Seminar in Mathematical Biology
Summer Semester 2024

Global AI Models for Multicellular Dynamics

Towards Learned Simulators for Cellular Migration

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Abstract

Spatiotemporal models are applied to study myriads of physical, chemical and biological phenomena, one of which is the problem of studying cellular dynamics. Global AI models are being applied to models that exhibit dynamics in spatial and temporal domain. Successful applications of such neural simulators can be found in the domains of physics, chemistry, and structural biology, amongst others.

Machine learning has become an increasingly fast growing field in computer sciences, bringing forth lots of different implementations suited for a huge variety of problems. In the presented work, the authors propose an autoregressive probabilistic model that can reproduce spatiotemporal dynamics of single cell migration, traditionally simulated with the Cellular Potts model.

1 Cellular-Potts Model

Based on the earlier Potts Model, this is a computational model usable to study and simulate the motion and dynamics of cells and tissues. Whilest also being used to simulate individual and collective cell behavior, tissue morphogenesis and cancer development.

Consisting of a rectangular **Euclidean lattice** where each cell is represented as a subset of lattice sites sharing the same cell number. Lattice sites which are unoccupied by cells are called the medium. Considering the function $x : L \to S$ each lattice site l_i gets mapped to its state $x(l_i) \in S$ where S is the set of all cell numbers.

Model Dynamics The dynamics of the model are governed by an energy function H. Starting from given initial condictions, at each iteration a lattice site l_i is chosen at random. Then, a proposal is made to modify x, changing its state from $x(l_i)$ to $x(l_j)$, where l_j is a lattice site adjacent to l_i.

Negative energy differences ΔH between two states, is favored as the system tends towards lower energy states.

Energy Function The original model proposed by Graner and Glazier [1] investigates cells of two types, with different adhesion energies for cells of the same type and cells of a different type. Each cell type has a different contact energy with the medium, and the cell volume is assumed to remain close to a target value.

The Hamiltonian is formulated as:

$$\mathcal{H} = \sum_{i=0}^{n} \mathcal{J}(x(l_i), x(l_j)) + \sum_{i=0}^{n} \lambda_v (V(c) - V^*(c))^2 \quad (1)$$

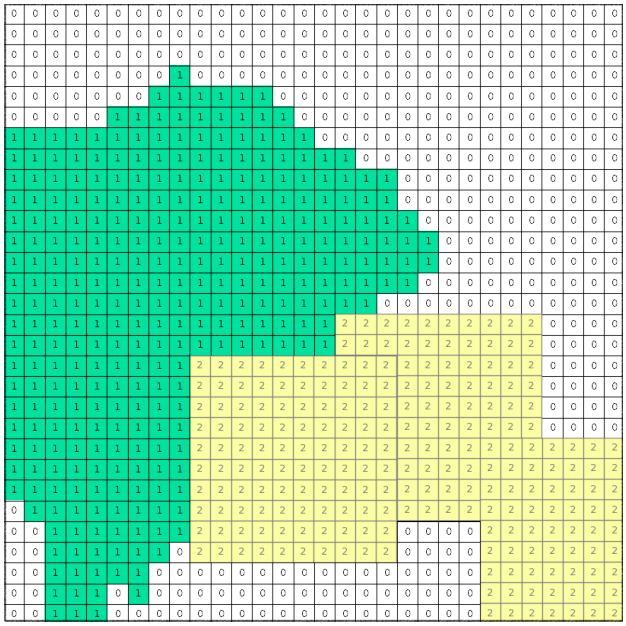

Figure 1: Euclidean Lattice of Cellular Potts model

If $\Delta H < 0$, the proposal state gets always accepted, following the physical intuition. However final states with $\Delta H > 0$, are also possible by introducing a latent system energy.

Resulting in a probability scaling with $e^{-\Delta H/T}$, using T as the Temperature. Increasing temperature thus increases probability for greater losses in system energy.

2 Machine Learning Formulation

The authors utilize a machine learning model, based on the Conditional Variational Autoencoder (CVAE) with an additional so called forward model to interpret images.

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2.1 Autoencoders

The simple autoencoder is an architecture, with the objective of encoding input data into a latent representation only containing core features and aspects of the original input [2].

