A Fuzzy Logic- Based ‘Evidence –Based’ Medicine Best Reflects Understanding of Disease Processes and Physician Behavior

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Abstract: - We hypothesize that the model for physician reasoning and behavior as well as the understanding of normal and pathogenic mechanisms in nature can best be represented and understood using Fuzzy logic rather than Probability theory. This hypothesis is within the context of clinical medicine as it relates to the diagnosis and treatment of the patient with stroke. In the present paper we summarize our work in this area so far.

Key Words: - fuzzy, stroke, evidence-based medicine, causation, interaction, nature, probability

1 Introduction
The clinical field of cerebrovascular disease (stroke) deals with the diagnosis and treatment of patients who have suffered brain infarction and hemorrhage. The first is due to blockage of an artery by either thrombotic or embolic material, and the latter due to vessel rupture. Physician decisions regarding the diagnosis and treatment of stroke are made using both knowledge of the basic pathophysiology of the disease and those solutions suggested by the results of large randomized double-blind trials. Always, these latter are far behind the knowledge base of the understanding of pathogenesis as observed biochemically and pathologically.

Presently, a dilemma has arisen for the physician because there is a push both in academia and by insurers to base medical decisions on what is called ‘Science’. But ‘Science’ in this context refers to methodology based only on probability theory. This means that behavior at the bedside should limit itself to the latter. The dilemma lies in the fact that the physician treats the individual, but ‘Science’ does not respect the context of the individual patient nor the experience and expertise of the physician. The physician practically deals with the individual patient context in all decisions. Context refers to the unique presence of variables, and their interaction in an individual patient at a particular point in time and location in space. ‘Evidence – based medicine’ (EBM), as ‘Science’ currently is called in medicine, is the buzzword for medical schools, teachers and students to be and is based in probability theory [1]. It studies the collective of patients.

In recognition of the above ethical and practical dilemma facing the physician who must treat the individual patient, we considered the possibility that Fuzzy logic could be applied to the clinical context of the individual patient in a way that is meaningful to the physician, and that it can further be used to better study and understand the disease process of vascular
occlusion and rupture. If Fuzzy logic can so be used, clinical ‘science’ need not limit itself to behavior based on the results of clinical trials founded in probability-based statistics. We further hypothesized that Fuzzy logic may best represent ‘Nature’ as she is expressed in vascular occlusion or rupture in the individual patient because the pathologic process can be best explained in terms of a world which is not black and white, but where shades of grey allow fuzzification, granulation and ultimately computation with basic concepts of variables and their interaction. [2] While our approach to understanding and decision making in the stroke process is clinical in essence, it might be used to further the goal of automation in this area: i.e., the robot physician.

The following narrative describes progress we have made in solving the above physician dilemma, i.e., that ‘Scientific’ medicine (EBM) demands on physician behavior are contrary to his understanding of the pathogenesis and treatment of the individual patient with stroke.

2 Problems and Solutions
2.1 Problem #1

The medical diagnosis of clinical stroke is its classification. The classification is based on perceived cause. Causation, or etiology as stroke experts call it, is the diagnostic language of stroke. The EBM diagnostic process is based on what we term a linear sequential diagnostic algorithm where underlying causal conditions are tested for in the individual patient, and importantly, in a particular order based on prior frequencies or probabilities of reported conditions in the population of patients with stroke. After diagnostic testing is begun, diagnosis is based on the first positive test result. This linear methodology is counterintuitive for the physician because multiple concurrent conditions are not allowed. Using the EBM algorithm, and faced with a patient who has symptoms of stroke, the all or none first diagnostic decision is to discern infarct from hemorrhage. Neuro-imaging, (computed-tomography and nuclear magnetic resonance) do this. The next diagnostic decision is to look for the cause of the stroke. The EBM algorithm calls for either or choices to be made by the physician: either the stroke was due to thrombosis or embolism due to atherosclerosis, or due to cardiac source for thrombo-embolism, or due to intrinsic disease of the small vessels of the brain, or due to an ‘other’ infrequently reported process. This ‘Scientifically’ mandated approach, is based on classical black and white logic, prior probabilities but ignores the known pathophysiologic process underlying vascular occlusion or rupture which involves the presence to degree, and interaction to degree of multiple variables. These latter are known from biochemical and microscopic techniques, those techniques. In other words, the pathophysiology of stroke does not involve either or conditions or variables, but is rather a process involving the interaction of multiple variables, each present to degree. This interaction is commonly understood in physiology to be forward and feedback in nature, but a chain of interaction events or confluence of variables may also be the causal process.

