patient data set D is the union $D_1 \cup \cdots \cup D_m$ of its covering subsets $D_1, \ldots, D_m \subseteq D$, and that these subsets may necessitate a large indication set $A_1 \cup \cdots \cup A_m$ as above, it appears reasonable to view every diagnostic-therapeutic setting as one that is best managed by a differential indication decision.

Definition 7. x is a differential indication structure if there are c, d, t, $\mathscr{D}$, $\mathscr{A}$, $D_1, \ldots, D_m$, $A_1, \ldots, A_m$, B, f, and O such that
(1) $x = \langle c, d, t, \mathscr{D}, \mathscr{A}, D_1, \ldots, D_m, A_1, \ldots, A_m, B, f, O \rangle$,
(2) For each pair $\{D_i, A_i\}$, $\langle c, d, t, \mathscr{D}, \mathscr{A}, D_i, A_i, f, O \rangle$ is a an indication structure,
(3) $B \subset A_1 \cup \cdots \cup A_m$
(4) $\langle c, d, t, \mathscr{D}, \mathscr{A}, D_1 \cup \cdots \cup D_m, B, f, O \rangle$ is an indication structure.

Definition 8. x is a well-ordered differential indication structure if there are c, d, t, $\mathscr{D}$, $\mathscr{A}$, $D_1, \ldots, D_m$, $A_1, \ldots, A_m$, B, f, O, and $\succ$ such that
(1) $x = \langle c, d, t, \mathscr{D}, \mathscr{A}, D_1, \ldots, D_m, A_1, \ldots, A_m, B, f, O, \succ \rangle$,
(2) $\langle c, d, t, \mathscr{D}, \mathscr{A}, D_1, \ldots, D_m, A_1, \ldots, A_m, B, f, O \rangle$ is a differential indication structure,
(3) $\succ$ is a binary relation on power(B),
(4) $\langle B, \succ \rangle$ is the performance order induced by f over B.

The last three definitions imply that every differential indication structure is an indication structure. The converse does not hold.

A re-examination of the solution path in Fig. 2 above will demonstrate that each of the selected paths $D_i \Rightarrow A_i$ in clinical decision-making may be construed as the outcome of a differential indication structure where a clinical decision function f selects, from among the physician's action space, the action set A_i as the indicated one in this situation. The entirety of the solution path in Fig. 2 may thus be viewed as a trajectory $D_1 \Rightarrow A_1 \rightarrow D_2 \Rightarrow A_2 \rightarrow \cdots \rightarrow D_n \Rightarrow A_n$ of data-based action planning in a dynamical system of differential indication structures generating the following sequence of well-ordered indication structures:

$$\langle c, d, t_1, \mathscr{D}, \mathscr{A}, D_1, A_1, f, O, \succ \rangle \quad \text{with } \langle D_1, A_1 \rangle \text{ at } t_1$$
$$\langle d, c, t_2, \mathscr{D}, \mathscr{A}, D_2, A_2, f, O, \succ \rangle \quad \text{with } \langle D_2, A_2 \rangle \text{ at } t_2$$
$$\cdot$$
$$\cdot$$
$$\langle c, d, t_n, \mathscr{D}, \mathscr{A}, D_n, A_n, f, O, \succ \rangle \quad \text{with } \langle D_n, A_n \rangle \text{ at } t_n.$$

Our problem posed in Section 2 above may now be reformulated as follows. Is it possible to render this data-action trajectory computable? To show that the answer is the affirmative, one must only demonstrate that the function f is a computable one [12].

6. The computability of differential indication

The computability of the decision function f will be demonstrated by constructing two series of computable sub-functions,

$$f_1, f_2, \ldots, f_n$$
$$g_1, g_2, \ldots, g_n$$

of which f will be composed.

Given the above series of differential indication structures with the initial patient data $D_1 = \{\delta_1, \ldots, \delta_m\}$ at time t_1, it is not hard to design a computable function f_1 such that

$$f_1(D_1) = A_1,$$
$$O(A_1),$$
$$\langle A_1, \succ \rangle \text{ is the performance order of the action set } A_1.$$

To this end, just write a definite program, Prgr-1, that offers the output $A_1 \subseteq \mathscr{A}$ as an answer to the input D_1 and says 'A_1 is obligatory with the performance order $\langle A_1, \succ \rangle$'. Thus, Prgr-1 computes a function, f_1, with $f_1(D_1) = A_1$. Hence, f_1 is a computable function.

