Introduction

John von Neumann sent a remarkable letter to Norbert Wiener on November 29, 1946. In his letter, von Neumann candidly discussed his views of the future prospects of two young scientific disciplines: neurophysiology and molecular biology.

Von Neumann's letter is remarkable for the accuracy and imaginative power of the scientific vision it expresses. As the reader will discover, von Neumann's vision was largely—but not wholly—realized during the ensuing fifty years. Those aspects of von Neumann's vision that still remain unrealized include some of the most important scientific challenges of the 21st Century.

The following is the complete text of von Neumann's letter [1]:

THE INSTITUTE FOR ADVANCED STUDY
School of Mathematics
Princeton, New Jersey

November 29, 1946

Professor Norbert Wiener
Department of Mathematics
Massachusetts Institute of Technology
Cambridge, Massachusetts

Dear Norbert:

1[2] This letter represents an effort to do better than I estimated in my letter of November 25, in which I proposed that we might get together for the afternoon or evening of December 4 in Cambridge, and indicated only somewhat vaguely what the subject was that I would like to discuss with you. I am now trying to give you a more detailed advance notice, hoping that this will make our discussion on December 4 more specific.

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[1] J. von Neumann, "Letter to Norbert Wiener from John von Neumann", in *Proceedings of the Norbert Wiener Centenary Congress, 1994*, eds. V. Mandrekar and P. R. Masani, Proceedings of Symposia in Applied Mathematics 52: 506–512 (1997):

[2] paragraph numbers have been added

2 Our thoughts—I mean yours and Pitts' and mine—were so mainly focused on the subject of neurology, and more specifically on the human nervous system and there primarily on the central nervous system. Thus, in trying to understand the function of automata and the general principles governing them, we selected for prompt action the most complicated object under the sun—literally. In spite of its formidable complexity this subject has yielded very interesting information under the pressure of efforts of Pitts and McCulloch, Pitts, Wiener and Rosenblueth. Our thinking—or at any rate mine—on the entire subject of automata would be much more muddled than it is, if these extremely bold efforts—with which I would like to put on one par the very un-neurological thesis of A. Turing—had not been made. Yet, I think that these successes should not blind us to the difficulties of the subject, difficulties, which, I think, stand out now just as—if not more—forbiddingly as ever.

3 The difficulties are almost too obvious to mention: they reside in the exceptional complexity of the human nervous system, and indeed of any nervous system. What seems worth emphasizing to me is, however, that after the great positive contribution of Turing-cum-Pitts-and-McCulloch is assimilated, the situation is rather worse than better than before. Indeed, these authors have demonstrated in absolute and hopeless generality, that anything and everything Brouwerian can be done by an appropriate mechanism and specifically by a neural mechanism—and that even one, definite mechanism can be "universal". Inverting the argument: nothing that we may know or learn about the functioning of the organism can give, without "microscopic", cytological work any clues regarding the further details of the neural mechanism. I know that this was well known to Pitts, that the "Nothing" is not wholly fair, and that it should be taken with an appropriate dose of salt, but I think that you will feel with me the type of frustration that I am trying to express. (H. N. Russel used to say, or to quote, that if the astrophysicist found a general theory uniformly corroborated, his exclamation should be "Foiled again", since no *experimenta crucis* would emerge.) After these devastatingly general and positive results one is therefore thrown back on microwork and cytology—where one might have remained in the first place. (This "remaining there" is of course, highly figurative in my case, who have never been there.) Yet, when we are in that field, the complexity of the subject is overawing. To understand the

brain with neurological methods seems to me about as hopeful as to want to understand the ENIAC with no instrument at one's disposal that is smaller than about two feet across its critical organs, with no methods of intervention more delicate than playing with a fire hose (although one might fill it with kerosene or nitroglycerine instead of water) or dropping cobblestones into the circuit. Besides the system is not even purely digital (i.e. neural): It is intimately connected to a very complex analogy; (i.e. humoral or hormonal) system, and almost every feedback loop goes through both sectors. If not through the "Outside" world (i.e. the world outside the epidermis or within the digestive system) as well. And it contains, even in its digital part, a million times more units than the ENIAC. And our intellectual possibilities relatively to it are about as good as somebodies vis-a-vis the ENIAC, if he has never heard of any part of arithmetic. It is true that we know a little about the syndromes of a few selected breakdowns—but that is not much.

4 My description is intentionally exaggerated and belittling, but don't you think that there is an element of truth in it?

5 Next: If we go to lower organisms from man with 10^{10} neurons to ants with 10^{6} neurons—we lose nearly as much as we gain. As the digital (neural) part simplifies, the analogy (humoral) part gets less accessible, the typical malfunctions less known, the subject less articulate, and our possibilities of communicating with it poorer and poorer in content.

