Integrating Artificial Intelligence Techniques in Cell Mechanics

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Muddasar Naeem
Department of Computer Engineering
Università Giustino Fortunato
Benevento Italy
Email: m.naeem@unifortunato.eu

Mario Fiorino
Politecnico di Torino, Italy
Email: mario.fiorino@polito.it

Pia Addabbo
Department of Computer Engineering
Università Giustino Fortunato
Benevento Italy
Email: p.addabbo@unifortunato.eu

Antonio Coronato
Department of Computer Engineering
Università Giustino Fortunato
Benevento Italy
Email: a.coronato@unifortunato.eu

***Abstract*—The Artificial Intelligence (AI) and Machine Learning (ML) techniques have been revolutionizing many subjects. The AI-empowered methods such as Reinforcement Learning (RL) and Deep Learning (DL) have been employed for various aspects of cell mechanics. This work reviews the state of art of AI and ML technologies that have been used to describe, analyze and predict the mechanics of cells as well as the use of numerical methods for cell mechanics. This review also considers the impact of utilizing physical constraints on the AI and ML models aiming at improved convergences during the training and validation phases. At the end, we will provide a statistical analysis of the reported studies and a discussion on the current challenges and future possibilities**

I. Introduction

THE DYNAMICS and structure of living cells are managed by the physical properties of the cytoskeleton [1]. But the cytoskeleton is the combination of complex biochemical circuits which controls its spatial organization and dynamics [2]. Untangling this interplay between biochemical and mechanical constraints is the major challenge faced when studying the physical biology of the cell. Traditional modeling techniques are learned mainly on intuition built on classical continuum mechanics, where conservation and symmetries laws control the variables which arise in these models and equations they follow [3]. However, cells are hierarchical, non-equilibrium dynamics, relying instead on distributed enzymatic activity, and non-classical structures [4]. Therefore, such characteristics may complicate system parameterization and coarse-graining with regard to a few collective simply-understood variables [5]. Although we have remarkable progress and research in the area of physical biology, but it is difficult to accurately predict the mechanical response of cells to biochemical perturbations.

Artificial Intelligence (AI) and Machine learning (ML) algorithms have the potential to overcome some of the key challenges faced by conventional modeling techniques by learning models directly from the statistics of data [6]. These modern technologies have useful applications in diverse areas like communication [7], [8], dynamic treatment regimes [9], risk management during nuclear examination [10], rehabilitation [11], health monitoring [12] The use of AI and ML is transforming the way biologists do research, demonstrate their findings, and utilize them to address problems in the field [13], [14] and many more. As science along with other fields have been becoming more interdisciplinary, researchers are taking benefits of AI and ML to solve challenging and emerging problems in cell mechanics and biology. The application of ML especially of Reinforcement Learning (RL) and Deep Learning (DL) in solving an array of research problems like drug discovery, genome analysis, classification of cellular images, and in correlating the genome and image data to electronic medical records. Moreover, AI-powered algorithms have other applications including protein function prediction, analysis of genome-wide association studies to investigate markers of disease, high-throughput microarray data analysis, and enzyme function prediction. In addition, modern AI and ML technologies have assisted the discovery of tools which are solving challenging research problems such as cell profile, DeepVariant, and Atomwise.

The objective of this work is to study cell related issues using AI and ML approaches to characterize the different aspects of the phenomena and highlight the mechanical, thermal, and chemical properties of the systems under scrutiny. The work is structured in different research lines to investigate the topics such as:

1- Analysis of discrete models at the microscale based on elements that exhibit multistability to study how the microscopic details are responsible for emergent phenomena at the meso and macroscale.

2- Study of the complex response of the cells' systems across the scales using AI and Finite Element-based numerical methods.

3- Studies related to experimental validation on adhered cell

cultures characterizing elastic properties, surface topography and adhesion phenomena of cells under specific load conditions to confirm the theoretical outcomes about the mechanical behavior.

4- Study of physics-based machine learning techniques that include information obtained from the developed models and the experimental validation and optimize the training phase to improve the output and predictive capabilities of these methods.

After a brief introduction on the scope of this work in section I, we will present an overview of the AI tools in section II. The section III will be the main section where we will present diverse applications of AI for cell mechanics. Then in the discussion section, we will present some of our findings and we will close this study with concluding remarks in section VI.

