Open Review

(x) I would not like to sign my review report

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English language and style

( ) Extensive editing of English language and style required

( ) Moderate English changes required

( ) English language and style are fine/minor spell check required

(x) I don't feel qualified to judge about the English language and style

	Yes	Can be improved	Must be improved	Not applicable
Does the introduction provide sufficient background and include all relevant references?	( )	( )	(x)	( )
Are all the cited references relevant to the research?	( )	( )	(x)	( )
Is the research design appropriate?	(x)	( )	( )	( )
Are the methods adequately described?	(x)	( )	( )	( )
Are the results clearly presented?	( )	(x)	( )	( )
Are the conclusions supported by the results?	( )	(x)	( )	( )

Comments and Suggestions for Authors

1. I read the paper with real interest. It proposes some new ideas, which seem to be fresh, but at the end it brings a bunch of provocative statements, which actually do not push the science ahead very far.

Reply: We sincerely thank the reviewer for the interests and comment. We will address the concerns and criticisms raised by the reviewer in the following sections. And we also understand that many related questions deserve further investigations (which we are currently working on).

Detailed remarks include:

1. You state, that the idea is novel and that it is substantially different from all that was published above. I rather feel, that the idea of Lempel and Ziv Algorithmic Complexity, being „the code of a shortest algorithm, which can build the analyzed sequence" is actually quite close to the idea of ladder path creation.

Reply: Indeed, ladderpath is substantially differently from Lempel-Ziv Algorithmic Complexity: Not only the way to calculate is different, the results are also different (we briefly mentioned this in the main text line 510-513). In order not to distract the reader we didn't write down the comparison in the main text, but we'd like to show the differences here. As the ladderpath outputs a partially ordered multiset and Lempel-Ziv outputs a compressed string, they are hard to compare directly. Nevertheless, in both approaches, the final results are actually determined by the calculated scheme of slicing the string, so we can compare their calculated slicing schemes. We use the example string "ABCDBCDBCDCDEFEF" (section 2.2 in the main text):

The slicing scheme of the shortest ladderpath (calculated from the algorithm provided) is

"A | BCD | BCD | B | CD | C | D | EF | E | F"

corresponding to the ladderpath Eq (1) in section 2.3 in the main text;

The slicing scheme of the Lempel-Ziv algorithm for the string is

"A | B | C | D | BC | DB | CD | CDE | F | E | F"

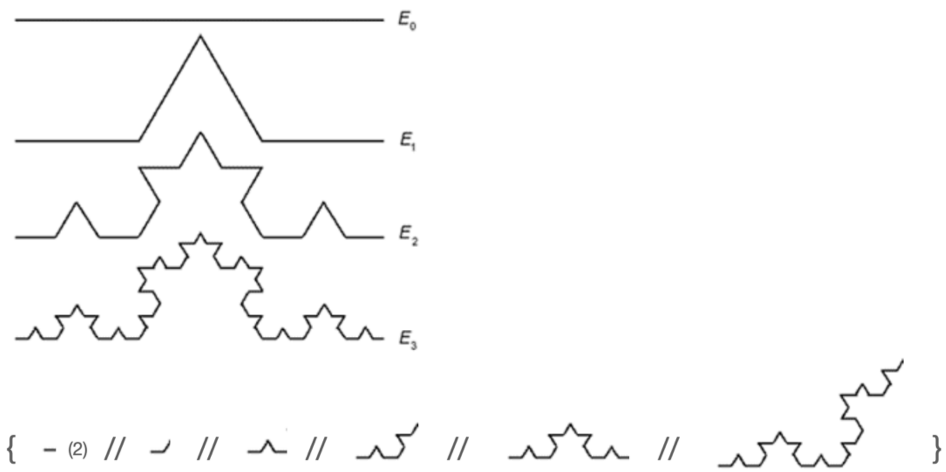
We can clearly see that they are different. Another main difference is that Lempel-Ziv can only deal with strings, but ladderpath can be applied to many types of entities.

As for "the code of a shortest algorithm, which can build the analyzed sequence" which we think the reviewer refers to Kolmogorov Complexity (KC) in a more general sense. The main difference between KC and ladderpath is that there is no universal method for calculating KC of an arbitrary string (we discussed this point in the introduction, too).

We have to say that "information" and "repetition" are interconnected by nature. No theory /approach that talks about information can avoid utilizing "repetition". It's not surprising to see some similarities at the level of ideas and intuitions between ladderpath and Lempel-Ziv or KC, but as we have discussed, the way to calculate and the results etc are distinct. Of course, the ladderpath approach is not out of the blue, and we actually discussed the history and related concepts in details in the introduction (line 102-130). The word "novel" might be too strong in the abstract, and we have revised the wording accordingly.