The dilemma facing the physician is due to the imposition of the probability-based statistical scientific model on physician decisions regarding both the understanding of diagnosis, treatment and basic disease process present in each individual patient. We recognized that neither do physicians make practical decisions at the bedside for the patient on this basis in good conscience, nor does that model reflect the physician understanding of disease causation. We therefore sought another model for representing what has been described as the pathologic tenet for vascular occlusion and rupture, that of Virchow’s triad [3]. Treatment decisions for the individual patient practically depend on the variables defined by Virchow and these variables can be diagnosed with common blood, heart and vascular tests.
Virchow’s pathophysiologic triad is the accepted biochemical-physiologic model for haemostasis and vascular integrity in both health and disease. It demands the interaction of blood components, the vascular wall and blood flow. As a result of this interaction, a thrombus (blood clot) forms to degree, the vessel wall to degree participates in blood clot formation or dissolution, and vascular integrity is to degree maintained. In order therefore to best represent the clinical pathophysiology of the patient with stroke, we needed a method to represent the variables of Virchow’s triad, each to degree, simultaneously and in each individual patient.

**Solution#1:**
The Fuzzy hypercube served as our representational model for the three variables of Virchow’s triad [3] [4]. Each axis of the hypercube is one variable of Virchow’s triad represented by values [0,1]. A three dimensional space was easy to visualize. Each individual patient could be represented as a point as set of the three variables, each present to degree, and importantly, without the constraint that they must when their values are added together, add up to one. We chose blood, heart and vessel for our variables, analogous to Virchow’s triad, and represented each patient as a set as point in the fuzzy hypercube [blood, heart, vessel], each variable expertly defined as degree of severity of pathology [0,1] [4][5].

In order to make the causal diagnosis for vascular occlusion in each patient, the entire causal spectrum (differential diagnosis) was tested for, as was clinical practice at the time, but as flew in the face of the newly defined ‘scientific’ EBM diagnostic algorithm. For each patient, therefore, many blood tests, heart tests and vessel tests were performed as was routine and as aimed towards defining the degree of severity of presence of each of the variables of Virchow’s triad. The cost of all tests is still, and was then well within the limits of the cost of a funeral for the patient and no test was unusual in performance for the clinical situation of stroke.

Two ‘fuzzy’ concepts were used in the above representational model: fuzzification of each concept, blood, heart, vessel as well as granulation (data compression) within each concept. The methods and results of this study have been published [5]. In short, each of 30 stroke patients was defined after testing as a set as point mapped into the fuzzy hypercube of 3 variables blood, heart and vessel. It therefore possible to represent the individual patient as a complex of multiple variables, all present to degree where each variable was unconfined by the valuation of the other variables, but simultaneously represented with other variables in the hypercube. Importantly, it was found that only one patient fell within the dimension (n - 1 dimension in the n – dimensional fuzzy hypercube) of probability[6]. In other words, after intuitive physician expert assignment of degree of presence of each of 3 variables in the individual patient, only one patient had variables present each to degree so that when added together in by value, the Measure was one[6]. This meant, that it was possible to define the stroke patient diagnostically without rounding off to 1 or 0 the natural presence of disease variables in each of 30 stroke patients. This showed then, that the ‘scientific’ all or none disease categorical choices demanded by EBM and used in all probability based large double-blind randomized trials was not the only way to represent biologic variables behind stroke in each patient. As no two patients occupied the same point in the hypercube, it meant that each patient was individually unique as to his combination of variables, each variable uniquely present to degree. This suggested that the clumping together of stroke patients into a collective where supposedly the pathologic process was the same for all patients was an oversimplified representation of the problem in addition to being non-representational for any individual patient. Finally, it suggested to us that each stroke (vascular occlusion or rupture) as represented by each individual patient was the result of interaction of the 3 variables, each present to degree. No
measure of such interaction has ever been the clinical basis for treatment in EBM. Yet, in practice such a measure might demand unique therapy for each patient.

It must finally be emphasized, that the process of conceptualization, fuzzification and granulation of the disease process for each patient came naturally to us as physicians[2], even though it flew in the face was what was being imposed on us as ‘scientific’ practice. We showed that an other mathematical approach, i.e. other than probability based, to the real patient problem was feasible.

**Problem #2:**
The second problem facing us grew out of the first solution, i.e., could we measure using fuzzy methods, mathematical, the interaction between the variables of blood, heart and vessel. We first asked if this could be done to better understand the disease process of vascular occlusion and second how much this measure of interaction is unique to each patient. In order to do this, collaboration with expertise in Fuzzy mathematics, engineering and computers was necessary. Julie Dickerson, Ph.D. of Iowa State University agreed to help us with the analysis of concurrent mechanisms in our 30 and then in 166 patients with ischemic stroke, all of whom had undergone the same examinations and designations as sets as points in the fuzzy hypercube for the 3 variables, blood, heart and vessel, each present to degree [0,1] as previously described [5]. We hypothesized that we would find a sensible strong measure of interaction between variables that pathologically made sense. We also hypothesized that individual variation might be present, though we would not be able to define why this is so.

**Solution #2**
Dickerson et al. first published the results of this study for the 163 ischemic (vascular occlusion) stroke patients in 1997 [7]. Using the fuzzy c-means algorithm, and non-hierarchical clustering techniques, structure and relationships amongst the three variables were sought. Results showed that there was an interaction that was strong between blood and vessel variables when each is present to moderately severe degree [7]. A less strong interaction was found between blood and heart. No interaction was found for heart and vessel. The clustering results suggested then that there was a causal interaction between these variables when each was present to certain degree. This finding may be important in the pathogenesis of vascular occlusion.