II. AI POWERED TECHNIQUES

In this section, we will introduce various AI technologies as also indicated in the Figure 1 that can be utilized for different aspects of cell mechanics.

A. Neural Networks

Neural networks (NNs) are computational models inspired by the human brain's ability to process information. They comprise interconnected units known as neurons, organized into layers: input, hidden, and output. These neurons engage in a learning process where they adjust their behavior based on the data they receive. Inputs are represented by numerical values, these are fed into neurons to convey features of the data. Each input is assigned a weight, signifying its impact on the neuron's output. These weights are adjusted during training to optimize the network's performance. A constant value known as bias is added to the weighted sum of inputs, allowing the neuron to learn even when inputs are zero. It helps in avoiding scenarios where the network would be overly influenced by certain features. Activation function is applied as a non-linear transformation to the weighted sum and enables neurons to learn intricate patterns in the data. This non-linearity is crucial for the network to capture complex relationships and avoid being limited to linear mappings.

B. Convolutional Neural Networks (CNNs)

CNNs are advanced forms of NNs tailored for grid-like data, such as images or audio. Filters or convolutions are used in CNNs to extract meaningful features from the input. A conventional CNN consists of some convolutional layers, then some pooling layers, and also fully connected layers.

The convolutional layers use filters to extract features from the input data such as textures or edges. While the use of pooling layers in CNNs is to minimize the dimensionality of the data, avoiding overfitting and simplifying the information.

Finally, the function of fully connected layers in CNNs is the features extraction by convolutional layers for final predictions.

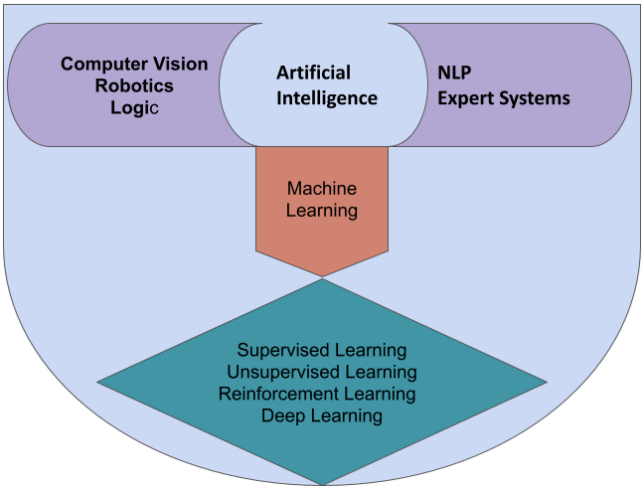

Fig. 1. An overview of AI-powered tools

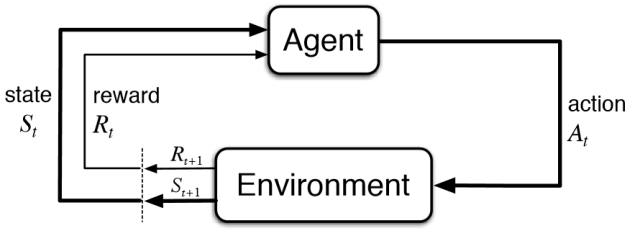

Fig. 2. A demonstration of RL workflow [15]

C. Transfer Learning

Transfer learning is a technique where a pre-trained model is used as a starting point for a new task. The idea is to leverage the knowledge the model gained from a previous task to improve performance on a new task. The pre-trained model, often a deep neural network trained on a large dataset like ImageNet, is modified for the new task by adding or replacing layers. Only the weights of the new layers are trained using the new dataset. Transfer learning is useful when the new dataset is too small to train a model from scratch. The new dataset is different but has some similarities to the original dataset. It has proven effective for tasks like image classification, object detection, and natural language processing, as it reduces the time and resources needed for training while enhancing performance on new tasks.

D. Reinforcement Learning

Reinforcement Learning (RL) is a type of machine learning where a computer program learns by taking actions in a given environment as also demonstrated in the Figure 2. It is similar to playing a game where you try different moves to get the highest score [16]. In RL, the program explores actions, learns from the results, and aims to make smart decisions to maximize its overall success.