2. In my opinion, in the introduction you omit various aspects of complexity and discuss only the ones that are relevant from the point of view of your theory. One specific example is self-similarity and scaling. They can be obtained very easily, which may be observed e.g. on Koch snowflake, the constructal law of which is trivial. Would you describe it as complex or ordered? Still if you use stochastic rules, like in IFS, you may obtain quite regular structures - and you seem to contradict randomness and order. There are many types of constructal laws, that induce self-similarity, including Murray Law, so the idea comes directly from the nature. However the introduction is clearly the best part of the paper, and the collection of papers cited there is interesting as such.

Reply: Thanks for this comment, and this is a very interesting point. First of all, our ladderpath only deals with finite entities (as mentioned in the Introduction section), whereas ideal fractals such as the ideal Koch curve ("ideal" means it goes through infinite number of iterations) have infinite details. So, the concept of ladderpath should be extended if applied to these cases (which beyond the scope of the current paper). Nevertheless, if we consider non-ideal fractals, say Koch curve (iterated 3 times) or Romanesco broccoli, we can apply our ladderpath approach. The following figure shows the ladderpath of this non-ideal Koch curve, with properly predefining the basic set as the small horizontal segment and the generation-operations as sticking next to each other and mirror flipping. From the ladderpath, we can also work out that the size-index is 64, the ladderpath-index is 7, and order-index is 57, which means, referring to Fig. 2 in the main text, it would be located around the y-axis (namely, high order-index but low ladderpath-index). There is no simple answer to whether it's complex or not, but if we hypothesize that both high ladderpath-index and high order-index means high complexity, then in this sense, this Koch curve would be relatively simple. In fact, the point of the whole Section 2.5 is trying to say that the "complexity" in our intuition should have two aspects: order-index and ladderpath-index, which is often mixed up and ambiguous, and our approach may help disentangle this.



As for rules with stochasticity, it would introduce irregularity, which decreases the order-index to some extent while increases the ladderpath-index. Therefore, if with the same hypothesis (that both high ladderpath-index and high order-index means high complexity), stochastic rules would generate more complex entities than the corresponding regular rules, e.g., generally speaking, non-ideal crystals would be more complex than ideal crystals.

These discussions on fractals and self-similarity are very interesting, but we think it might be too much to add in the Introduction (before we explain our approach). We thus only discuss it here, and we hope we can ease the concern of the reviewer here. We thank the reviewer again for the appreciation of the introduction.

3. Also, you don't refer to statistical vs sequential order. Shannon entropy is insensitive to sequence, it is only a popularity contest against basic symbols. Algorithmic complexity or dictionary compression algorithms are, in turn, sensitive to sequence. Having written as much on complexity, you should consider adding this classification.

Reply: Thanks for this comment and advice. We added this classification and revised this part in the Introduction accordingly.

4. Negative multiplicity is not natural. Consider the change.

Reply: Thanks for this comment. The "negative multiplicity" appears in Section 2.2 where we introduce the definition of "generation-operation". But the "negative multiplicity" is only a transient notation for the sake of simplicity. For the calculated ladderpath in the end, there is no negative multiplicity. To avoid this confusion, we added a sentence in Section 2.2.

5. My first questions at line 202/203 was, is the order in sequence DDFAC important or not, but soon I realized that it is much more. In mathematical terms, I would say, that ladderpath, order and size index are under constraint, which is the actual build set. The build set already contains certain information, which is either known a priori (as the alphabet) or derived from the data, which makes this build set case-specific. So there is a clear relation between the ladder path indices and the complexity of the build set itself, and this issue is completely left behind. Also the frequency of occurrence of certain building blocks is not discussed, and this would lead the

measures closer to Shannon. The indices you introduce are not sensitive to the popularity of building blocks that are used in the ladderpath.

Reply: Thanks for this comment. The reviewer raised two important points here. (1) First, the reviewer said that the build set (which we called basic set) is case-specific which has been completely left behind. We completely agree with the reviewer in this regard and we actually discussed this in details at the end of Section 4.1 (line 646-663). The point is that based on the particular questions, we should predefine the basic set and then analyze (as long as the basic set is fixed, it should not be changed). We also briefly mentioned this point at line 346-352 as it may affect the size-index calculation. To make this point clearer, we added a sentence after the definition of the basic set in Section 2.2.