6 Further; I doubt that the "Gestalt" theory, or anybody's verbal theory will help any. The central nervous system is complicated, and therefore its attributes and characteristics have every right to be complicated. Let not our facile familiarity with it, through the medium of the subjective consciousness, fool us into any illusions in this respect.

7 What are we then to do? I would not have indulged in such a negative tirade if I did not believe that I see an alternative. In fact, I have felt all these doubts for the better part of a year now, and I did not talk about them, because I had no ideas as to what one might say in a positive direction.

8 I think now that there is something positive to be said, and I would like to indicate in which direction I see it.

9 I feel that we have to turn to simpler systems. It is a fallacy, if one argues, that because the neuron is a cell (indeed part of its individual insulating wrapping is multicellular), we must consider multicellular organisms only. The cell is clearly an excellent "standard component", highly flexible and suited to differentiation in form and in function, and the higher organisms use it freely. But its self-reproductivity indicates that it has in itself some of the decisive attributes of the integrated organisms—and some cells (e.g. the leukocytes) are self-contained, complete beings. This in itself should make one suspicious in selecting the cells as the basic "Undefined" concepts of an axiomatism. To be more *par terre*: Consider, in any field of technology, the state of affairs which is characterized by the development of highly complex "Standard components", which are at the same time individualized, well suited to mass production, and (in spite of their "standard" character) well suited to purposive differentiation. This is clearly a late, highly developed style, and not the ideal one for a first approach of an outsider to the subject, for an effort towards understanding. For the purpose of understanding the subject, it is much better to study an earlier phase of its evolution preceding the development of this high standardization-with-differentiation. I.e. to study a phase in which these "Elegant" components do not yet appear. This is especially true, if there is reason to suspect already in the archaic stage mechanisms (or organisms) which exhibit the most specific traits of the simplest representatives of the above mentioned "late" stage.

10 Now the less-than-cellular organisms of the virus or bacteriophage type do possess the decisive traits of any living organism: They are self reproductive and they are able to orient themselves in an unorganized milieu, to move towards food, to appropriate it and to use it. Consequently, a "true" understanding of these organisms may be the first relevant step forward and possible the greatest step that may at all be required.

11 I would, however, put on "true" understanding the most stringent interpretation possible: That is, understanding the organism in the exacting sense in which one may want to understand a detailed drawing of a machine, i.e. finding out where every individual nut and bolt is located, etc.

12 It seems to me that this is not at all hopeless. A typical bacteriophage, which can be multiplied at will (and hence "counted"—by the colonies it forms on a suitable substrate as reliably as elementary particles can be "counted" by a Geiger-counter) is a phage that is parasitic, I think, on the Bacillus *Coli*. It has been extensively worked with, e.g. by Delbruck at Vanderbilt. It is definitely an animal, with something like a head and a tail. Its dimensions are, I think, 60 nm x 25 nm x 25 nm, i.e. its volume is $60 \times 25 \times 25 \text{ X } 10^{-21}$ cm^3 = 3.7×10^{-17} cm^3. The density may be taken to be 1, hence its mass is about 3.7×10^{-17} gr, i.e. the same as about 2.5×10^7 H atoms. Since the average chemical composition of these things is usually about C or N or O per one or two H, the average atomic weight of its constituents is about 6. Hence the number of atoms in it is about 4×10^6. Furthermore, it is known from the behavior of physiological membranes, that they are monomolecular—or oligomolecular—Langmuir-layers, which exercise their function in a highly mechanical way. E.g. the so-called "active permeability": The peculiar ability to "permit" ions to pass through the membrane against an electrical field—an activity which clearly must, and demonstrably does, require an energy supply from the metabolism—and which is therefore better described as "Pushing the ions across": than as "Permitting them to pass". I understand that here an ion simply gets seized by the opposite-polarity end of one of the rare (charged) radicals in the membrane.* Very similar things can be said about the functioning of the "phosphate bond", which seems to be the main physiological device for localized, short time energy storage, i.e. the equivalent of a spring. Thus one can really talk of "mechanical elements", each of which may comprise 10 atoms or more. Thus the organism in

* which then turns around and deposits the ion on the other side of the membrane

question consists of six million atoms, but probably only of a few hundred thousand "mechanical elements." I suppose (without having done it) that if one counted rigorously the number of "elements" in a locomotive, one might also wind up in the high ten thousands. Consequently this is a degree of complexity which is not necessarily beyond human endurance.