Now, write a second definite program, Prgr-2, that achieves the following. It asks the doctor (a) to perform A_1 in a particular manner, (b) to answer a list of specific questions concerning the outcome of the performed action set A_1, and (c) to answer another list of specific questions so as to update the previous data set D_1. Based on (a) through (c), the program then composes the patient data set $D_2 = \{\text{outcome of step (b)}\} \cup \{\text{outcome of step (c)}\}$. Thus, Prgr-2 computes a function, g_1, such that $g_1(A_1) = D_2$. Hence, g_1 is a computable function.

Now, write a third definite program, Prgr-3, that provides the output 'A_2 is obligatory with the performance order $\langle A_2, \succ \rangle$' as an answer to the input D_2. Thus, Prgr-3 computes a function, f_2, with $f_2(D_2) = A_2$. Hence, f_2 is a computable function.

...and so forth until the final action set A_n is recommended by the final program Prgr-n at time t_n. We will in this way have available two series of computable functions:

$$f_1, f_2, \ldots, f_n$$
$$g_1, g_2, \ldots, g_n$$

such that

$$f_1(D_1) = A_1$$
$$f_2(D_2) = A_2$$
$$\vdots$$
$$f_n(D_n) = A_n = \{\text{terminate decision-making}\},$$

and

$$g_1(A_1) = D_2$$
$$g_2(A_2) = D_3$$
$$\vdots$$
$$g_n(A_n) = \{\text{decision-making terminated}\}.$$

The concatenation of the programs Prgr-1, Prgr-2, ..., Prgr-n will yield a program that interlinks the two function series above in the following order:

$$\langle f_1, g_1, f_2, g_2, \ldots, f_n, g_n \rangle.$$

Thus, it executes a computable function $f = \langle f_1, g_1, f_2, g_2, \ldots, f_n, g_n \rangle$ which, as demonstrated above, provides the mapping

$$f\colon \text{power}(\mathscr{D}) \to \text{power}(\mathscr{A})$$
$$f\colon \text{power}(\mathscr{A}) \to \text{power}(\mathscr{D})$$

for the management of clinical judgment and acts as required regarding the computability question posed in Section 2. Hence, *there is a ccdf*, a computable clinical decision function f, that is defined as follows:

$$f(X) = \begin{cases} f_1(D_1), & \text{if } X = D_1 \\ g_1(A_1), & \text{if } X = A_1 \\ \vdots & \vdots \\ f_n(D_n), & \text{if } X = D_n \\ g_n(A_n), & \text{if } X = A_n \end{cases}$$

Sufficient empirical evidence is available in favor of this existence claim. Every clinical expert system designed to provide advice in a particular clinical domain Dom, is a restriction of the ccdf f to Dom. Analogously, a comprehensive clinical expert system covering the entire clinical medicine would represent an instance of the total function f, i.e. a particular ccdf.

The latter remark suggests that one may conceive of a variety of different, competing ccdfs each of which will render clinical judgment computable in a particular manner. The question of how to determine which one of them may be preferred to the rest, is among the core problems of the experimental science of clinical practice that is emerging from the current medical knowledge engineering research.

As it is obvious from the design of the sub-function series $g_1, g_2, \ldots, g_n$ above for performing the indicated actions, the argument of any such function g_i is a set of actions, A_i, having the data set D_{i+1} as its value, $g_i(A_i) = D_{i+1}$. The physician is involved in each g_i of the series in that the computation of $g_i(A_i)$ requires of her to perform the recommended action set A_i and to assist g_i in gathering data for building the next data set D_{i+1}. Thus, the physician is physically involved in the computation of the whole function f. For this reason, one may raise the objection that none of the sub-functions $g_1, g_2, \ldots, g_n$ is a computable one in the proper sense of this term, and may conclude that there is no ccdf as maintained above.

