INTELLIGENCE-BASED MEDICINE

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Summary

Despite seven hundred thousand new medical references last year, the relationship between a given set of medical features and specific pathophysiology, treatment, and criteria of improvement is often weak. Moreover, the generalization of evidences obtained in specific settings may lead to under-treat or to over-treat a significant proportion of patients. We expose an application of the cybernetic loop, based on traditional medical steps: nosology, semeiology, pathophysiology, therapy and on the four transitions between these steps. This approach leads to formulate eight basic questions evaluating the steps in terms of reproducibility and the transitions in terms of predictivity. We detail two practical applications: 1) the evaluation of a medical decision (implantation of an internal cardioverter-defibrillator) and 2) the evaluation of a specific study (EPHESUS). Using this loop allows to determine clearly when evidence is lacking and/or to which extend an evidence really increases the medical knowledge or just creates a market.

Medical knowledge can be schematically scored by four successive degrees of reliability: belief, logic, experience, and evidence.[1] Is evidence the final step? This is questionable.[2,3] One can hardly generalize a physiologic mechanism observed in a specific setting. On the contrary, a given therapy, effective or ineffective in a large population, may have large inter-individual differences. Moreover, with improving methodology, past evidence may no longer be considered valid today.[4,5] Therefore, in practice, it is often necessary to deal with the different degrees of knowledge.[1,6]

Modelization may represent a step forward; giving, whenever possible, more stable, more analytic and more didactic expression of knowledge.[7] Despite being underused in clinical medicine, this approach has proven to be fruitful in radiology, [8,9] ,biology,[10,11] and many other scientific disciplines. Clinicians may have interest in sharing some tools with researchers in modelization. The cybernetic (or systemic) loop is a comprehensive schema of any system involving control and decision,[12,13] that any physician intuitively knows. Its formalization can help them in: 1) making a hierarchy between numerous elementary pieces of knowledge, and including them into a comprehensive schema for decision making; 2) determining when new evidences are really necessary to markedly improve practical decisions.[14,15] Since medical research is increasingly granted by the industry, distinguishing medical knowledge from marketing interest is of growing importance.[16]

This article introduces clinicians to a simple cybernetic loop applied to pieces of evidence found in the literature, with no attention to their methodology. These examples illustrate the usefulness and didactic interest of this loop in scoring the reliability of any medical decision. This is an attempt to take Evidence-Based Medicine (EBM) to a larger concept that can be defined as Intelligence-Based Medicine (IBM).

The Cybernetic loop

A cybernetic loop basically includes four steps as shown in Figure 1: 1) delimitation of the domain where the loop is relevant, 2) definition of the input items needed and sufficient to describe the reasoning process, 3) formalization of the reasoning process, 4) choice and definition of actions triggered by the reasoning process.[17,18]

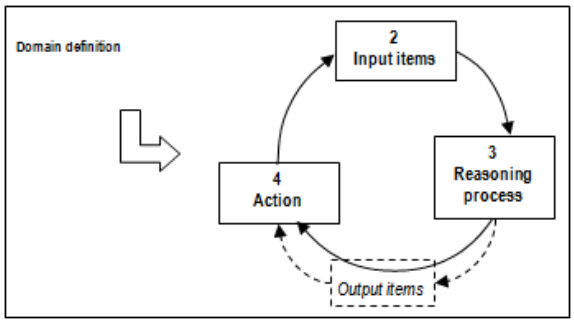

Figure 1. A simple cybernetic loop. Boxes are the steps of the loop. Arrows represent the transitions between steps. The transition between the domain (step 1) and the loop (entirely included in the domain) is represented by a large angled arrow.

These four steps correspond schematically to well known medical translations: nosology, semeiology, pathophysiology, and therapy, respectively. An additional step, referring to as "output items" or "diagnosis" in Medicine may be added between "reasoning process" and "action". When the reasoning process is complex or poorly understood, or when there is no clear action, a set of output (diagnostic) items is merely required for inter-observer communication. In this situation, frequently observed in systemic diseases for example, the loop may be difficult to close due to a lack of knowledge and therefore, the cybernetic approach may have limited interest. In contrast, when a clear pathophysiology leads to clear

therapy, a diagnostic step is unnecessary and can only be viewed as a potential loss of information.

Practical applications of the loop in Medicine

Any system control and decision may be analyzed with a cybernetic loop (Figure 2). Since degrees of knowledge are cumulative, the reliability attributable to each step and transition may be schematically scored by a pictogram representing the actual knowledge as a sum of layers stacked like the layers of the brain from archeo knowledge (belief) to neo knowledge (evidence).

