CPS: Medium: An AI-enabled cyber-physical-biological system for cardiac organoid maturation

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Project overview

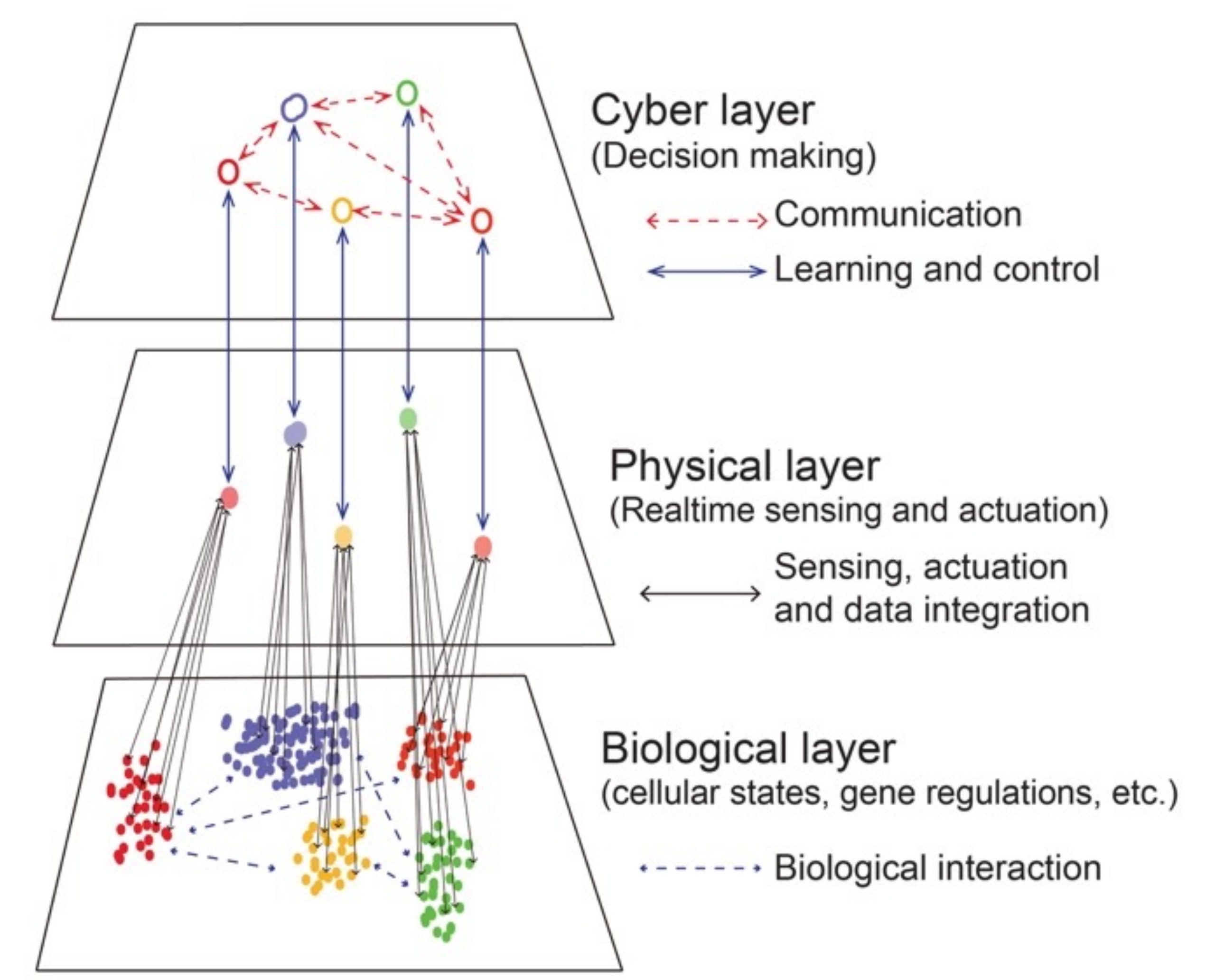
Develop a seamless integration of cyber-physical systems with biological systems, enabling a close-loop control to real-time, bidirectionally, and long-term stably interrogate and intervene cellular activities across the three-dimensional (3D) volume of tissue networks at a single-cell resolution.