13 The question remains: Even if the complexity of the organisms of molecular weight 10^7–10^8 is not too much for us, do we not possess such means now, can we at least conceive them, and could they be acquired by developments of which we can already foresee the character, the caliber, and the duration. And are the latter two not excessive and impractical?

14 I feel that the answer to these questions can already be given, and that it need not be unfavorable. Specifically:

15 I am talking of molecular weights 10^7–10^8. The major proteins have molecular weights 10^4–10^5 (the lowest one known actually appears to be only about 7,000) and the determination of authorities like Langmuir and Dorothy Wrinch consider it promising. Langmuir asserts that a 2-4 year effort with strong financial backing should break the back of the problem. His idea of an attack is: Very highly precision x-ray analysis, Fourier transformation with very massive fast computing, in combination with various chemical substitution techniques to vary the x-ray pattern. I realize that this is in itself a big order, and that it is still by a factor 10^3 off our goal—but it would probably be more than half the difficulty.

16 In addition there is no telling what really advanced electron-microscopic techniques will do. In fact, I suspect that the main possibilities may well lie in that direction. The best (magnetic) electron-microscope resolutions at present are a little better than 10 Å = 1 nm. With 4×10^6 atoms in a volume of 3.7×10^{-17} cm^3 = 3.7×10^4 nm^3, the average atomic volume is 10^{-2} nm^3 and hence the average atomic distance about 1/5 nm. Hence the 1 nm resolution is inadequate—but not very far from what might be adequate. A resolution that is improved by a factor of 10^2 might do. It is dubious whether electron lenses can be improved to this extent. On the other hand, the proton microscope need not be more than 2–4 years in the future, and it would certainly overcome these difficulties.

17 Besides all these developments might be pushed and accelerated. Of course, everybody knows that a 1-1/2 Å resolution would mean: One could "look" at an H atom, and with a little more, say 1/5 Å, one could "see" the Schroedinger-charge-cloud-of the orbital electrons. But the physiological implications are even more extraordinary, and they should receive a great deal of emphasis in the immediate future.

18 At any rate, I think that we could do these things: Study the main types of evidence: Physiology of viruses and bacteriophages, and all that is known about the gene-enzyme relationship. (Genes are probably much like viruses and phages, except that all the evidence concerning them is indirect, and that we can neither isolate them nor multiply them at will.)

19 Try to learn a reasonable amount about the present state of knowledge and opinions concerning protein structure.

20 Study the methods of organic-chemical structure determination by x-ray analysis and Fourier-analysis with their necessary complement of manipulations.

21 Study the principles and methods of electron-microscopy, both in the direction of electron optics and in the direction of object-manipulation. Try to get oriented to the possibilities of proton-microscopy.

22 Finally: Compile for our common use two lists: (1) Relevant publications, with the main emphasis for the immediate future, considering our lack of education, on books and survey articles. (2) Persons from whom we might learn most about the state of affairs and the outlook in these fields.

23 I did think a good deal about self-reproductive mechanisms. I can formulate the problem rigorously, in which Turing did it for his mechanisms. I can show that they exist in this system of concepts. I think that I understand some of the main principles that are involved. I want to fill in the details and to write up these considerations in the course of the next two months. I hope to learn various things in the course of this literary exercise, in particular the number of components required for self-reproduction. My (rather uninformed) guess is in the high ten thousands or in the hundred thousands, but this is most unsafe. Besides, I am thinking in terms

of components based on several rather arbitrary choices. At any rate, it will be necessary to produce a complete write-up before much discussing is possible.

24 Certain traits of the gene-enzyme relationship, of the behavior of some mutants, as well as some other phenomena, seem to emphasize some variants of self-reproductivity, which one would be led to investigate on purely combinatorial grounds as well. E.g.: Self-reproductivity may be symbolized by the schema A→A. What about schemata like A→B→C→A, or A→B→C→D, or A→B→C→D→ E→ C, etc.?

25 This is as far as my ideas go at this moment. I hope you will not misinterpret the anti-neurological tirade at the beginning of this letter. Of course I am greatly interested in that approach and I have the greatest respect for the important results that have been obtained in that field, and in our border area with it. I certainly hope these efforts will continue. I wanted to point out, however, that I felt that the decisive "break" was more likely to come in another theater. I was trying to formulate and to systematize my motives for believing this, and the simplest literary mode to do this is the controversial one. I hope, therefore, that I have not given you a false impression of the spirit in which I am starting a "controversy".

26 I am most anxious to have your reaction to these suggestions. I feel an intense need that we discuss the subject extensively with each other.

27 Hoping that this letter has not been unbearable by its sheer length, and hoping to hear from you and to see you again soon, I am, with the best regards,

Yours, as ever,
John von Neumann