(2) Second, the ladderpath approach involves the frequency of occurrence of building blocks, indeed. In fact, the whole idea of the "multiplicity" of ladderons (the repetitive building blocks in the ladderpath) refers to the frequency of occurrence. However, it's not directly the count of occurrence; Instead, roughly speaking, the multiplicity is the net count after excluding the effect of hierarchy (in this way, the multiplicity holds the nice property expressed in Eq.3), referring to Eq.7 in the main text where the basic building block B's multiplicity is 2, while B also appears in other ladderons such as AB, CAB, etc (if you care about the frequency of B, then the multiplicities of AB, CAB etc should also be considered). The same argument applies to other ladderons, e.g., AB. The multiplicity (together with the size of each ladderons) is closely related to the order-index. So, in this sense and imaging all other conditions the same, the higher multiplicity, thus the higher order-index, and thus the smaller the Shannon entropy. But we need to emphasize that the ladderpath and Shannon entropy are distinct, no matter from the calculation or the results, or the statistical nature of Shannon, although in some sense, they are consistent (which of course they should).

6. If you extrapolate the relation that less ordered sequence carries more information, you get to a contradiction, that the most information is carried by white noise of no structure. And this is exactly what you tried to avoid (in introduction). Therefore, the theoretical framework, which has been developed, is not consistent with the assumptions.

Reply: Thanks for this comment. But there might be some confusions about "information" and "complexity". In the introduction, we didn't mean that "higher complexity" and "more information" are interchangeable (which people may not agree but this is our argument). In fact, the whole section 2.5 was trying to disentangle information and complexity where we proposed that complexity has two axes: the ladderpath-index and the order-index.

There are two different angles to answer whether "the most information is carried by white noise of no structure". (1) To repeat the particular sequence of a white noise, we need to memorize the whole sequence, which does require the most information in this sense; (2) Yet, complexity does not only mean the "difficulty to repeat" but also the hierarchical information that involves repetition and selection, which is another layer of information. We argue that the second layer of information is taken care of by the two properties of ladderpath-systems (detailed in Section 3), i.e., the ability of generating new blocks and some blocks can replicate (on which selection can act), which can be reflected on both the ladderpath-index and the order-index considered together. That is, only when the ladderpath-index and the order-index are both high, this type of information that is associated with selection is rich. Therefore, in this sense, white noise almost has no such information, since its ladderpath-index is high whereas its order-index is extremely low. Thanks for the reviewer to mention this, and we added a paragraph at the end of Section 3 to make this point clearer.

7. In 423-431 I started to think of alphabet of alphabets. The idea of recoding is absent, however e.g. in proteins it is obvious: nobody describes NA or Ach by its genetic code.On different levels of organization we have different alphabets

Reply: Thanks for this comment. It is indeed an important aspect, which has been raised at point 5. As we have explained there and also discussed in the main text, the basic set should be predefined, based on the question that is asked. As long as the basic set is chosen, our ladderpath approach provides a concrete/ well-defined mathematical tool to analyze. We totally agree with the reviewer in this regard.

8. In 591-594 you mention analysis of digraphs, which has its long tradition in cryptography - i.e. exactly where the work of Shannon is rooted.

Reply: Thanks for this comment and reference. In fact, we are not particularly interested in digraphs here. The point here is just to show how we can interpret this unknown message based on ladderpath, and these EF, MU, BCDEF etc just happened to appear a few times, and are the patterns that are caught by the ladderpath.

9. 611 the „qualifier ahead" sets the context of the information, and the context changes with the communicate. If I start the sentence with: don't listen to the next statement, as it does not carry information, then the information related to this statement is irrelevant. There is an interesting book by Lind and Marcus, An Introduction to Symbolic Dynamics and Coding, which i.a. covers this topic.

Reply: Thanks for this comment and reference. What we want to say here is that the information in the repetitive part [*mother made a chocolate cake*] would not change no matter what "qualifier" is added ahead, actually nothing else. After serious reflections, we think the reviewer's comment here may not be very relevant, in this paper we only care about the syntactic information and leave the second level of meaning untouched (namely, semantic ones) as mentioned in the Introduction section.

The example the reviewer gave here is a very good one relating to semantic information: Only when I understand this semantic information of "don't listen to the next statement", I will say that the next statement is irrelevant; but if I don't understand the semantic information of "don't listen to the next statement" (say, someone speaks Chinese, but I don't understand Chinese), I will still think the next statement contain some information, which means I need to analyze the ladderpath (or using some other approaches) of "don't listen to the next statement" and the next statement altogether (and the full interpretation comes at the second level afterwards, which beyond the scope of the current paper).