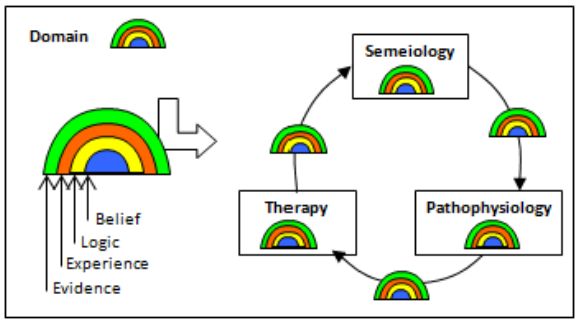

Figure 2. The cybernetic loop applied to Medicine. For each of the eight elements of the schema, the reliability of the available knowledge can be scored using a pictogram. The knowledge of the transition between the domain and the loop has been enlarged to show the four layers distinctly

Two examples, shown below, are intended to clarify the practical interest of the cybernetic loop for medical purpose; first in evaluating a medical process, then in evaluating a specific study. The reliability of a given decision is tested simply by formulating four basic questions on the four steps and four basic questions on the four transitions. It is likely to enter the loop

at any step, but it is often convenient to first identify the pathophysiologic process. From any start point, other steps and transitions are determined subsequently. Basically, steps (boxes in all figures) are explored in terms of reproducibility (is the box clearly delimited?) and transitions (arrows in all figures) are explored in terms of predictivity (sensitivity and specificity, see figure 3). The global reliability of the loop is that of its lowest element. A negative answer in one element invalidates the reliability of the whole loop.

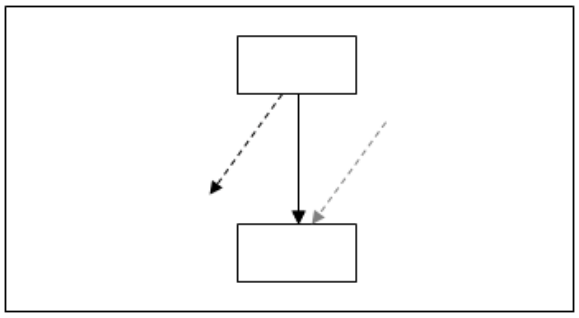

Figure 3. Representation of a part of the loop restricted to two steps with their transition. Boxes are the steps of the loop, arrows are the transitions. Black arrow = sensitive and specific transition. Dotted black arrow, lack of sensitivity, dotted grey arrow = lack of specificity.

a) Evaluation of a medical process

The ACC/AHA/HRS 2008 guidelines recommend implanting an internal cardioverter-defibrillator (ICD) to patients having ischemic or non ischemic cardiomyopathy with left ventricle ejection fraction ≤35% and New York Heart Association functional class II-III despite appropriate treatment.[19] Our purpose is to evaluate the global reliability attributable to this decision, based on the actual knowledge. In this example, the occurrence of a major arrhythmia leading to death is the pathophysiologic process that we want to treat. For clarity, the example is restricted to ventricular fibrillation and electric shock delivery but the same reasoning can be made for other major arrhythmias and the various algorithms used to stop them before shock delivery. Hence, the review starts at the pathophysiologic step.

1. Step pathophysiology. Is the pathophysiologic process reproducibly formalized?

Ventricular fibrillation is a chaotic electrical re-entrant wave front leading to cardiac pump failure, then to tissue dysoxia (especially brain), and ultimately death.[20,21] Spontaneous recovery of ventricular fibrillation is very exceptional.[22,23] Any ventricular fibrillation will lead to death with a degree of evidence (Figure 4).

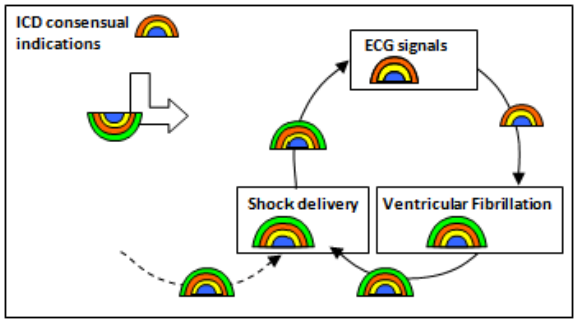

Figure 4: Cybernetic loop applied to "implanting an ICD". Ventricular fibrillation leads to death with a degree of positive evidence leading to add four layers of knowledge in the pictogram of the box "pathophysiology". When the answer to the question is negative, the pictogram is inverted (transition between domain and loop). The dotted arrow indicates that shock may be delivered without major arrhythmia (low specificity).

2. Step semeiology. Are input items reproducibly defined?

Input items are not clinical data in this example but a set of heart electric signals sensed by the ICD to determine the presence or not of ventricular fibrillation. The reproducibility of this set of items is debatable. We can score it at a belief degree because we have no other choice than accepting the manufacturer's guarantee. However, reliable technologies are available.[24-26] Even though unpublished, internal studies are required for regulatory approval. We can therefore admit a degree of experience.