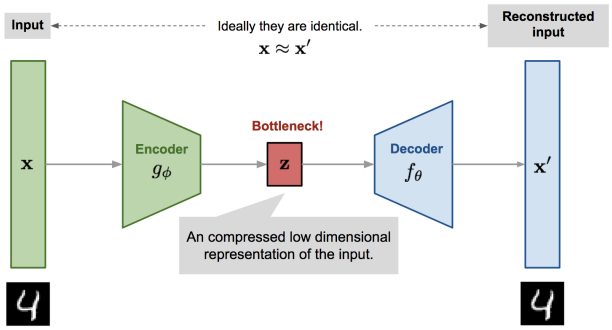

Figure 2: Autoencoder Architecture

To achieve this, we optimize parameters of an encoder $g_\theta(x_n)$, projecting a high dimensional input X into a lower dimensional latent space z and the parameters of a decoder $f_\phi(g_\theta(x_n))$ which reconstructs it into X'. This optimization is done in such a way, that the reconstruction is nearly lossless.

$$\mathcal{L}_{\phi,\theta}(x, x') = \frac{1}{N}\sum_{n=1}^{N}(x_n - f_\phi(g_\theta(x_n)))^2 \qquad (2)$$

Variational Autoencoders Instead of mapping the input space X into a fixed vector, variational autoencoders map it into a distribution p_θ parameterized by z [3], and allow sampling the latent space to obtain a combination of multiple aspects of the input space.

To train VAEs, the Evidence Lower Bound (ELBO) loss function can be used.

Conditional Variational Autoencoders Whereas the simple autoencoder formulates the latent representation as the probability of z given X, conditional variational autoencoder adds just an additional conditional variable, with encoder $p_\theta(z|X, c)$, and decoder $q_\phi(X|z, c)$ [4].

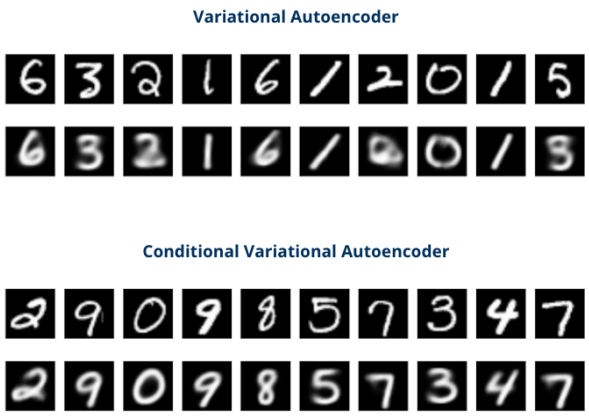

Figure 3: Improved reconstructed images with CVAEs

2.2 Modelling Cellular-Potts

At each time t the system is described by its state x^t, a categorically-valued function on a fixed grid. Correspondingly, a system evolution is specified by a sequence of states $x^{[0:T]}$. The authors postulate a ground-truth probability distribution $p_*(x^{[0:T]})$ [5] over system evolutions $x^{[0:T]}$ from which we can sample using the CP simulator.

Hence, our aim is to learn the parameters θ of the model p_θ to maximize:

$$\mathbb{E}_{t\sim U_{\{0,T-1\}}}\mathbb{E}_{x^t\sim p_*}\log p_\theta(x^{t+1}|x^t) \qquad (3)$$

This is achieved with a conditional variational autoencoder, where latent variable z is conditioned on previous state x^t according to conditional prior $p_\theta(z|x^t)$ and the subsequent state x^{t+1} follows the distribution $p_\theta(x^{t+1}|x^t, z)$.

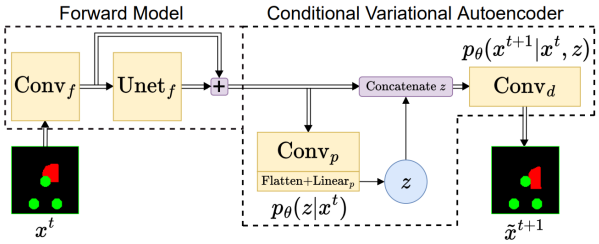

Figure 4: Model Architecture

As this model is an autoregressive model, it consists of a forward model that evolves the state of the system to the next state. However, rather than directly producing the pixel-wise parameters of a distribution to sample the next state from, the representation produced by the forward model is used to first condition the prior distribution of the latent variable. Then, to produce a sample of the next state, the latent variable is sampled from this prior and combine it with the forward representation, which is subsequently decoded.

$$L_{\phi,\theta} = -D_{KL}(q_\phi||p_\theta) + \mathbb{E}_{q_\phi}[\log p_\theta(x^{t+1}|x^t, z)] \qquad (4)$$

During training, the Evidence Lower Bound (ELBO) on the log-likelihood (equation 4) is optimized. During trajectory generation we sample latent variable z from the prior distribution $p_\theta(z|x^t)$.