Rather than representing each patient as an all or none one pathogenic mechanism for stroke (blood, or heart, or vessel), the fuzzy logic representation and analysis of the data provided for the presentation of pathogenic interactive mechanism. The interaction that was implied biologically made sense to the physician and could be interpreted as interaction between vessel lining and blood components. In addition, the fuzzy logic analysis better represented the individual patient’s pathologic complexity because not all patients belonged to any one cluster to the same degree. These results generated a new hypothesis, and that was that the fuzzy logic approach to stroke diagnosis would be important for the study of the basic mechanisms involved in vascular occlusion/rupture and that as a measure of interaction between variables did not require their separation from the object of interest, the individual patient. Such representation could be used in clinical trials and ultimately improve the individualized quality of treatment for prevention of recurrent stroke.

**Problem #3**
The problem remained as to which method of gathering and interpreting clinical data, the EBM probability based statistical analysis used in ‘Scientific’ clinical trials, or the fuzzy analysis techniques would best reflect the cause of stroke in the individual patient. We hypothesized that a fuzzy approach would do this best. The hypotheses was tested using the same patient data, but with collaboration with a different group of fuzzy experts. The problem we faced was that ‘science’ was defined by probability based statistical analysis of patient data, and
indeed laboratory data, and the results of large double-blind randomized trials. If fuzzy logic best represented individual pathogenesis of stroke, then we had to show that it best captures the situation variable interrelation in natural objects, patients, when compared to probability based statistical analysis of collective pathology. We therefore decided to visit the issue of separation of variables from the natural object of interest, the patient, as is required for probabilistic statistical analysis. Separation was viewed as a discarnation of the variables, blood, heart and vessel from the natural physiologic system of the patient [8]. It was felt that in no way could such a procedure allow for the measurement of the natural interrelationship of variables as they co-exist in the individual patient. It is the physiologic system of the patient and not that of the collective of patients in which variables react chemically, physiologically, and biologically.

In order to compare the results of variable interaction as they occur in nature, i.e., in the physiologic system of the patient, we used the same patient data from the 30 original patients studied by Helgason [5]. Fuzzy measures—hierarchical clustering techniques—and standard statistical analysis (Pearson’s product–moment correlation (regression analysis) and Spearman’s rank correlation were applied to the data consisting of ‘fit’ values [0,1] for the 3 patient variables blood, heart and vessel condition severity. Real patient variable combinations (real patient ‘sets as points’ in the fuzzy hypercube) and fabricated patient variable combinations (patients as sets as points made from real patient variable values after their shuffling) were studied. Real patients occur in nature, fabricated patients did not represent the naturally observed unique real patient=natural combination of variable values. Natural real patient variable values for blood, heart and vessel were separated from the real patients and shuffled. By this means three groups of fabricated patients were formed. The hierarchical fuzzy clustering method reflects in a natural way, the structure of the given data. This method was therefore different from that applied in the study with Dickerson [7] which used non-hierarchical clustering techniques using the same patient data set, but where the clustering problem specified the desired number of clusters. Two hierarchical fuzzy clustering methods were used, and three measures of fuzziness.

Solution #3
Importantly, the results of this study did agree with that of Dickerson, though different clustering technique was used [7]. More importantly, there was a difference between the measure of variable interaction in real natural patients when compared to that in fabricated patients. In the real patients, the fuzzy measures found variable interaction to be strong between blood and vessel. All fuzzy measures found this. The same variable interaction was found by all the fuzzy measures in the first fabricated patient data set (after one shuffle). In contrast, the two statistical measures of variable interaction did not consistently find the same variable interaction in real patient data, and in addition found different variable interactions in the shuffled (non-natural) data, i.e., in fabricated patients. The interaction described in the fabricated patients was that of heart and blood and was statistically ‘significant’ [8]. (It is of interest that this was the weaker interaction found by Dickerson [7]. This may reflect the impression that the interaction between vessel and heart is very remote.)

We concluded from this study that probability based statistics, because of its need to separate variables from each other as they occur naturally in an object of interest creates the potential for artifact in measurement of non-natural variable interaction. This in turn, suggests that the extrapolation and application to the individual patient of results of clinical trials using the above standard statistical techniques must be called into question on two counts. First, probability based statistics is not the only way to represent and study patient data, and second, the results of studies using these techniques cannot be
extrapolated to the individual object of interest, in this case the patient, reliably.

**Conclusion**
The above narrative describes historically our attempt to use Fuzzy theory as the basis for representation of natural causal processes as well as physician behavior. It represents an attempt to redeem the individual patient as the object of compassion and competent care based on the best science available. We have shown that probability-based approach to these issues is limited in its scope and must not be the only basis for decisions regarding diagnosis and treatment of patients with stroke.

**References**