signal carried by the lysosomal enzyme and becomes responsible for carrying the protein to its correct destination.

Both the bound lysosomal enzyme and the low density lipoprotein receptor then move in vesicles to the *medial* and then to the *trans* cisterna. Here they part company, each being separately packaged into budding vesicles. The lysosomal enzyme is carried to lysosomes, where the mannose-6-phosphate tag is hydrolysed. This releases it from the receptor, which recycles back to the *cis* Golgi cisterna for further rounds of lysosomal transport. It is not known how the low density lipoprotein receptor is directed to the cell surface. Many argue that this is the default pathway—that is, everything that leaves the endoplasmic reticulum is sent to the cell surface unless it is either removed or retained on the way.

Once on the cell surface the low density lipoprotein receptor begins to cycle. To do that it must contain information that causes it to be trapped selectively in coated pits. The tag for this selective trapping resides in that part of the receptor exposed to the cytoplasm. Mutations in this part yield receptors which are expressed on the cell surface and bind low density lipoprotein, but they are not efficiently internalised. Cholesterol cannot be taken up, and children with this defect suffer from familial hypercholesterolaemia. The tag is extremely efficient, allowing a

5000-fold purification of the receptor in a single step. This ensures that only those proteins that are meant to go to the endosomes are delivered there. All others are excluded from coated pits. The mechanism which carries out this selection is still unknown.

In summary we should remember that the three dimensional organisation of the cell demands two types of information: information to transfer the protein to that part of the cell where it is to function, and information which allows it to carry out its function. In the simplest case this entails merely keeping it in a particular compartment. In the more complicated case information is needed to move it specifically between compartments. Future work will uncover more of the signals which encode this information and determine the nature of the mechanisms which decode it.

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Logic in Medicine

An outline of formal logic and its applications in medicine—II

JOHN K SLANEY

III—Logic and life: the application of formal systems

Any science—physical, biomedical, or any other—has as its outcome theories. Theories may, as suggested in the last section, be considered as sets of statements closed under logic. Thus logic is the abstract theory of theories. A system of logic works on theories in two ways. Firstly, it issues permissions to argue in certain ways. It offers guarantees that certain forms of argument—the ones that it delivers as valid—will never introduce falsehood into any body of theory. Arguing in the permitted ways may bring hidden falsehoods to light but will not itself be the source of any error. Secondly, it prohibits certain sorts of theory. Specifically, it prohibits theories that do not contain all their own logical consequences. The significance of this fact will become apparent in the next section. In that it provides a characterisation of the concept of “theory,” logic relates to medical science in just the same way as to other sciences, no more and no less closely.

A second way in which logic impinges on medicine is by imposing constraints on actual passages of argument. All rational activity is subject to rules; it is a virtue of the way in which it is governed by

rules that it counts as rational. The rules of formal logic are culled from those of natural discourse and must be measured against such discourse to assess their adequacy. It is clear that valid and accurate reasoning is needed not only in research but also in the day to day practice of medicine—for instance, in diagnosis and in the decision making that goes with treatment. Much of this reasoning, where it is complex enough to need doing consciously, will require far more elaborate parts of language than are covered by the example of & and → calculus given previously. It will be partly mathematical, particularly probabilistic, for instance. But its basic structure will still be logical, and there is no reason why reflective awareness of the qualitative logical structure of inference should not add some clarity to the thought processes required. At the very least, fluency with formal languages often confers a facility in grasping and manipulating intricate or convoluted statements or reasonings, keeping track of several layers of hypothesis, and so on.

