

Rozzano, May 25, 2023

Dear Andrzej S Tarnawski, DSc, MD, PhD,
Editor-in-Chief
World Journal of Gastroenterology

Please find attached the revised manuscript entitled “**The fractal nature of human gastro-intestinal system: exploring a new era**”, by Fabio Grizzi, Marco Spadaccini, Maurizio Chiriva-Internati, Mohamed A.A.A. Hegazi, Robert S. Bresalier, Cesare Hassan, Alessandro Repici, Silvia Carrara, which we would like to submit for publication in *World Journal of Gastroenterology* as Invited Article (ID: 00503442).

First at all we would like to thank the Reviewers for her/his feedback and the Editorial Committee for their precious suggestion. We have included in the manuscript all the requested amendments highlighted in red.

Detailed replies to the Reviewers' comments are provided below.

Reviewers' Comments:

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: Fractal structures may help to characterize tumor growth lots better than anything else we use as potential risk factors... Prognosis can depend on the development of certain fractal geometry as well.... in depth description of fractal structures within the GI tract.

A. We would like to express our gratitude for the exceptionally positive feedback regarding our manuscript. Thank you for your kind words.

Reviewer #2:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: Dear Authors, This is a very innovative and well-written manuscript. The presented research may have important clinical implications and provided some impulse for further studies in the future. I have no questions or queries pertaining to your manuscript and wish you good luck in publishing your work. Best Regards

A. We would like to express our gratitude for the exceptionally positive feedback regarding our manuscript. Thank you for your kind words.

Reviewer #3:

Scientific Quality: Grade D (Fair)

Language Quality: Grade A (Priority publishing)

Conclusion: Rejection

Specific Comments to Authors: This paper presents different studies of the literature dealing with fractal nature of several organs of the gastro-intestinal system. The paper is not well organized. Many elements were provided about fractals but none about the gastro-intestinal system. What are the objectives and the contributions of the study? It is not clear. Please clarify. Is this a review paper? The abstract does not reflect the content of the paper. Please improve. The introduction should first present the context, which is related to the gastro-intestinal system. Then, fractals. Finally, fractal organs, etc. The title of the paper is not appropriate. Please improve.

A. Thank you for the valuable feedback on our manuscript. We are grateful for the comments aimed at enhancing our study. Based on the suggestions provided by the Reviewer, we have made the following modifications:

R. Many elements were provided about fractals but none about the gastro-intestinal system. What are the objectives and the contributions of the study? It is not clear. Please clarify. Is this a review paper?

A. We express our gratitude to the Reviewer for their insightful suggestions. As per their recommendations, we have incorporated a new introductory paragraph in our manuscript. This paragraph serves to provide an overview of the gastrointestinal system, including its physical properties, and highlights the relevance of fractal geometry in characterizing its structural geometry and changes that occur during pathological states. Different authors have confirmed the utility of fractal geometry as an alternative or complementary approach for understanding the intricate structures underlying the gastrointestinal system, both in its natural state and during pathological conditions. Fractal geometry also facilitates the measurement of its functions. The gastrointestinal system exhibits dynamic processes that are irregular in both time and space, which underlie its natural function. When these processes are altered, either gradually over time or suddenly, they impact the structural-functional relationship.

Therefore, fractal geometry offers a novel perspective to study the gastrointestinal system and characterize new properties. It can complement existing knowledge, aiding in the explanation of complex processes, the discovery of new biomarkers, and the exploration of the physics of the gastrointestinal system.

The primary objective of our research is to introduce the principles of fractal geometry, discuss the current studies focusing on its application in gastroenterology, and explore its potential in investigating the structure and function of the gastrointestinal system under both natural and pathological conditions.

R. The abstract does not reflect the content of the paper. Please improve.

A. We appreciate and acknowledge the valuable suggestions provided by the Reviewer, and we wholeheartedly agree with their recommendations. As a result, we have thoroughly revised the Abstract to ensure that it accurately reflects and succinctly summarizes the content of our manuscript. We are now confident that the revised Abstract effectively captures the essence of our research.

R. The introduction should first present the context, which is related to the gastro-intestinal system. Then, fractals. Finally, fractal organs, etc.

A. We appreciate and fully agree with the Reviewer's suggestions. Accordingly, we have incorporated a new paragraph into the structure of our manuscript to provide a comprehensive context for the study. This new paragraph serves to introduce the background and significance of the research. We then delve into the discussion of the fractal properties that underlie the anatomical structures of the gastrointestinal system. Finally, we present a detailed overview of the existing studies that have investigated the fractal nature of the gastrointestinal system, encompassing both its natural state and pathological conditions. By incorporating these elements into our manuscript, we aim to present a thorough examination of the subject matter and contribute to the existing body of knowledge in the field.

R. The title of the paper is not appropriate. Please improve.

A. We appreciate the Reviewer's suggestion and apologize for any confusion caused. While we do not have specific knowledge regarding the substitution of the manuscript title, we have taken their input into consideration. In our revised version, we proposed an alternative title that aligns with the content of the manuscript ("Fractals and the human gastrointestinal system: a new perspective"). This alternative title emphasizes the utilization of fractal geometry as a tool to comprehend the physics of the gastrointestinal system, including its structure and function under both normal and pathological conditions. We believe this revised title accurately represents the essence of our research and the role of fractal geometry in our study.

6 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor:

The manuscript has been peer-reviewed, and it's ready for the first decision.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, the relevant ethics documents, and the English Language Certificate, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: <https://www.referencecitationanalysis.com/>.

A. We would like to thank the WJG Editorial Office for their valuable comments. We have carefully revised the manuscript based on the recommendations of the reviewers. Furthermore, as requested, we have reviewed and standardized all the figures included in the manuscript. The figures have been included into a single PowerPoint file. All the figures are original, and we have provided copyright information in the bottom right-hand side of each image within the PowerPoint. The References have been also updated and new References have been added and incorporated in the main text.

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We hope you will find now the manuscript of sufficient merit and interest to warrant its publication in your Journal.

Please for any other information do not hesitate to contact me.

Sincerely,

Fabio Grizzi

Correspondence to:

Dr. Fabio Grizzi
Head Histology Core
Department of Immunology and Inflammation
IRCCS Humanitas Research Hospital
Via Manzoni 56 - 20089 Rozzano, Milan, Italy.
Phone: +39 02 82245262-5177
Fax: +39 02 82244590
Mobile: +39 392 8532436
Email: fabio.grizzi@humanitasresearch.it
fabio.grizzi@hunimed.eu
histology@humanitasresearch.it

www.humanitas.it