By then sampling $\tilde{x}^{t+1} \sim p_\theta(x^{t+1}|x^t, z)$ and repeating the entire process, we can simulate longer trajectories.

3 Training and Analysis

We trained our own version of the model proposed by paper since, to our knowledge, a pre-trained model is not publically avaiable yet. Slight modifications of the original code were done. Our code is also available on Github[1].

[1] https://github.com/zrthxn/EPNS

Dataset and Training To generate training samples we have used a Morpheus[2] [6] model for Cellular-Potts. We generated initial conditions with random stationary walls and one cell and two cells, ti get two datasets, each with 800 training samples, 100 validation and test samples. We then trained two models using the aforementioned two datasets, using one NVIDIA A100 provided by HPC at ZIH, TU Dresden.

3.1 Results and Analysis

We run the models on the test split of both of the datasets that we generated. Both models, one and two cells, are tested with both datasets.

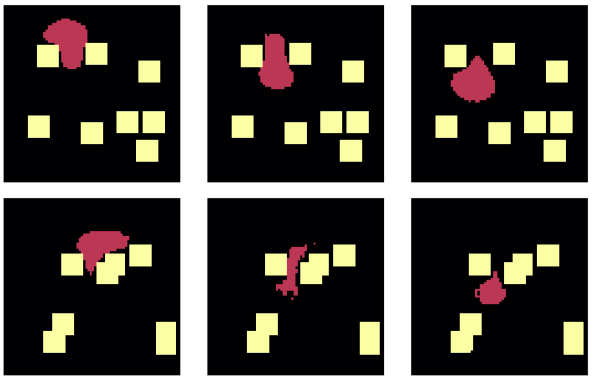

Figure 5: Neural Simulator: Dynamics of One Cell

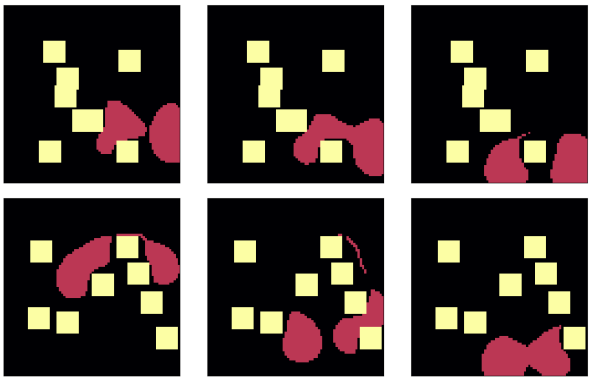

Figure 6: Neural Simulator: Dynamics of Two Cells

The model was able to learn the expected dynamics of the cells. Similarly we can observe an expected output from the two-cell model. Intersting is the cases, where the single cell model was applied to two cell initial conditions and was able to transfer well towards expected dynamics.

Edge Cases However edge cases where the model breaks down are rarely observable. Sometimes we can see gaps and holes in the cells, as well as some movement of the walls. Also, cell volume preservation is not guarenteed in many cases, sometimes even resulting in vanishing cells.

[2] https://morpheus.gitlab.io/

Figure 7: Edge Cases: Destruction of volume

4 Conclusion

We conclude that the problem of predicting cell motility is non-trivial, and that specific architectural choices for machine learning models are well suited to the problem. Edge cases, while present, are rarely observed.

Applications to real-world microscopy data should be possible with minimal changes to the model. Explainability analysis may help understand how cells decide their motility. Most notably, this approach bypasses the need for a mechanistic understanding of the system.

Contributions

Review of the paper was done collaboratively. To produce the results shown, Paul worked on data generation and Ali on model training. Both authors contributed equally to presentation slides and this article.

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