Counterexample

A system of formal logic is a catalogue of valid forms of inference, but it is not going to be used as a straightforward diagnostic tool like a chart or handbook. Appeals to logic occur in more complicated dialectical contexts. Suppose, for example, someone makes a claim C, of which you are unconvinced. You may well reply by asking why C is thought to be true. Its proponent might then produce an argument with C as its conclusion. At this point you have several rational options. One option is to challenge the validity of the argument, perhaps backing up your challenge with a counterexample

—that is, another argument of the same form but with true premises and a manifestly false conclusion. For example, if the proffered argument were:

If there is an Act of God on Saturday United stand a chance of winning
There will be no Acts of God this week
Therefore United don't stand a chance

a suitable counterexample might be the parallel argument:

If Edinburgh is part of Glasgow it is in Scotland	(true)
Edinburgh is not part of Glasgow	(true)
Therefore Edinburgh is not in Scotland.	(false)

If the argument were:

No car is dangerous unless badly driven
Jimmy drives a Porsche very badly
Therefore Jimmy's car is dangerous

we could counter that you might as well argue:

No car is legal unless it has brakes	(true)
Jimmy drives a wreck with brakes	(suppose true)
Therefore Jimmy's car is legal.	(false, as it has bald tyres and no lights)

A counterexample, however, may not end the debate, as there is room for disagreement about whether the two arguments are really of the same form, whether the first is also of some other, valid, form, and so on.

One direction that the discussion could then take would be an appeal by the proponent of C to formal logic. An argument form might be found that is provable in the formal system and whose conclusion fits the form of C. This is what Euclid did in geometry with problematic propositions like Pythagoras's theorem, as already noted. The debate, however, might still not end, for you have the options of criticising the formalisation—the mapping between natural and formal language—and of course of denying or questioning one or more premises of the formalised argument. You might even question the correctness of the formal system itself, as we shall see. The debate over support for C can go on for a long time, getting more and more convoluted. Appeals to logic may sometimes settle the matter; sometimes they bear on it less directly by exposing hidden assumptions, contentious definitions, and the like, advancing understanding of what is at stake. Much of philosophy, natural theology, and (more frivolously) the activities of the Flat Earth Society show the lengths to which this kind of rational investigation may go. Lakatos provides an illuminating and profound discussion, in delightful style, of some of the intricacies arising particularly in mathematical reasoning.¹

Philosophy of medicine

Questions demanding definitions can easily lead to investigations into the conceptual foundations of medicine. Think of simple questions such as "Is the common cold one disease with many causes or many diseases with similar symptoms?" This may seem to be fairly trivial, but it quickly leads to harder issues such as: How many diseases be individuated? Have biological discoveries taught us more about diseases or have they given us a new concept of "disease"? Is the concept of a disease useful at all? As there is in any case no treatment (apart from lessening the symptoms) what purposes, if any, are served by the possible finer distinctions?

In approaching questions of this sort we are no longer studying medicine but studying the philosophy of medicine. Medical explanations are another source of philosophical tangles. Consider the old joke about the patient with the arthritic hip:

DOCTOR: How old are you?

PATIENT: 82.

DOCTOR: Well then, it's probably due to old age.

PATIENT: Can't be. The other hip's just as old, and there's nothing wrong with that.

The joke rests on a misunderstanding of the way in which the explanation is to be taken. What does it show about the concept of explanation in medicine? How does such explanation compare with explanation in natural science? In the social sciences? In everyday

life? Answers to questions like these cannot simply be read off a formal logical calculus, but logical reasoning will certainly be required if they are pursued seriously.

IV—The future: logic in computation

One way in which logic is going to be important to medicine is through the impact of computer technology. Because the factual basis of medicine is so immense and detailed, and because the day to day diagnostic and other problems it poses are set up in terms of these complex empirical facts, observed symptoms, case histories, known effects of treatments, and so on, medicine is a natural home for what are now becoming known as knowledge based expert systems. The science fiction dream of a robot doctor, a specialist in everything, is closer to reality than was thought possible even a few years ago. Not, perhaps, the smartly dressed tin man with the perfect bedside manner but the micro in the corner of the surgery with access to a database equal in information content to the accumulated knowledge of many specialists; this is just next year's handy gadget. Next year? Well, perhaps the year after; certainly within a decade. The necessary hardware—cheap, fast microprocessors, compact discs, and so on—is either in the shops now or just about to be. Many aspects of the software still need much work, but progress is reported almost constantly. Clearly, some knowledge based systems will soon be common, and their scope and their automatic reasoning ability will increase manyfold over the next few years.