Specific goals

Demonstrate a seamlessly integrated CPS with human induced pluripotent stem cells (hiPSCs) derived cardiac organoids, enabling a close-loop control to real-time, bidirectionally, and long-term stably control tissue development.

Major challenges

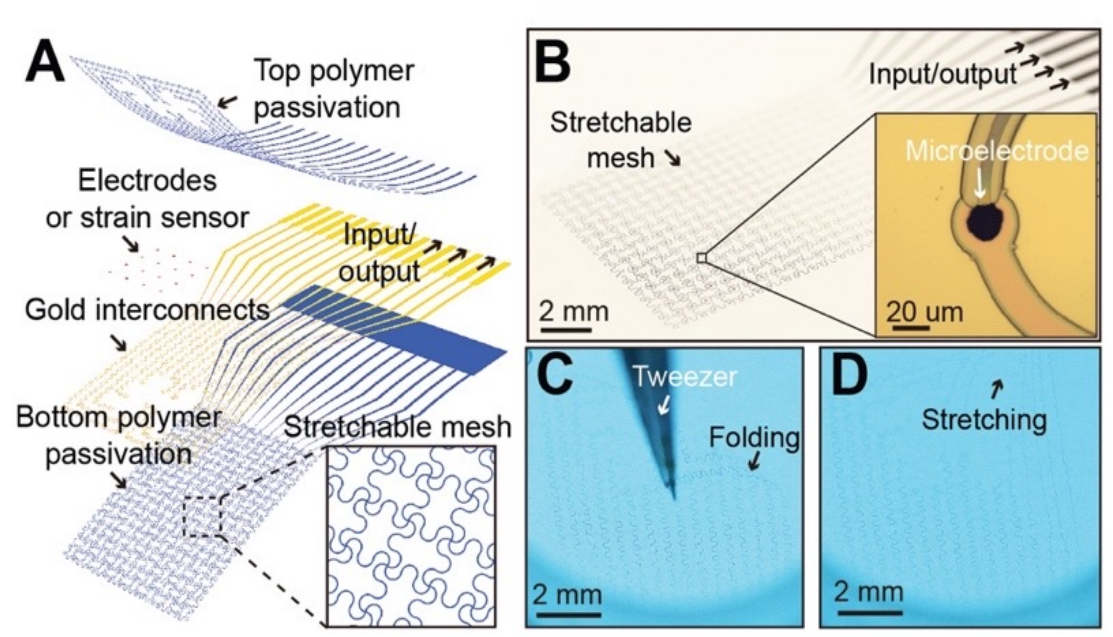
- **A physical sensing and actuating system** that can seamlessly 3D integrate with biological systems, capable of recording and controlling tissue-wide, single-cell activities in a long-term stable manner without interrupting the natural tissue development, differentiation, and proliferation.
- **A predictive model** that can on-the-fly accurately predict the underlying cellular molecular activities from the continuous physical sensing data with statistical reproducibility and accuracy.
- **A cyber-physical control system** that can make decisions based on the sensing data and subsequently provide the minimal feedback stimulus to a group of cells through the physical systems to precisely guide, promote, and ameliorate the whole-tissue level functions and dysfunctions.