10. The weakest part is the discussion, and in my opinion it fails to demonstrate the scientific quality of the method and convince us to use it. Moreover, the important relation between the indices and the basic set is not disclosed in the definition of the measure. Its only merit seems to be the opening possibility to coin journalistic statements as: „Life is not as complex as expected". Really? Concerning DNA (740) there is an interesting example, that there exist non-coding

parts, so the information may be judged only ex post by observation which proteins are being synthesized and the apparent complexity of non-coding parts is not important at all

Reply: First of all, as discussed at point 5 and 7 above, we have discussed the importance of the choice of the basic set. Second, the DNA example the reviewer raised here is very interesting but might be a bit over-simplified. If researchers are asking questions about the DNA sequence, the non-coding parts should be considered altogether. The ladderpath approach can help analyze the information stored in the sequence even in the non-coding part (as we know, the non-coding parts do play some roles such as regulation, control or some other unknown functions). If researchers are asking questions about amino acid sequence, they don't have to consider the non-coding DNA; but if the evolution of this amino acid sequence or protein is considered, the non-coding part should also be considered altogether. As we have mentioned in point 5 and 7, the basic set and the allowed generation-operations should be predefined, based on the questions to be asked. Finally, we revised the phrase "life is not as complex as expected" accordingly to avoid any over-simplified journalistic statement (we totally agree with the reviewer here).

11. 750 I cannot agree that the complexity of the system is much smaller than the complexities of each individual part. How about emergent phenomena? Coordination, synchronization etc, they are important everywhere, from life science to modern warfare.

Reply: Thanks for this comment. What we said in the paper is that the complexity of the system could be smaller than the SUM of the complexities of each individual part. We think the reviewer and us are on the same page.

12. 763: if the molecules are placed randomly, any pattern is legitimate. Likewise, nine, nine, nine is a legitimate result of random number generator (Credits to Dilibert)

Reply: Thanks for this comment, and we totally agree with the reviewer in this regard. Imagine the metaphor of junkyard tornado and origins of life, if a literally infinite number of experiments were tried, anything can happen. What we meant is that the probability is so small that it cannot happen in this way within a reasonable time scale. That's what Section 3 trying to say where we put forward the definition of ladderpath-system that has two important properties, i.e., the ability to generate new blocks, and some or all blocks can replicate. With these prosperities, we argue that the origin of life might occur in this way. We couldn't agree more with the reviewer that any pattern or nine, nine, nine is legitimate in this sense.

13. When you mention the patterns that appear when ladders get in relation, you forget, that this relation may obtain several distinct forms, depending on environmental conditions. The „+" sign shows itself as unique, which it isn't.

Reply: Thanks for this comment. The reviewer is absolutely correct that when ladderons get in relation (e.g., for molecules), there could be several different forms. When we gave the definition of generation-operation, we briefly discussed this point (line 194): For different systems in question, the generation-operation should be defined accordingly. Indeed, we should have stated this point clearer. We thank the reviewer for mentioning this, and we added a few sentences and revised the texts accordingly around lines 196 and 771-776, to avoid confusions.

14. 770 When you describe degrees of freedom, you mention quantum, but the majority of states you refer to are classical. Also the description of micro state is rather vague. Also such terms as state space or number of degrees of freedom will be helpful.
15. Consideration on Second Law of Thermodynamics are imprecise. The fact, that der Entropie der Welt streibt ein Maximum zu does not rule out the possibility, that in certain area of the state space the entropy actually decreases.

Reply: Thanks for these comments and advice. For point 14, we changed those terms and revised this part accordingly.

For point 15, we absolutely agree with the reviewer that the second law of thermodynamics does not rule out the possibility, and this is also actually we what said here. The only point we were trying to make in this Discussion part is that the ladderpath approach provides a different angle to look at this question, i.e., the two properties of ladderpath-systems (the ability to generate new blocks and some or all blocks can replicate) may paly vital roles in evolution.

By taking this criticism into account, we decided to move the part about the connections between the ladderpath and Shannon entropy to Appendix F with revisions accordingly, as it is indeed a bit off from the main. We are fully aware that much more work, both theoretically and empirically, is needed to provide concrete conclusions (as what we have written at the end of Section 4.4), but here we intended to first raise the attention and to say that this might be a different angle (we are actually working on this currently).

16. The paper made me think. Are small proteins more popular than large? Is the protein popularity contest won by the shortest sequences?
17.

Reply: We are very happy to hear that this paper made the reviewer think, and we appreciate that the reviewer mentioned this. We don't know the answer for these questions currently, but they are definitely interesting ones and deserve investigations. In fact, we are currently analyzing real amino acid sequences with our ladderpath approach, and we found quite a few interesting results, e.g., the further away the species in the evolutionary tree, the more different patterns of their amino acid sequences display, statistically speaking (we're working on interpreting these patterns).

We highly appreciate the reviewer's comments, we understand the criticism, and we are also fully aware that there is much more future work to be done. We hope we could convince the reviewer by this reply and revision accordingly, at least partially, that this paper proposes some interesting ideas /tools, and opens some space for future research.

Thanks again for your time.