Artificial intelligence

The theory of computation is in part an offshoot of mathematical logic. It has recently been joined by another offshoot: the new science of artificial intelligence. "Expert" systems addressing large bases of data need to be artificially intelligent to some degree. In particular, to arrive at answers to unforeseen questions they have to make deductions using the data as premises. For this purpose they have to use some sort of logic. An expert system must, therefore, be in part an inference system.

Thus formal logic is about to re-enter the practical sphere in a very important way through developments in artificial intelligence. In the remainder of this paper I want to outline just one aspect of the new development of logic, showing how certain abstruse reflections coming from philosophical logic could turn out to be pertinent to these very practical matters. Such relevance cannot readily be predicted and is one of the urgent reasons why basic research needs to be fostered without much reference to short term profits or visible products.

Recall that systems of logic like that set out in section II are intrinsically simply abstract algebras. They gain their importance from analogies between their formal rules and reasoning processes in real life. There are at least two reasons why this leaves it rather indeterminate whether a given formal system is a correct account of logic. Firstly, there are just not enough facts about natural reason to settle all the questions. Real life reasoning is not that precise. Secondly, logic is a theory not about how people do reason but about how they ought to reason. Thus adopting a system of formal logic as a template for arguing, theorising, and the like will tend to influence the rules actually in force governing rationality.

To illustrate the indeterminacy of logic consider the argument:

If grass is green then snow is white then grass is green
Therefore grass is green.

If you have any firm intuitive sense of whether this is valid or not then you are on your own. The corresponding argument form $(P \rightarrow Q) \rightarrow P$, therefore P is invalid in the system set out in section II but valid according to the account of $\rightarrow$ more usually offered by logicians. How can the issue be decided? Certainly not by appealing to one off intuitions. Formal logical investigations will show that it makes a large systematic difference which way we decide, and philosophically based preferences may then sway us one way or the other. The mathematical and philosophical publications on this point are many

and mostly rather abstruse, though Van Dalen gives a good account of the issues.² Argument forms like the one above get labelled valid or invalid on the basis of some larger theory, not on their individual merits; different choices of theory may well label them differently.

Deviant logic

Led by reflections like these or by convictions that the usual logical theories were in error, logicians of adventurous dispositions have developed many rival formal systems and offered them as being more or less adequate reconstructions of natural reasoning. Over the past hundred years or so there has been a steady growth both in the number of well investigated alternative systems made available and in the realisation of how wide the choice of logics is. Research in non-standard logic, however, has always been a minority interest, tending to be regarded by mathematicians as philosophical dabbling and by philosophers as mathematics gone awry. "Deviant" logic has never been a quick road to academic tenure. Recently, however, the situation has begun to change since the arrival of computer scientists who have practical problems to solve, no axes to grind, and no particular resistance to the idea that logical theorems might be open to question. At least two groups of "deviant" logicians are becoming recognised as having much to offer to the new science of automated reasoning. They are the advocates of "fuzzy logic" and of "relevant logic."

The guiding notion of fuzzy logic is that truth and falsehood, rather than being all or nothing, are matters of degree. In models for this kind of logic there is a continuum of values between absolute truth and absolute falsehood, so that on interpretation statements can lie vaguely in a middle range. Associated with fuzzy logic are fuzzy theories. Fuzzy set theory is particularly important and gives rise to theories of fuzzy functions, fuzzy numbers, and so on.^{3,4}

Quite apart from the advantages of sensitivity to the vagueness typical of most of natural language, fuzzy values are useful in representing information that is either imprecise or true or false to a degree, or both, but that does not involve probabilities. Descriptions of medical symptoms are often of this kind: degrees of severity, extensiveness, persistence, and so on, are very important and are more readily mapped formally on to fuzzy values than on to probabilities. There is a lively debate among users of the theory of information retrieval systems over the merits of a basis of fuzzy logic for evaluating descriptions of items in a database.⁵ Although the issue is by no means settled and is unlikely to be settled quickly, claims made for the increased accuracy and suitability of responses in fuzzy based systems at least need to be met. With or without a fuzzy logic probability theory is necessary for any formal reconstruction of diagnostic logic. The intricacies of combining probabilities with fuzzy reasoning are generating further, often difficult, research.