3. Step therapy. Is the action (delivery of an internal electric shock) reproducible?

Electric shock is reproducibly delivered until the ICD battery contains enough power. There are similar concerns as that for question 2, but considering that it is a widely used technology, we can admit again a degree of evidence.

4. *Transition from semeiology to pathophysiology. Is the set of input items (electric items) sensitively and specifically linked with the pathophysiologic process (death from ventricular fibrillation)?*

This transition is sensitive if eventual disconnection of the sensors can be eliminated. It is specific if artefacts are properly filtered. It depends also on the ability of the system to determine if the electric signal is chaotic or not. For the same reasons as in question 2, let's admit a degree of experience.

5. Transition from pathophysiology to therapy. Is the pathophysiologic process (death from ventricular fibrillation) sensitively and specifically linked with therapy (shock delivery)?

This transition is sensitive because it has been shown that any ventricular fibrillation is followed by shock delivery. In contrast, the specificity is not perfect because inappropriate shock is possible.[27,28] In our schema, this is indicated by another arrow going in the box "therapy" (figure 4). The degree of knowledge is evidence for both high sensitivity and low specificity.

6. Transition from therapy to semeiology. Is therapy (shock) sensitively and specifically active on input items (a chaotic electric signal become not chaotic)?

Internal electric shock is proved to be efficient in treating ventricular fibrillation.[29] It is also exceptional that the ECG returns to normal when no shock is delivered.[22,23] Hence, the degree is evidence.

7. Step domain (nosology). Is the domain (ICD indications) determined reproducibly?

ICD indications have been consensually established, based on specific criteria for different cardiac pathologies.[19] The reproducibility of these individual criteria such as left ventricle ejection fraction ≤35%, or high stages of congestive heart failure has been

evaluated and found acceptable, [30,31] However, no studies have been designed to evaluate the reproducibility of specific associations of criteria. Then, we can consider this step as moderately reproducible with a degree of experience.

8. Transition from domain to loop. Is the domain sensitive and specific to the studied loop?

Using the ICD indications above, the important question turned out to be: are all patients at risk of ventricular fibrillation going to be implanted and are all implanted patients going to experience ventricular fibrillation? The answer is no with a degree of evidence. In MADIT II, 70% of the implanted patients will never experience ventricular fibrillation.[32] In these patients, the process is unnecessarily harmful because the surgical risk and discomfort are not balanced.

Finally, it is not surprising to find that, except its transition with the domain, the ICD loop is reliable with a global degree of experience since it is an automatic device, and therefore, uses a high level of modelization. Our approach allows anyone to point out quickly where new evidences are necessary as reported by experts.[33,34] Confidence with ICD would benefit by reporting the reliability of ICD electrical signal acquisition and analysis. Improving the specificity of shock delivery is also necessary and may be linked with better signal analysis. The major weakness is the poor link between the loop and the domain. Then, most of the patients with ICD will not use it. Optimizing the decision of implanting an ICD would require more reproducible and more specific domain definition (criteria for implantation). As examples, it has been suggested that black people may have no benefit of an ICD implanted according to MADIT II

indications.[35] Also in SCDHeFT, benefit from ICD was only seen in NYHA functional class II patients and not in class III/IV patients.[30]

a) Evaluation of a study

The cybernetic loop is also useful to weigh the interest of a specific study. To illustrate this usefulness, we will take the example of EPHESUS. This study published in the *New England Journal of Medicine* proved that an anti-aldosterone therapy by Eplerenone improves survival in patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure.[36] In this example, we can start with the step therapy. The basic questions seem in a) are not reformulated.

1. Step therapy: Pharmacological properties and therapeutic effects of Eplerenone were not investigated in EPHESUS, but we know from other studies that they are stable although a limited number of humans were studied.[37,38] In EPHESUS, observance was good. Therefore, we can admit that the therapeutic effect of Eplerenone is reproducible with a degree of evidence.

2. Step pathophysiology: The question that arises is: on which pathophysiologic process is Eplerenone active? The problem is that Eplerenone is suspected to impact at least three different pathophysiologic processes in addition to its well known potassium sparing effect: myocardial wall remodelling,[39] conduction tissue (electric) remodelling,[40] and endothelial protection, with coronary circulation improvement.[41] Then, in our cybernetic loop, we are obliged to consider three different "pathophysiologic" boxes (Figure 5). The degree of knowledge attributable is different

for the three processes: We can admit “evidence” for wall remodelling, “experience” for coronary perfusion improvement, and “experience” for electric remodelling. In order to simplify our schema, we can admit here that hypokaliemia is not a potentially fourth pathophysiologic step since correcting eventual