Scientific impact

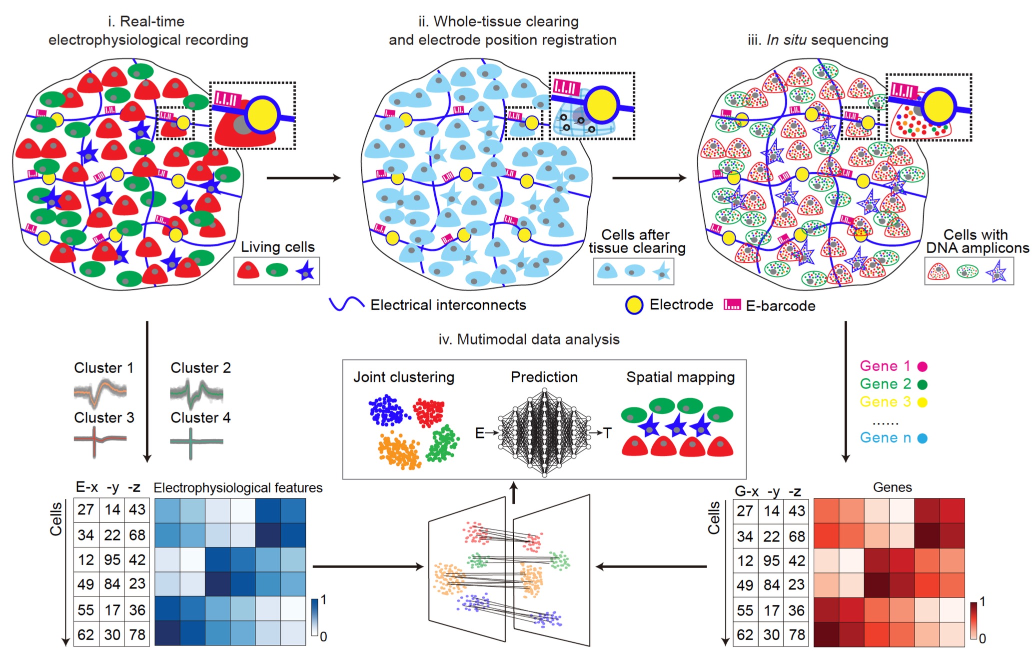
- **The flexible bioelectronic devices** can be applied to virtually any developing biosystems (e.g., *in vitro* brain organoids, and *in vivo* brain and heart) beyond the cardiac organoid system.
- **The developed AI (machine learning and reinforcement learning)** will greatly advance both its algorithm development and practical application, especially for complex dynamical and stochastic systems.
- **The tight integration between the physical and cyber components** will greatly advance the real-time decision-making for CPS.
- The additional integration with the biological systems will open up tremendous opportunities for **CPS application in enabling the patient-specific healthcare systems** through the multimodal non-invasive sensing and on-demand control.

1. Multifunction flexible bioelectronics



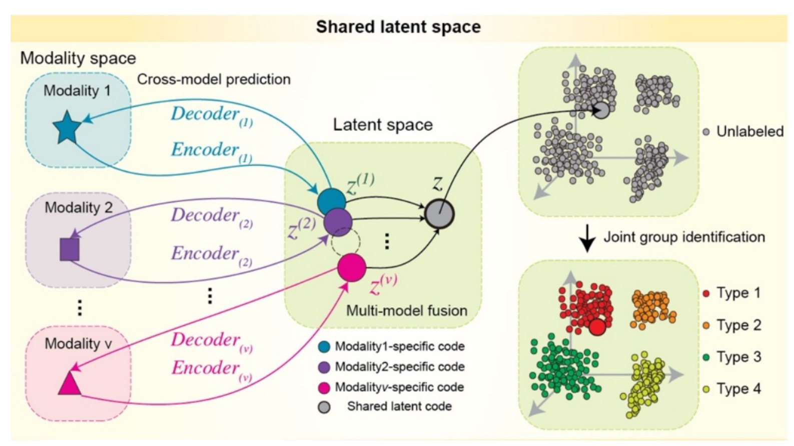
Flexible, stretchable, and mesh-like nanoelectronics that fully mimic the physiochemical properties of tissue scaffolds and possess tissue-like bending stiffness

