The analysis presented in this paper is most welcome because it looks at the logic behind the RNA World hypothesis rather than arguing for its plausibility without questioning the adequacy of its basic assumptions as an explanation for the origin of life.

This paper is suitable for publication in Life subject to some clarification and attention being paid to some significant omissions.

My first reaction when I read the abstract and agreed to act as a referee was that some points about self-sustaining were at variance with some of my own recent findings, but when I received the whole text I modified my point of view. While I thought I would not have much to say, I found the paper very engaging and have attempted to be as helpful as I can be to the author in making minor improvements.

At the very beginning of the abstract I think it would be more appropriate to describe Darwinian evolution and self-sustaining as "two of life's distinct aspects", rather than implying that these two aspects offer a sufficient definition of life, even at its earliest stages. Although the paper has a brief discussion of what "self-" means, no distinction is made between descriptions couched in terms of physics and chemistry (events only HAPPEN in this world) and those couched in terms of biology (things are DONE in this world; there is agency at a level higher than the laws of nature).

I think it has to be acknowledged that the priority given to genetic information over self-sustaining (as if "you can't have the latter without the former") is a plausible but unproven assumption. The possibility of the simultaneous co-dependent emergence of the two together is also a possibility (as outlined in my own work: see below). In the sentence of lines 67-69 the author comes very close to the idea that life requires inheritance of a (self-sustaining) "interpreter" of the genetic information. The sentence on lines 75-78 begs the question of what degree of autonomy, what degree of organisation the "self-sustaining" needs. Could you just transfer the genes back into the system and expect it to still function as normal? Or do the non-genetic components have to be organised, not just in terms of relative concentrations and confinement, but also in terms of internal spatial arrangement of the molecules? Would such order have to be created among the components before you could put the genes back in and expect the system to function and survive? So, can you attribute the causation to the genes as "instructors"? That is why I say that the sentence on lines 90-93 should be portrayed as an premise, not something about which we have 100% certainty. (I personally find the simultaneous emergence version closer more likely to produce what is observed in molecular biological systems, not the genes first version.)

The sentence lines 127-129 is a breath of fresh air in discussions of the RNA World.

Lines 134-136 introduce an idea of "encoding" without discussing the fact that this has often been posed as THE central question for the origin of life: the
catalytic properties of RNA were grabbed as a facile solution to this problem concerning the emergence of an informatically regular mapping from genotype to phenotype in biology. The mapping from RNA sequences onto phenotypic properties is nothing like the mapping from nucleic acids onto proteins. The essence of molecular biology is an informatic mapping, not a physico-chemical mapping, providing molecular biological systems with a degree of computational control that transcends physico-chemical determination. The molecular biological mapping needs the components it makes to produce the mapping. In my view this is the main "self-sustaining" that distinguishes biology from other non-thermodynamic systems. The RNA world completely lacks this sort of self-sustaining because the genotype to phenotype mapping requires only the chemistry of RNA folding, not special system components.

Any thermodynamic system that is in a state far from equilibrium is a self-sustaining system. Prigogine started writing about this, and its relationship to biology, 50 years ago. So, I would be much happier if the two (very nice) sentences in lines 155-158 included a statement to the effect that the simultaneity of genetic information and function could be the source of a self-sustaining that was much more than thermodynamic. I have written about this possibility quite extensively and my two recent papers with Charlie Carter relate this to the RNA world hypothesis (see below). It would be appropriate to add some acknowledgment of this work in lines 180 and 194.

It is very refreshing to read a paper about the RNA world which refers to the need for some kind of spatial organisation (like reaction-diffusion coupling or compartmentation) or "tagging" to overcome the problem of parasitism. The main discussion in Section 3 of the paper justifies its publication in Life, but what is evident at the end of Section 3.3 (lines 382-384) is that previous discussion of the RNA World has been focussed almost entirely on bringing together various material components, not how the information contained in the genetic polymer may actually be USED AS INFORMATION by the system to sustain itself.

The sentence in lines 393-395 needs to be justified in relation to Eigen's threshold criterion. One can only say that "it could have spread in the system" if it operated ("sustained itself") above the error threshold for its own replication.

Then, at lines 435-436, the assertion "the chromosome, as an RNA molecule itself, serves as the ultimate target of natural selection" can only refer to true Darwinian selection if the genotype to phenotype mapping is somehow fixed. Already at this stage of evolution, surely the ultimate target of selection is the co-dependent unit of chromosome and functional components and the latter may have already attained a meta-stable, far-from-equilibrium dynamic state which was semi-autonomous in response to environmental boundary conditions (selection pressure). A comment on this point would be welcome here.

I would dispute the generality of the claim (lines 445-446) that it was through the invention of linked genes on chromosomes "that our living world achieved its fundamental potential to become complicated". I do not dispute the importance of chromosomally linking genes, just the relative importance of this compared to
other factors. It would be good to see other views acknowledged, like those expressed by Charlie Carter and me, that the acquisition of computational capability (information-processing beyond copying) was much more fundamental to the evolution of functional complexity, as seen in the evolution of coding.

Once again, the first paragraph of section 3.5 (lines 448-455) would benefit from consideration of the work of Eigen. For any "master molecule" to survive, it must be "kinetically self-sustaining" in the sense that it must have the property of being able to keep itself, in the presence of its quasi-species mutant distribution, above the error threshold. And then again, in the next sentence (lines 456-460), RAF systems are self-sustaining in the sense of making all of their necessary components from the food set, and they must likewise be in some dynamic configuration that holds them away from the basin of attraction of extinction. The next paragraph (lines 461-469) add a new dimension, but relating it back to the discussion of the meaning of "self-" in lines 55-88 would be helpful. Considering lines 461-500, is it being asserted that "self-" can only refer to a system that is spatially enclosed in a membrane, reminiscent of Gánti’s chemoton?

Line 524 talks about "a different one [scenario]". Reference to the alternative quite detailed elaboration in the two Carter/Wills papers would be appropriate here. The "succinct" world discussed in this paper misses what these other authors have taken to be what is absolutely essential to any consideration of the origin of "life", that is, a kind of informatic (or "computational") self-sustaining which involves a reflexivity in information processing just as profound as the reflexivity in reaction chemistry required for thermodynamic self-sustaining. However, I wish to compliment the author for ending with such a modest and sensible conclusion.

The Carter/Wills papers I have referred to are both now accepted for publication:


I also offer the following indicators of problems in the use of English. The list is probably incomplete.

39 talked
89 concerned about
208 obtain
274 no matter WHAT the membrane is composed of, [COMMA]
275 sufficiently
Overall I think this is an excellent, thoughtful, helpful paper about the logic of the RNA world.