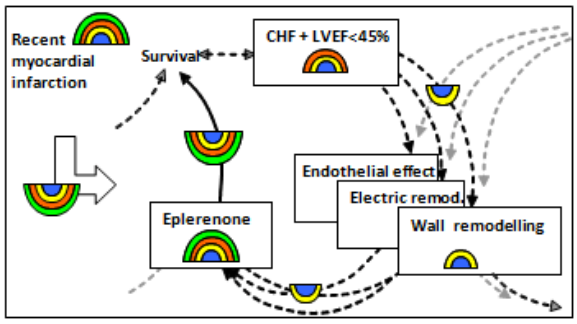

Figure 5. The EPHESUS loop shows that it is a very complex loop. Three different patho-physiologic boxes are necessary to represent the pathophysiologic processes on which the therapeutic action is based. Grey arrows represent transition from one or many other loops.

3. Step semeiology. Inclusion criteria in EPHESUS were: 1) recent myocardial infarction, 2) left ventricle ejection fraction< 45%, and 3) Clinical signs of congestive heart failure. There is some confusion here; “Recent infarction” is not changed by the therapeutic action and is consequently at a domain level, while the remaining two criteria susceptible to recovery by therapy, are input items. These two criteria are simple and acceptably reproducible.[42,43] Although their reproducibility in association has never been investigated, we can admit that few patients with the criteria have been excluded, while few patients without the criteria have been included (degree of experience).

4. Transition from semeiology to pathophysiology: Although recent severe infarction is likely to act very frequently on the three suspected pathophysiologic processes, these processes may be observed in situations without congestive heart failure and left ventricle ejection fraction <45%. Then the transition is not specific with a degree of experience.

5. Transition from pathophysiology *to therapy:* Are the three pathophysiologic processes sensitively and specifically linked with therapy by Eplerenone? We know little about electric remodelling therefore we cannot estimate the sensitivity and specificity of this transition. We do know that wall remodelling may justify other drugs therapy than Eplerenone (converting enzyme inhibitors for example). For this reason, the transition between wall remodelling and Eplerenone is not sensitive. However, this drawback is limited because inclusion criteria, recommended using converting enzymes inhibitors. Similarly the transition between the endothelium effect and Eplerenone is not sensitive, many other mechanisms are involved.[44] The specificity is also poor because other physiologic processes than the three processes involved here may be changed by Eplerenone, such as blood pressure and kidney function. In light of this, in EPHESUS, the link between known pathophysiologic processes and therapy is neither sensitive, nor specific (degree of evidence).

6. Transition from therapy to semeiology: The endpoint of the study was not the recovery of input items (impaired left ventricle ejection fraction and congestive heart failure), but survival; a global criteria on which the studied pathophysiologic processes and others are effective. Although improvement in survival is an important final goal, it

must be obtained by improving the input items of the pathophysiologic process. If this link is not ascertained Eplerenone may increase survival by improving other unsuspected pathophysiologic processes that can be found in this domain but also in other domains. Alternatively, Eplerenone may have an inconstant effect hiding important unpredictable inter-individual differences. Therefore many patients may be under treated or over treated.

7. Step Domain: Although the domain is not clearly identified in EPHESUS, we have seen that one of the inclusion criteria (recent infarction) was not at an input item level but at a domain level. So, the domain definition can be considered as being 'recent infarction" and being acceptably reproducible with a degree of evidence.[45]

8. Transition Domain-Loop: Most patients with recent infarctions are likely to have the three identified physiological processes. The transition is then sensitive. However, other domains such as dilated cardiomyopathy, myocarditis, or ischemic cardiomyopathy without recent infarction may act on the same three pathophysiologic processes. This transition is not specific (degree of evidence).

Hence, in this example, although Eplerenone increases survival, EPHESUS *considered alone* brings little intelligence as shown in figure 4. The link between pathophysiology and therapeutic action is neither sensitive nor specific. Even combined with past medical knowledge, EPHESUS did not tell us if all patients of the studied population are likely to benefit by Eplerenone or if the global result hides significant subpopulation discordances. In other words, Eplerenone is statistically good for the EPHESUS

population but we are not sure that it is good for each individual patient and that other patients not studied may not benefit from Eplerenone. Subsequently EPHESUS calls for additional studies.

Although more and more studies provide clinicians with undisputable pieces of evidence, the practical usefulness of these evidences in the daily practice is sometimes low. A medical application of the cybernetic loop, based to eight basic questions, may help in including evidences in a comprehensive schema for medical decision making and in determining which new research needs high priority. For better insertion in an intelligence-based medicine, we would expect any new study to initially recall the steps and transitions that are already controlled, to detail the methods of steps and transitions that the study intends to improve, and to summarize in conclusion which studies remain to be done. Because any medical domain is also a medical market, this tool will also throw light on when the loop is working for improving the knowledge or for enlarging a market.

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