Peer-Review

Choo, Jaejoon. 2025. “Emerging Technologies for the Integration of Flexible Electronics into Heart-on-a-Chip Platforms.” *Journal of High School Science* 9 (3): 68–93. https://doi.org/10.64336/001c.142193.

The review is very well researched, written and presented. However, it does not satisfy the Journal’s expectations for a review manuscript as seen here: https://jhss.scholasticahq.com/for-authors , types of manuscripts, review papers.

To make this review meet the Journal’s guidelines and expectations, I suggest that the following content be researched and incorporated into the manuscript.

1.Identical ECG or cardiomyocyte contractility (force, velocity and power) changes can be caused by many factors; such as accumulation of reactive oxygen species, autophagy or mitochondrial dysfunction, ion levels, transport and flux, abnormal ECM deposition, vasculature changes, genetic mutations (esp. of myosin), hormone and neurotransmitter levels, as well as a variety of diseases and other organ dysfunction. Therefore, regardless or improvements in flexible electronics, these (in many cases identical) generic mechanical stress/strain signals or generic electrophysiological signals cannot be attributed to specific cellular or metabolic dysfunction;hence effectively blunting the values of these devices in deciphering cardiotoxicity or cardiac dysfunction mechanisms. Is there any research that correlates the spatio-temporal mechano-electrical changes to specific disease mechanisms? Until then, attribution of changed ECG or stress/strain curves or magnitudes of contractility to specific disease mechanisms is likely to remain elusive. Does the field need to invest in research along this trajectory, so as to incentivize greater and rapid changes in flexible electronics? Is this one of the reasons why the commercial field of HoC has not advanced at as rapid a pace as that of other organoids ? Please present, discuss, analyze in the manuscript with relevant references.

2.To expand on point 1, can various measurements in tandem such as impedence, conductance, resistance, their spatio-temporal magnitudes, times (initiation, propagation, decay) when processed in specific mathematical configurations, distinguish between these specific mechanims presented in point 1? Is there any research available in this area? Please present, discuss and analyze in the manuscript with appropriate references.

Adequate discussion of the points above will allow the manuscript to meet the Journal’s expectations. You are - of course - free to think of any other ideas and incorporate into the manuscript.

Reviewer #1:

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Response to Reviewer Comments:

Dear Reviewer,

I appreciate you for your thoughtful and constructive comments on my manuscript entitled *"Emerging Technologies for the Integration of Flexible Electronics into Heart-on-a-Chip Platforms."* Your comments have significantly improved the clarity and depth of my discussion, particularly regarding the interpretability of sensor-derived signals and their relationship to biological causes in disease modeling and drug screening.

I have revised the manuscript extensively, especially Chapter 4, by incorporating new sub-sections and up-to-date references.

Below, I provide a point-by-point response to your comments, indicating the corresponding revisions in the manuscript.

Reviewer's comment #1:
Identical ECG or cardiomyocyte contractility (force, velocity and power) changes can be caused by many factors; such as accumulation of reactive oxygen species, autophagy or mitochondrial dysfunction, ion levels, transport and flux, abnormal ECM deposition, vasculature changes, genetic mutations (esp. of myosin), hormone and neurotransmitter levels, as well as a variety of diseases and other organ dysfunction. Therefore, regardless or improvements in flexible electronics, these (in many cases identical) generic mechanical stress/strain signals or generic electrophysiological signals cannot be attributed to specific cellular or metabolic dysfunction;hence effectively blunting the values of these devices in deciphering cardiotoxicity or cardiac dysfunction mechanisms.

Response to comment #1:
This is a key limitation in current heart-on-a-chip (HoC) systems, and I have directly addressed this issue in the newly added Section 4.1: Disease Modeling in Heart-on-a-Chip. This section discusses how HoC platforms can reproduce pathophysiological features but still face difficulty in disentangling

causative mechanisms based solely on mechanical or electrophysiological outputs. Several examples are provided, including modeling of ischemia, mitochondrial dysfunction in Barth syndrome, and the use of organoid models to replicate complex morphogenetic signaling.

Modification:
A new Section 4.1 has been added to address the ambiguity of signal origin.

Reviewer's comment #2:
Is there any research that correlates the spatio-temporal mechano-electrical changes to specific disease mechanisms? Until then, attribution of changed ECG or stress/strain curves or magnitudes of contractility to specific disease mechanisms is likely to remain elusive.

Response to comment #2:
Yes. I have expanded both Section 4.1 and Section 4.3 to include studies that demonstrate early correlations between signal patterns and specific pathologies. For example, the integration of intracellular nanopillar and extracellular MEAs has been shown to associate action potential narrowing with ATP-sensitive K^+ channel activation under hypoxia. Additional discussion is included on the importance of spatially distributed multifunctional sensors and the limitations of current single modality systems.

Modification:
Section 4.1 and 4.3 expanded to include references related to sensor outputs with disease processes.

Reviewer's comment #3:
Does the field need to invest in research along this trajectory, so as to incentivize greater and rapid changes in flexible electronics?

Response to comment #3:
Yes, and I fully incorporated this recommendation in Section 4.2, "Drug Screening and Pharmacological Profiling." I highlight how integrating flexible electronics with biochemical sensors (*e.g.*, for calcium, ROS, ATP) can increase interpretive precision and enhance the translational relevance of these platforms.

Modification:
Expanded Section 4.2 to highlight the need for multimodal sensors.

Reviewer's comment #4:
Is this one of the reasons why the commercial field of HoC has not advanced at as rapid a pace as that of other organoids ? Please present, discuss, analyze in the manuscript with relevant references.

Response to comment #4:
This is an insightful observation, and I agree. I note in Section 4.4 that while organoids often rely on phenotypic or genomic profiling with clear diagnostic markers, HoC systems, especially those relying only on mechanical/electrical readouts, lack this clarity. This creates a confidence gap for end-users, such as pharmaceutical developers, who require clear linkage between observed changes and biological targets.

I argue that improving sensor recording data to specific disease processes will be crucial in increasing industry confidence and accelerating commercial adoption.

Modification:
Added discussion of translational gaps and commercialization barriers in Section 4.4.

Reviewer's comment #5:
To expand on point 1, can various measurements in tandem such as impedence, conductance, resistance, their spatio-temporal magnitudes, times (initiation, propagation, decay) when processed in specific mathematical configurations, distinguish between these specific mechanims presented in point 1? Is there any research available in this area?

Response to comment #5:
Yes. This insightful suggestion is now addressed in Section 4.3 and 4.4. I reference computational modeling studies that use multimodal signal datasets to improve diagnostic inference. These include inverse modeling frameworks that map tissue-level signals back to upstream molecular states. I also propose the integration of biochemical sensors to enrich data inputs, which will help validate these computational models.

Modification:
Added computational interpretation strategies in Sections 4.3 and 4.4.

I am grateful for your insightful feedback. It has significantly strengthened this manuscript, particularly in contextualizing the limitations and future directions of flexible bioelectronics within heart-on-a-chip systems.

All added or revised content is now marked in red in the revised manuscript for easy review.

Please let us know if any further clarification or adjustments are needed.

Sincerely,

Jaejoon Choo

Thank you for addressing my comments. Accepted.