This objection is based on the assumption that the doctor's involvement in the execution of the sub-functions $g_1, g_2, \ldots, g_n \in f$ is necessary to this execution. However, this *necessity* is a mere physical necessity for the time being, but not a logical necessity. To prove this claim, replace the doctor by a robot that acts as a mobile peripheral of the machine that computes f.

The circumstance that robots are not yet able to match the sensorimotor proficiency of doctors as machine peripherals, does not concern the computational aspect of our problem. So, we need not enter into a philosophical discussion on robotics.

7. Practical consistency of clinical decision functions

A clinical decision function cannot be acceptable if in isomorphic clinical settings it does not behave consistently. It should be able to identify for a particular patient p one and the same diagnostic or therapeutic action if this patient is subject to clinical setting 1 with data set D_1, and to clinical setting 2 with data set D_2, *and* $D_1 = D_2$. Analogously, two different doctors or groups of doctors who independently of each other apply the function to the same patient, must arrive at the identical diagnostic or therapeutic indication for this patient. In other words, a clinical decision function must be constrained in such a manner that practical inconsistencies are excluded. The following three constraints illustrate this discussion:

Reliability Axiom 1. If $\langle p_1, d_1, t_1, \mathscr{D}, \mathscr{A}, D_1, A, f, O\rangle$ and $\langle p_2, d_2, t_2, \mathscr{D}, \mathscr{A}, D_2, B, f, O\rangle$ are indication structures with $p_1 = p_2$ and $D_1 = D_2$, then $A = B$.

Reliability Axiom 2. If $\langle p, d_1, t_1, \mathscr{D}, \mathscr{A}, D, A, f, O\rangle$ and $\langle p, d_2, t_2, \mathscr{D}, \mathscr{A}, D, B, f, O\rangle$ are indication structures with $d_1 \neq d_2$, then $A = B$.

Reliability Axiom 3. If $\langle p_1, d_1, t_1, \mathscr{D}, \mathscr{A}, D_1, A, f, O\rangle$ and $\langle p_2, d_2, t_2, \mathscr{D}, \mathscr{A}, D_2, B, f, O\rangle$ are indication structures with $p_1 \neq p_2$ and $D_1 = D_2$, then $A = B$.

Additional constraints may be formulated in a similar manner. The same applies to differential indication structures. Constraints of this type imposed on a clinical decision function are practically and theoretically useful in that they establish uniting cross-connections both between application domains and individual applications of the function, and in this way prevent it from being unintelligible, unjust, and subjective as some physicians sometimes are.

8. Diagnosis

A detailed analysis of diagnosis and differential diagnosis will be undertaken in a forthcoming part of this article. Within this perspective and present framework, however, it can be provisionally sketched how the concept of indication structure, as introduced above, may be further specialized to provide an anchorage for metadiagnostic inquiries [3,9].

The intuitive idea in medicine of diagnosis is that some phenomenon causally accounts for the patient's complaint, and that the diagnosis is just the description of that phenomenon. The appropriate understanding and refinement of this vague idea must be based on the awareness that
(1) the patient's complaint must be something pathological to require a diagnosis,
(2) a clear concept of causality will be beneficial, and
(3) diagnosis should be based upon the acquisition of specific diagnostic information to exclude doubtful methods comparable to tossing a coin.

All of these criteria are met by the sketchy Definition 9 below.

Let N be a set of evaluation predicates such as {normal, pathological, very pathological, extremely pathological, not very pathological,...}. Each of these predicates can be used to qualify, within a particular population PO to which the patient belongs, a given patient data δ as normal, pathological, etc. The set N will therefore be termed normality values. In this way, the *normality value*, nv, of a patient data δ with respect to the population PO the patient belongs to may be symbolized by a functional statement of the form

$$nv(\delta, PO) = y$$

which says that the normality value of δ in PO is y. For example, $nv(\langle$cough, severe$\rangle$, women$)$ = pathological. Finally, let the functional statement

$$cr(X, Y, PO) = z$$

express that the *causal relevance*, cr, of event X to event Y in the population PO equals z. For instance, it may be that cr(smoking, lung cancer, men with high vitamin C consumption) = 0.1, while cr(smoking, lung cancer, men with low vitamin C consumption) = 0.3. The definition of this numerical causality function cr requires too much formalism and must therefore be omitted here. Roughly, the causal relevance of an event X to an event Y in a population PO is the extent to which in this population the occurrence of X raises or lowers the probability of the occurrence of Y, given that some additional requirements are satisfied (for details, see [4,8,16]).

