

Review I:

As I understand it, this paper finds an arrangement of the 4 nucleotides, the 64 codons, and the 20 amino acids such that they correspond to particular symmetries of the icosahedron. This seems like an exercise in searching a large combinatorial space of possibilities for a solution that appears more or less isomorphic to a predefined target. Unfortunately, this is surprisingly easy to do even for completely unrelated systems: it is unclear why the fact that such an arrangement exists would make the genetic code (or codes, if the variations in organelles and certain nuclear genomes were to be taken into account) in any way special compared to an appropriate class of random codes.

While it is logically possible that DNA and protein interact by some sort of 'molecular encryption' as posited in this paper, the paper makes no compelling grounds for abandoning the (empirically remarkably successful) hypothesis that nucleic acids and proteins interact through peculiarities of their molecular shapes as revealed by NMR and X-ray crystallography rather than some hidden and unexplained informational mechanism. It seems perverse to treat, say, myosin as some sort of ciphertext rather than a very specific molecular machine.

Review II:

This is an interesting manuscript.

The author has to discuss the biological implications of his genetic code representation. In particular, he has to discuss why "several physical properties of amino acids, such as molecular size, charge, and most significantly, water affinity" (on page 3), are seen in his representation. Furthermore, he has to discuss his dodecahedron representation in the framework of existent theories on the genetic code origin. After this, I think this paper could be published.

Review III:

This paper describes a complex geometric pattern that can be used to view the codon assignments of the genetic code. It urges us, by analogy, that this view may be useful in looking at the relationship between the genetic code and protein folding.

It is, sadly, wholly unfit for publication. Incredibly, the author seems to believe that he is almost the first to notice a more-than-1-dimensional pattern in the genetic code. In fact, nothing here goes further than what has already been said in the biological literature over 3 decades ago. Since then, several hundred papers have explored these patterns, developed general explanatory models and tested competing hypotheses. May I suggest he looks at some of the following?

Woese, C. R.: 1965, On the evolution of the genetic code, Proc. Natl. Acad. Sci. USA 54, 1546 - 1552
Alff-Steinberger, C. 1969 The genetic code and error transmission. Proc. Natl. Acad. Sci. USA 64, 584 - 591
Sonneborn, T. M.: 1965, Degeneracy in the genetic code: extent, nature and genetic implications, Evolving Genes and Proteins. V. Bryson and H. J. Vogel. New York and London, Academic Press.
Zuckermandl, E. and L. Pauling: 1965, Evolutionary divergence and

convergence in proteins. *Evolving Genes and Proteins*. V. Bryson and H. J. Vogel. New York and London, Academic Press
Wong, J. T.-F.: 1975, A co-evolution theory of the genetic code, *Proc. Natl. Acad. Sci. USA* 72, 1909 - 1912

or, more recently,

Szathmary, E. and E. Zintzaras: 1992, A statistical test of hypotheses on the organization and origin of the genetic code, *J. Mol. Evol.* 35, 185 - 189

Taylor, F. J. R. & Coates, D. 1989 *The Code Within the Codons*. *Bio Systems* 22, 177-187

DiGiulio, M. 1997 On the origin of the genetic code. *J. theor. Biol.* 187, 573 - 581

Knight, R. D., S. J. Freeland, Landweber, L. F.: 1999, Selection, history and chemistry: the three faces of the genetic code, *Trends in the Biochemical Sciences* 24, 241 - 247

These represent just a *tiny* fraction of publications (including some reviews) detailing non-random patterns in the genetic code and hypotheses to explain why they exist. This latter point is extremely important. Since the discovery of the genetic code (and, indeed, even before), there has been a steady stream of literature demonstrating unusual and superficially interesting patterns in the code. It has been shown time and time again that codons, bases and amino acids can be "linked" in all sorts of pseudo-meaningful ways that, on further investigation, just do not reveal anything other than the imagination of the observer (e.g. PLEASE see Hayes, B.: 1998, *The Invention of the Genetic Code*, *American Scientist* 86, 8 - 14 for a review of misleading patterns). Within the last decade, such reports of patterns have become ever more involved and complex: Golden Means, Supersymmetry, Graph Theory and Topology are just a handful of claims to have emerged since the mid-90's. Divorced from any sort of explanatory theory, these reports of patterns are signally unhelpful. To take just one example, it has been *proved*(!) that codon assignments reflect the number of oxygen atoms found in amino acids' side chains. No one (especially not the author) has been able to tell us why this might be the case, other than that it might be a sense of humor from God. The inclusion of a detailed, testable hypothesis to explain the reported pattern is an absolute pre-requisite at this point in the field otherwise science deteriorates into numerology. We need less patterns and more hypotheses.

In the current manuscript, the analogy that cracking the Enigma code was useful to the war effort in the 1940's is just not enough grounds to warrant publication of yet another pattern! Moreover, the apparently complete ignorance of an extensive, sprawling literature of previously reported patterns-WITH-HYPOTHESES in the field which the author is seeking to address is incredible: to conclude "nucleotide messages are input and then appear as random amino acid cyphertext" is unforgivable for an author seeking to contribute to this research frontier.

This is a fascinating field, with important research questions, and I encourage the author to pursue his interests, BUT at this stage it would be quickest to start again: begin by reading some reviews of what has already been said, and then develop a hypothesis, and then show us a test of how your hypothesis relates to existing knowledge. By the time this is done, the manuscript will be so different that it would warrant an entirely new submission.

I therefore strongly recommend rejection of the current manuscript

without the option of re-submission: sorry, but there is so much work that would have to be done to place this pattern in the context of what is already known, so little here that is actually new, and all of this would still leave us short of a hypothesis to explain why we should place this pattern above countless others.