Relevant logic is harder to characterise briefly. It differs from orthodox logic in not allowing as valid those arguments whose premises are not related in subject matter to their conclusions.^{2,5} An example is P , therefore $Q \rightarrow Q$, proved as follows:

(1)	P	Premise
(2.1)	Q	Assumption for subproof
(3)	$Q \rightarrow Q$	From 2, by rule 5.

Proofs like this are blocked in relevant logic by the requirement that premises be used before anything counts as a derivation from them. Specifying what is a "use" turns out to be a delicate matter. The formal development of relevant logics is also complicated, their model theory especially presenting difficulties.

That relevant logic is a stable and workable system that is weaker than orthodox logic—that is, allowing fewer inferences—turns out quite unexpectedly to be useful. As the logic is weaker than usual it prohibits fewer kinds of theory than usual and has more models than usual. At the same time relevant logic is strong enough to allow the

reconstruction of most—arguably all—of the proofs that anyone actually needs. In constructing automated reasoning systems it is advantageous to use a logic no stronger than necessary, because automatic reasoning is not so much a matter of driving derivations forward along valid lines as of avoiding attempts to reach conclusions by means that are not going to work. The automated reasoner looks at the desired conclusion and asks how such a thing could have been derived. There are usually many possible answers to try out, and the trick is to reject false trails as efficiently as possible in order to leave the correct one.

Discovering that a possible route leads nowhere is often a very complex and difficult matter. One way to make it simple is to use an interpretation of the logic in which counterexample to the proposed derivation is exposed. And the more models—especially "small" ones—that the logic has the more chance there is for this strategy to succeed. Some of the extra models are wildly unintended but show easily that theories have intended properties. For example, relevant arithmetic has an interpretation in which $0=2$. This is absurd, of course, but none the less suitable for showing that we cannot relevantly prove $0=1$ (something surprisingly difficult for orthodox arithmetic). As automated reasoning is so much a matter of avoiding the unprovable, rather than advancing directly to proofs, systems in which disproofs are easy to determine could well be more efficient than their orthodox counterparts. Again, the practical investigations and the debate over their use are at an early stage, but at least some results seem to be non-trivial.⁶

Unorthodox benefits

I do not wish to give the impression that research in unorthodox logic is the only or even the main source of what is valuable in artificial intelligence. The two examples just given are intended to show how research programmes that have confused and impractical beginnings may bear unexpected fruit. Both relevant and fuzzy logic grew out of philosophical concerns of at best debatable intrinsic worth and have been pursued for years by small groups well outside the mainstream of research in logic. Yet both are now set to deliver insights beneficial to information technology and thus to its applications, including those in medicine. Both illustrate the view of logic that I have tried to present throughout this essay. Formal logic is not a technique for making diagnosis easier, though it does bear obliquely on that problem. It is an abstract and beautiful study of how the attempt to describe reality is self coherent. Practical applications arise indirectly, sometimes from its most unlikely facets.

When I was first asked to write an article outlining my subject for a medical audience I confess to having found the prospect daunting, standing as I do a little in awe of the sheer volume of knowledge characteristic of medicine in contrast with the pure speculation more often found in logical research. Having arrived at this end of the business, I hope to have caused people to have some new and perhaps unfamiliar thoughts. And of course if anyone reading this is moved to develop an interest in logic or its kindred disciplines the task was worth doing.

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