AFTERWORD

The Anti-Expert System: Hypotheses an AI Program Should Have Seen Through

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One of the most difficult steps in the development of an expert system is the recruitment and exploitation of the domain wizards. Almost always it is necessary to establish teams of specialists to deal with the programming issues and the user interfaces as well as the incorporation of domain specific knowledge. Experts will communicate how they read a gel, or what is the canonical biological interpretation of DNA sequences conserved over phyletically diverse organisms. The computer scientist will rarely have an independent base of knowledge and experience for critical judgments about the wisdom thus received.

Therein may lie the greatest hazards from the proliferation of expert systems; for much of that expertise is fallible.

It is 14 years since I have been actively involved in the collaborations that led to the DENDRAL and MOLGEN projects; and I am just now at an early stage of planning a resumption of research on theory formation and valida-

tion, as applied to molecular biology. But I recall how easily the most primitive errors could become locked into firm rules – which would sometimes persist for a long time until revealed by lucky accident. For example, we had what we called a *badlist* in DENDRAL, intended to filter out substructures that experience told were unstable or otherwise untenable. This can give enormous economy in pruning back a combinatorial explosion. One such rule was quite plausible: *badlist* included a proscription against substructures with 2 -NH_2 (amino) groups pendant on a single carbon; C..$(NH_2)^2$ can be expected to split off ammonia. But one of us overlooked two outstanding exceptions, namely urea (NH_2)-C=O-(NH_2) and guanidine, (NH_2)-C=NH-(NH_2). We were too fixated on prohibitions that would apply successfully to much larger molecules.

I intend, however, to put that self-skepticism to a larger, constructive purpose. My first target is an examination of many of the central doctrines in the history of micro- and molecular biology, especially those that we have learned to have led us to egregious error. I call those the "Myths we have lived and died by." By and large they are half-truths whose domain of veracity and application was perceived to go far beyond the evidentiary basis that led to their adoption. And we cannot live with prolonged suspension of disbelief in these myths, or we would be practicing nothing but an unremitting nihilism.

I will examine the logical structures that founded the adoption of these beliefs, and again the data and reconstructions that led to their demise. This will require a system of knowledge representation that will enable a more formal examination of these theories, and in turn a computer based system for critical scrutiny (theorem-proving) and new hypothesis generation. All of this work is a direct extrapolation of the DENDRAL effort, which used essentially the same approach for "theories" (postulated chemical structures) in the more readily formalizable domain of organic chemical analysis. There the data came originally from mass spectrometry and NMR; later we developed a more flexible interactive system (CONGEN) that enabled all source inputs. One of the interesting uses of CONGEN was as a theorem-prover, namely to reexamine the purported proofs of structure that had been published in a leading journal of organic chemistry. You guessed it, many of those proofs were at least formally defective; and in at least one case that had eluded the human reviewer, substantively so.

My intention is to review the principal doctrinal themes of molecular biology from a similar perspective. But armed with an easy retrospectroscope, I thought it only fair to be put on the line for some as yet unsubstantiated future revulsions of thought. These are to illustrate objectives. As yet I have done no explicit programming on this issue. Nevertheless, I have found great value in the style of thinking that is evoked in the context of designing the computer systems. (Harking back to DENDRAL, it also led to a style of crit-

ical mental chemistry that matches in importance the first order assistance from the machine.)

So here are two intended *bona fides*—Contradictions to the existing regime of thought that, I believe, will be experimentally tested in the near future. Both of them are deeply embedded in the conventional wisdom!

1. The 3-dimensional shape and functionality of (folded) proteins is fully determined by the primary amino-acid sequence, and this in turn by the nucleotide sequence of the gene. [The latter part of this statement is already eroded by knowledge of messenger RNA splicing, and further by some remarkable examples of post-transcriptional editing of RNA]. This doctrine has been essential for the development of mechanistic ideas of cell and organelle assembly, and especially for our modern views of antibody formation.