2. Multimodal *in situ* biology

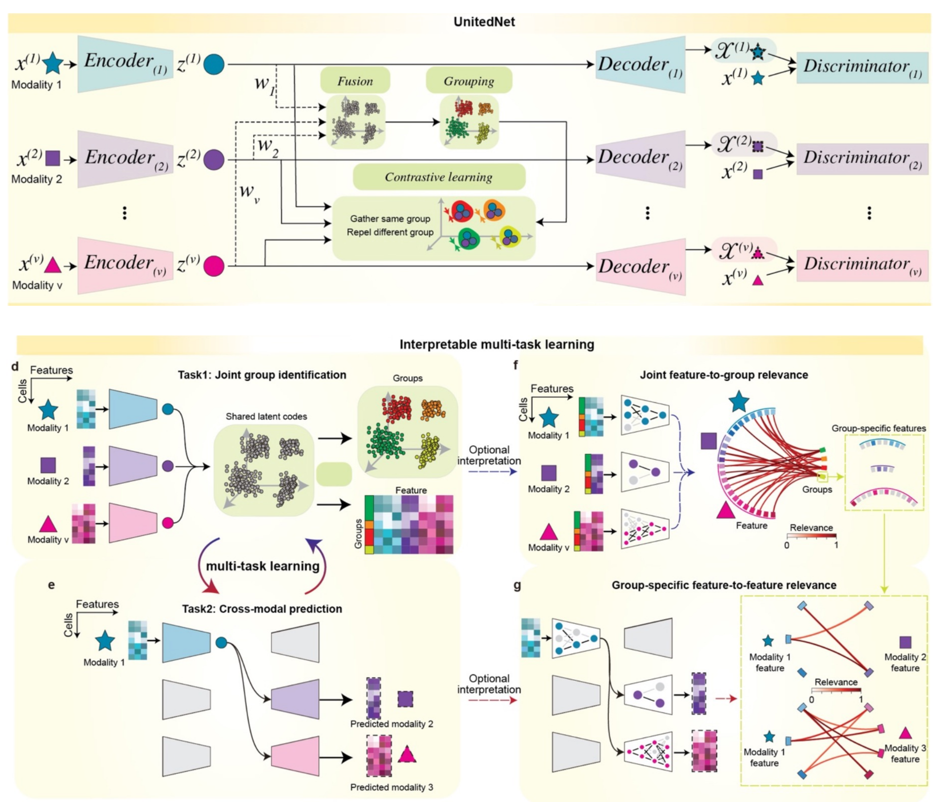


Cyborg organoids: flexible nanoelectronics integration with developing cardiac organoids for organoid-wide multimodal recording and multisite stimulation

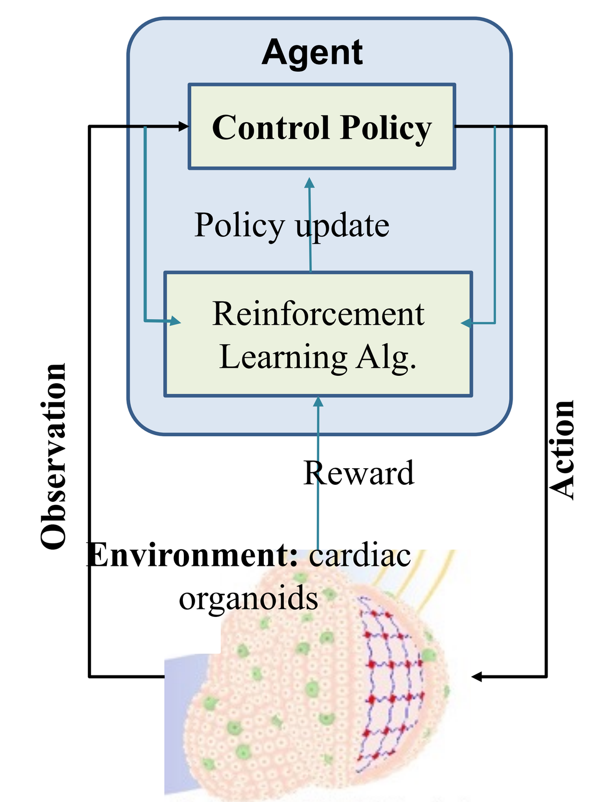
3. Online learning from multimodal biology



Build a **multitask learning model** to illustrate multi-modal data from cyborg organoids, their multimodal representations in the feature space, nonlinear modeling to **relate the features (as input) to single-cell gene expressions (as output), and post-processing to determine the cell states** to make decisions or to aid the feedback control



4. CPS control



Broader impact on society

- The success of this project will further **merge the field of AI, bioelectronics and biology**, bringing unlimited opportunities for the application for CPS in biology, bioengineering and biomedicine.
- The success of this project will enable the applications of CPS in **representation learning, nanobioelectronics, soft bioelectronics, stem cell biology, cardiology and neuroscience**.

Broader impact on education and outreach

- Provide **interdisciplinary education** to students. Host college panels for middle school students and provide mathematic training to first grade students at weekly basis.
- **Research fundings** are reported through scientific publication, BioRxiv, and Github. **A company** will be established around the developed technologies.

Broader impact

- Build **flexible bioelectronics**, capable of providing bidirectional interfaces with hiPSC-derived cardiac tissue over 3 months.
- Establish **multitask learning algorithms**, capable of predicting cell states based on real-time recording and electrophysiology-to-gene translation.
- Develop **reinforcement learning algorithms** to control stem cell developmental trajectory based on cell states and developmental pseudo-time interpretation.

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