Definition 9. x is a diagnostic structure if there are p, d, t_1, $\mathscr{D}$, $\mathscr{A}$, D_1, A, f, O, t_2, D_2, D, Δ, PO, N, nv, cr, and dg such that

(1) $x = \langle p, d, t_1, \mathscr{D}, \mathscr{A}, D_1, A, f, O, t_2, D_2, D, \Delta, PO, N, nv, cr, dg \rangle$,
(2) $\langle p, d, t_1, \mathscr{D}, \mathscr{A}, D_1, A, f, O \rangle$ is an indication structure,
(3) t_2 is the same time as or later than t_1
(4) $f(A) = D_2$
(5) D_2 is a subset of $\mathscr{D}$ accepted by d at t_2
(6) $D \subseteq D_1 \cup D_2$
(7) $\Delta \subseteq D_1 \cup D_2$
(8) PO is a set such that $p \subseteq PO$,
(9) N is a set of predicates such as {normal, pathological, very pathological,...},
(10) nv: $\mathscr{D} \times \{PO\} \rightarrow N$,
(11) cr: power($\mathscr{D}$) $\times$ power($\mathscr{D}$) $\times \{PO\} \rightarrow [-1, +1]$,
(12) dg: power($\mathscr{D}$) $\times \{PO\} \rightarrow$ power($\mathscr{D}$),
(13) $nv(\delta, PO) = y \in N \neq$ normal, for all $\delta \in D$,
(14) $cr(\Delta, D, PO) > 0$,
(15) There is no $X \subseteq D_1 \cup D_2$ such that $cr(X, D, PO) > cr(\Delta, D, PO)$,
(16) $dg(D, PO) = \Delta$.

Axioms 2–5 state that a diagnostic inquiry has generated new information on the patient. Axiom 13 qualifies some part of patient data as being pathological in the population PO referred to. According to Axioms 14–15, the subset Δ of patient data is in some positive degree causally relevant, in the population PO, to the pathological part D of patient data, and no other part of patient data is causally more relevant to D than Δ. In Axiom 16, the new function dg assigns to the pathological part of patient data, with respect to the population PO, the causally most relevant set Δ, referred to as *diagnosis*.

On the basis of the structure above, one may define diagnosis as a ternary set-function in the following way. The functional relation 'Diagnosis(p, D, FR) = Δ' says that the diagnosis for patient p with data D relative to the frame of reference FR is Δ.

Definition 10. Diagnosis(p, D, FR) = Δ if there are d, t_1, $\mathscr{D}$, $\mathscr{A}$, D_1, A, f, O, t_2, D_2, PO, N, nv, cr, and dg such that

(1) $\langle p, d, t_1, \mathscr{D}, \mathscr{A}, D_1, A, f, O, t_2, D_2, D, \Delta, PO, N, nv, cr, dg \rangle$ is a diagnostic structure,
(2) FR is the knowledge base and methodology of the functions f and dg.

For instance, it may be that a diagnostic examination of our female patient above, undertaken within a particular frame of reference FR, reveals: Diagnosis({Hilary},

{⟨cough, severe⟩, ⟨body temperature, high⟩, ⟨heart rate, 102 beats per minute⟩, ⟨heart beats, irregular⟩, ⟨blood pressure, low⟩, ⟨substernal chest pain, intermittent⟩}, FR) = {⟨bronchitis, chronic⟩, ⟨pericarditis, acute⟩}. It is of course most realistic to assume that another frame of reference could generate another diagnosis [3].

From Definition 9 it follows that every diagnostic structure is also an indication structure. The converse does not hold. It goes without saying that the computability proof as demonstrated in Section 6, can be extended to the diagnostic function *dg* sketched in Definition 9, and to the ternary function defined in Definition 10.