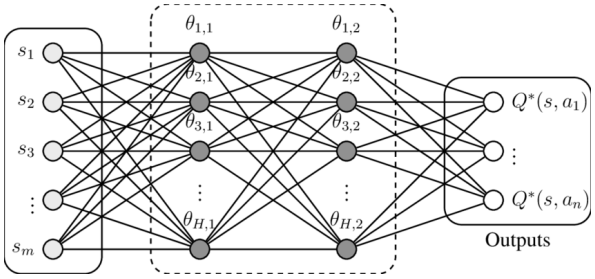

Fig. 3. Structure of the neural network used for the Deep Q-learning Network [18]

In a RL framework an agent has to interact with the given environment. The environment contains a set of states where a state at time t can be represented as S_t as also shown in the Figure 2. The agent has to choose an action at time t, represented as A_t out of set of actions for a state S_t and for each action, the environment returns a reward to the agent which helps an agent to learn and act optimally in an environment. An RL Agent is the program or "player" that makes decisions in the virtual world. Environment is the virtual world where the agent takes actions. Each environment contains different situations or states and the choices the agent can make in those situations are known as actions. The environment returns a reward against each action taken in a state.

The agent starts by randomly trying actions and learning from the outcomes. At first, it doesn't know much about the environment, but with each attempt, it figures out what works and what doesn't [17]. Over time, it gets better at choosing the best actions in different situations. The ultimate goal is to have a strategy (policy) for making the best decisions in any state of the environment. For example, consider the Multi-Arm Bandit (MAB) problem where we have many slot machines. The agent's goal is to learn which machine gives the best reward. It's a simplified RL scenario with only one state, and the agent balances between trying new machines (exploration) and sticking to the best one (exploitation). An advanced form of the RL is the use of NN to accomodate a larger state space environment. One such widely used algorithm is Deep Q-Network (DQN) as also demonstrated in the Figure 3.

III. AI FOR CELL MECHANICS

In this section, we will present some recent and interesting applications of AI in cell mechanics.

Authors in [19] develops interpretable machine learning models of cell mechanics from protein images and neural networks (NN) are used to predict traction forces from a single focal adhesion protein field. NN generalize to unseen biochemical perturbations, cell types and cells. Agnostic as well as physics-constrained methods learn interpretable rules for prediction. A DCell is developed in [20] which is a visible NN embedded in the hierarchical structure of 2,526 subsystems that encompasses an eukaryotic cell. DCell after training on millions of genotypes, can simulates cellular growth with good accuracy. This framework offers a foundation to decode the drug resistance, genetics of disease, and synthetic life.

Similarly, Deep RL (DRL) are exploited in [21] to infer collective cell behaviours and cell–cell interactions in tissue morphogenesis from 3D time-lapse images. Authors use hierarchical DRL to examine cell migrations from the images with an ubiquitous nuclear label. The hierarchical DRL method HDRL reveals a modular, multiphase organization of cell movement to Caenorhabditis elegans embryogenesis. A hybrid RL model is employed in [22] to guide process control efficiently. A probabilistic knowledge graph framework is created characterizing the science and risk-based understanding of quantifying inherent stochasticity and biomanufacturing process mechanisms. The proposed model can assist in learning from heterogeneous process data. Authors also used computational sampling technique to produce posterior samples quantifying model uncertainty while Bayesian RL is utilized for model uncertainty and inherent stochasticity for dynamic decision making.

A DRL method is introduced in [23] to study cell movement in the embryonic development of C.elegans. This agent based modeling mechanism captures the complexity of cell movement patterns in the embryo and addresses the local optimization issues. The model is tested with the rearrangement of the superficial left-right asymmetry and anterior movement of the Cpaaa cell via intercalation. A generic framework based on RL and convolutional NN is introduced in [24] to study navigation rules during cell migration. The proposed system uses a flexible model-free method that directly accepts raw images to the sensory input. The framework manages simulation scenarios involving cell division during embryogenesis.

Inverse RL is applied in [25] to analyze cellular heterogeneity. Authors showed the uses of inverse RL to datasets containing cellular states and actions for inferring how each cell selects actions in heterogeneous states. Authors have also discussed the applications of inverse RL to three cell biology problems. Moreover, the diverse uses of machine learning methods in systems biology are discussed in [26]. Authors also explored the combination of machine learning and mechanistic modeling for systems biology.