   But this is probably an overstatement. My counter-prediction is that we will discover examples where ambiguous and divergent patterns of folding will enable a given primary protein sequence to fold into two or more well defined, and biologically distinctive final conformations. It is hard for me to imagine that evolution has not exploited this potentiality for flexibility in use of a given blueprint. Evidence for this has been counter-selected, and often discarded as precipitates or "noise". A number of experts of folding have agreed, that "yes", this should be more carefully considered.

2. The germ line in multicellular animals is completely segregated from the soma. This Weismann's doctrine is the foundation of the refutation of lamarckian and lysenkoist ideas, and perhaps for that reason has never been critically examined, except with the crude anatomical methods of the last century. It is certainly very nearly true! However exceptions could be of critical importance, for evolution, pathology, and biotechnology.

I am seeking a still more systematic way to discover issues where a computer-aided custodian could be a help, not of mere incremental advance, but of further scientific and technological revolutions. The following list is a brief history of biological myths that took substantial effort to overthrow. Could a computer program help us overthrow today's myths faster?

1. *Bacteria are Schizomycetes* i.e., divide only by fission. But Lederberg [1946] showed they had sex.

2. *Bacteria reproduce sexually* was a radical revision, but Lederberg [1951] took it too literally and missed the unique mechanisms of progressive DNA transfer (takes 100 minutes!) discovered by Jacob.

3. *Toxins kill* is an important paradigm in history of infectious disease. But the world (and Koch in particular) was misled for 80 years in searching for the "cholera toxin" as an agent lethal by parenteral assay. That toxin

"merely" promotes the secretion of water into the gut. The misunderstanding has cost tens of millions of lives that could have been saved by feeding salt water.

4. DNA → RNA. True enough, but it overlooked the reverse transcriptase (DNA ← RNA), which earned a Nobel Prize for Baltimore and Temin.

5. *Colinearity of DNA with protein* (1:1 theory) and *enzymes are proteins* were the key ideas in the classic work of Beadle and Tatum; Benzer; and Yanofsky. However, they overlooked mRNA processing and introns, which earned Cech a Nobel prize (for ribozymes).

6. *Only germ cells mate.* But somatic cells can be fused too [Lederberg 1955], and enable somatic cell genetic analysis; see the second "future myth," above.

7. *Mutations are deleterious*. This was long believed, but based on entirely circular reasoning, namely: most visible mutations are visible. But 99% of nucleotide substitutions are invisible. This myth delayed the evolutionary theory of drift [Kimura, 1991] and engendered gross miscalculations of the genetic disease load attributable to mutation.

8. *Mutations are spontaneous.* But they are chemical changes in DNA, and this is by no means homogeneous in molecular structure throughout the genome. In addition, DNA is deformed in a wide variety of ways as part of the mechanisms of regulation of gene expression. There is abundant chemical evidence that "activated" DNA is more accessible to reagents like dimethyl sulfate and DNAse-1; but the biological consequences of this differential reactivity have scarcely been examined.

9. *Genes have a fixed locus and segregate 1:1* (Mendel onward) But some genes jump! (McClintock) Segregation is not so rarely perturbed by "gene conversion"

10. *Infinitude of antibodies* and Pauling's instructionist theories. These ideas slowed the development of clonal selection theory, which is now the accepted explanation of antibody formation.

11. *Tetranucleotide DNA* - P.A. Levene's model was at most a tentative recapitulation of primitive data, but it was taken too rigidly, and greatly delayed the recognition of DNA as the genetic material

12. *Chemicals cause cancer.* Some do, but this idea greatly oversimplifies the multifactorial basis of carcinogenesis, and leads to enormous misfocus in managing environmental hazards.

13. *Life evolved on earth* - (Oparin, Miller-Urey). but chemical evolution probably started with cosmic condensation. Open possibility: all organic

material on earth is derived from cometary and meteoritic infall, may now be leading hypothesis.

With a few exceptions I have been personally involved in these bifurcations. At least once (2, above) to my chagrin!!

References

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