9. Knowledge-based systems as functions

As it was alluded to in Section 6 above, a clinical knowledge-based system may be conceived of as a computable clinical decicion function that controls diagnostic and differential indication structures eliminating physicians' confined and biased clinical judgment. Due to the experimental and technological nature of clinical knowledge-based systems research it is reasonable to view this emerging discipline as an *experimental engineering science of clinical practice* that produces different species of computable clinical decision functions: ccdf_1, ccdf_2, ccdf_3, and so on [15]. The implementation of any such function will be referred to as a *clinical expert machine*, *cem* for short. For example, cem_1 may be a MYCIN machine, cem_2 may be a QMR machine, etc.

Given a particular type i of clinical expert machines, cem_i, with its domain-specific knowledge base denoted by KB_i and its underlying methodology M_i, and given a patient p with the data set D and her doctor d using that machine, we have that

$$cem_i(p, d, D, KB_i \cup M_i) = X. \tag{2}$$

The machine cem_i operates on the quadruple $\langle p, d, D, KB_i \cup M_i \rangle$ producing the value X that may be the recommendation of an indicated action, a diagnosis or something else. The objectivity of an indication or diagnostic structure governed by the operator cem_i is provided by the fact that for all patients p with the data set D and for all doctors d, the output X remains the same guaranteeing the exchangeability of doctors, as if the operator cem_i were constrained in the sense discussed in Section 7 above. We can therefore remove the doctor variable d and agree upon the syntax:

$$cem_i(p, D, KB_i \cup M_i) = X \tag{3}$$

instead of formula 2. The three-place function cem_i in formula (3) may be construed as a composite operator consisting of at least two parts, a diagnostic operator written $diag_i$, and an indication operator termed $indic_i$, such that:

$$diag_i(p, D, KB_i \cup M_i) = \Delta$$

$$indic_i(p, D, KB_i \cup M_i) = O(A).$$

This syntax may be based and interpreted upon the conceptual apparatus already available, for instance, in the following manner:

Definition 11. $diag(p, D, KB \cup M) = \Delta$ if there are d, t_1, $\mathscr{D}$, $\mathscr{A}$, D_1, A, f, O, t_2, D_2, PO, N, nv, cr, dg such that
(1) $\langle p, d, t_1, \mathscr{D}, \mathscr{A}, D_1, A, f, O, t_2, D_2, D, \Delta, PO, N, nv, cr, dg \rangle$ is a diagnostic structure,
(2) $KB \cup M$ is the knowledge base and methodology of the functions f and dg.

Definition 12. $indic(p, D, KB \cup M) = O(A)$ if there are d, t, $\mathscr{D}$, $\mathscr{A}$, and f such that
(1) $\langle p, d, t, \mathscr{D}, \mathscr{A}, D, A, f, O \rangle$ is an indication structure,
(2) $KB \cup M$ is the knowledge base and methodology of the function f.

A clinical knowledge-based system, reconstructed in this way as a composite operator, maps patient data in diagnoses and indications. And it does so always relative to its underlying knowledge base and methodology, $KB \cup M$. Any change in the variable $KB \cup M$ will generate changes in diagnoses and action recommendations. Stated explicitly, this means that:

If for a particular patient p with the data set D

$$diag_i(p, D, KB_i \cup M_i) = \Delta_i$$

$$indic_i(p, D, KB_i \cup M_i) = O(A_i)$$

and

$$diag_j(p, D, KB_j \cup M_j) = \Delta_j$$

$$indic_j(p, D, KB_j \cup M_j) = O(A_j)$$

then

it is very likely that $\Delta_i \neq \Delta_j$ and $A_i \neq A_j$ if $i \neq j$.

Diagnoses and therapies are thus context dependent in that they are epistemically and methodologically relative. There are no such things as the patient's disease and health independently of theories, epistemologies and methodologies applied [3]. This fact diminishes the absolute value of quality researches exploring the reliability and validity of diagnoses and treatment decisions, and exploring treatment efficacy [7,10].

Moreover, due to the inevitable vagueness of medical language most parts of patient data and clinical knowledge are based on inherently fuzzy concepts and are therefore fuzzy statements, independently of how they are internally represented. For these reasons it will be of vital relevance for medical expert systems technology to produce fuzzy cems rather than unrealistic, crisp constructs incapable of competing with the cerebral fuzzy machines of physicians. The logical and metatheoretical aspects of fuzzy diagnostic-therapeutic operators will be studied in the sequel. [4]

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