Supervised machine learning and generative NN are combined in [27] for patient-derived melanoma xenografts classification as "inefficient" or "efficient" metastatic. Moreover, predictions are validated regarding melanoma cell lines with unknown metastatic efficiency in mouse xenografts, and then the network is used to produce in silico cell images that improve the critical predictive cell features. The proposed work demonstrates how the application of AI can assist in the identification of cellular attributes that are predictive of integrated cell functions and complex phenotypes but are too abstruse for a human expert to identify. A computational framework using machine learning is developed in [28] for individual cell's deformability investigation. This system can reproduce a physical microfluidic. The datasets for the training and testing are produced with high-fidelity fluid-structure interaction simulations.

Similarly, in another work [29], machine learning is applied for extraction of the cellular force distributions from the microscope images. The authors divided the process into three stages. Initially, cells are cultured on a special substrate to measure the cellular traction force and the corresponding substrate wrinkles simultaneously. Then, the extraction of wrinkle positions from the microscope images is performed. At the end, machine learning model is trained with generative adversarial network by using input and traction field images. An analysis pipeline using deep learning is considered in [30] to perform classification of cell morphometric phenotypes from multi-channel fluorescence micrographs. Authors illustrated classification of definite morphological signatures observed when epithelial or fibroblasts cells are available with distinct extracellular matrices using residual NN with squeeze-and-excite blocks.

The intersection between cellular image analysis and deep learning are investigated in [31]. The authors studied about augmented microscopy, object tracking, image segmentation, and image classification. Taxol and cytochalasin D are known chemicals for interaction with the cytoskeleton and affect the cell motility and morphology. Therefore, quantitative measurements of the influence these two chemicals on human neuroblastoma are presented in [32]. The authors have designed customized deep learning and encoder-decoder based cell detection and tracking mechanisms.

The authors of [33] analyzed signal processing techniques such as matched filtering and spectral filtering of the video signal for detection of cellular micromotion. Moreover, they also considered 1D and 3D convolutional NN acting on pixel-wise time-domain data. An interesting and useful software package is proposed in [34] for cell tracking. The software package contains a manual tracking function, a pattern matching based sequential search-type tracking function, and a conventional tracking function composed of link processing and recognition processing. A deep learning based recognition function is also part of the package which is useful for several targets including stain-free images.

A foundation work has been done in [35] to promote genetic research and cellular biology. The authors constructed a novel model called scGPT for single-cell biology. The model is based on a generative pretrained transformer using a repository of more than 33 million cells. The scGPT efficiently distills critical biological insights concerning cells and genes. The model is useful but it can be optimized to obtain better performance across different downstream applications with further use of transfer learning. For example, transfer learning is used in [36] for data denoising in single-cell transcriptomics. Single cell RNA sequencing data are sparse and noisy. Therefore, authors used transfer learning across datasets to improve the quality of the data. A Bayesian model is coupled with a deep autoencoder to extract transferable gene-gene relationships across data from labs.

A data-integration infrastructure consists of deep generative models and adversarial training is proposed in [37] for both supervised and unsupervised integration of multiple batches. The authors employed six real bench-marking datasets to show that the proposed framework can address critical challenges including conservation of development trajectory, large number of batches, nested batch-effects, and skewed cell type distribution. Moreover, 1 million cells dataset are utilized to illustrate that the given framework can perform atlas-level cross-species. Similarly, authors in [38], consider the generalizability of another AI tool such as natural language processing in single-cell genomics. The authors found the necessity for careful consideration of data distribution and presented a subsampling method to overcome the effect of an imbalanced distribution.

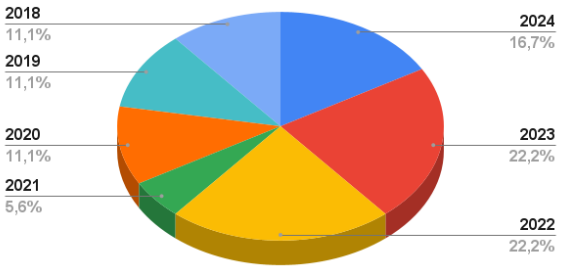

Fig. 4. Distribution of reported studies: Publication year

A symbolic data modeling approach “Evolutionary Polynomial Regression,” is adopted in [39]. The technique integrates genetic programming paradigm with regression capabilities to derive explicit analytical formulas. The authors have presented the main benefits of our multiscale numerical approach using spider silk case. Similarly, the authors in [40] suggest that integration of multiscale modeling and ML can offer new insights into disease mechanisms, assist in identification new targets and treatment plans, and help in decision making to benefit of human health.

In an interesting work of [41], the authors proposed a reduced order method for active force generation in cardiomyocytes. The model is designed by ML of a physics-based high-fidelity model. The authors trained an ANN within a grey-box technique. Then they validate the model under various pathological and physiological cell conditions.

IV. Discussion

This section highlights the key points by discussing challenges and future directions. We have also reported in the Figure 4, a distribution of the studies that we analyzed in Section III according to their publication year

We found after an in-depth study that the AI technologies, particularly Reinforcement Learning (RL) techniques can be used for the development of optimal decision support agents able to assist in the definition of models’ features, such as the topology, and the prediction of some dynamics in single cell and cell aggregates (cell adhesion, growth, and remodeling). We observed that RL algorithms are much more focused on

goal-oriented learning from interaction with the environment (system to control) than other machine learning approaches. Next we outline the list of our key findings:

- Deep RL (DRL) can be used to infer cell–cell interactions and collective cell behaviors in tissue morphogenesis from three-dimensional (3D) time-lapse images. In particular, Hierarchical DRL, which is known for multiscale learning and data efficiency, can be applied to examine cell migrations based on images with a ubiquitous nuclear label and simple rules formulated from empirical statistics of the images.
- Hybrid model-based RL can be employed for cell therapy manufacturing process control. Specially, hybrid model-based Bayesian RL approaches, accounting for both inherent stochasticity and model uncertainty are useful to guide optimal, robust, and interpretable dynamic decision making.
- Deep learning can be used to model the hierarchical structure and function of a cell.
- Cell movement in the early phase of Caenorhabditis elegans development is regulated by a highly complex process in which a set of rules and connections are formulated at distinct scales. We found that the DRL method can be utilized within an agent-based modeling system to characterize cell movement in the embryonic development of C.elegans.
- Cell migration modeling is a longstanding biological challenge, which is regulated by a highly complex set of regulatory mechanisms at multiple scales in a developmental system. We can use RL and convolutional neural networks to better study navigation rules and mechanisms during cell migration.
- Inverse RL can be integrated into data-driven mechanistic computational models. Inverse RL can be applied to datasets to infer how individual cells choose different actions based on heterogeneous states. Inverse RL techniques also have potential applications in three cell biology problems.
- We observed that including physical information in machine learning approaches can be useful to optimize the training phase and improve the output and prediction power of the methods. This is due to fact that sometimes established RL methods may have limitations in a scenario like: i) definition of the goal that in this case is a set of goals (i.e., structural equilibrium, local stiffness of structures, etc), ii) incorporation of initial knowledge such as a basis topology derived from biological images, iii) dimension of the state-space, and iv) interplay in cell aggregates.
- Deep RL approaches have application in studying cell–cell interactions and collective cell behaviors. Similarly, deep RL method can be utilized within an agent-based modeling system to characterize cell movement in the embryonic development of C.elegans.
- Bayesian RL techniques which account for both inherent stochasticity and model uncertainty are useful to guide optimal, robust, and interpretable dynamic decision making. Similarly, Deep learning and neural networks can be used to model the hierarchical structure and function of a cell.
- Moreover, RL and convolutional neural networks are suitable to study navigation rules and mechanisms during cell migration. Lastly, Inverse RL can be integrated into data-driven mechanistic computational models. Inverse RL can be applied to datasets to infer how individual cells choose different actions based on heterogeneous states.

V. Conclusion

This review has presented an overview of the use of artificial intelligence and machine learning for various aspects of cell mechanics. We also analyzed applying physical constraints on the AI and ML models in order to obtain better convergences during the training and validation phases. We observed that the AI technologies such as reinforcement learning techniques can be used for the development of optimal decision support agents able to assist in the definition of models' features, such as the topology, and the prediction of some dynamics in single cell and cell aggregates (cell adhesion, growth, and remodeling). We noted that RL algorithms are much more focused on goal-oriented learning from interaction with the environment (system to control) than other machine learning approaches.

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