Seminar in Mathematical Biology
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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.

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. According to them, a neural simulator for cellular dynamics can augment lab experiments and traditional computational methods to enhance our understanding of a cell's interaction with its physical environment.

1 Cellular-Potts Model

Based on the earlier Potts Model [1], this is a computational model that can be used to study and simulate the motion and dynamics of cells and tissues. It is also used to simulate individual and collective cell behavior, tissue morphogenesis and cancer development.

The model consists of a rectangular **Euclidean lattice** where each cell is a subset of lattice sites sharing the same cell number. Lattice sites that are not occupied by cells are the medium. Consider function $x : L \to S$ that maps each lattice site l_i to its state $x(l_i) \in S$ where S is the set of all cell numbers.

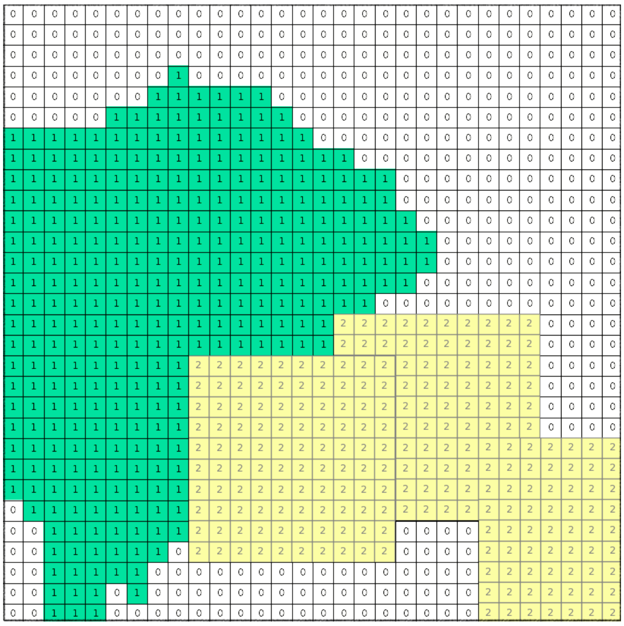
Model Dynamics The dynamics of the model are governed by an energy function H. At each iteration of the model a lattice site l_i is chosen at random. Then, a proposal is made to modify x such that state $x(l_i)$ is changed to $x(l_j)$, where l_j is a site adjacent to l_i.

The difference in energy ΔH between the two states is calculated, by using the energy function formulated as a Hamiltonian as in equation 1. Difference in energy ΔH decides if the new proposed state is accepted.

Energy Function The original model proposed by Graner and Glazier [2] contains cells of two types, with different adhesion energies for cells of the same type and cells of a different type. Each cell type also 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:

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



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0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	2	2	2	2	2	2

Figure 1: Euclidean Lattice of Cellular Potts model

If $\Delta H < 0$, the state is always accepted because systems tend to the lowest enegy state. But if $\Delta H > 0$, accepted with probability $e^{-\Delta H/T}$ where T is a parameter called Temperature. A higher temperature makes it more likely for higher enegy states to be accepted.

2 Machine Learning Formulation

The authors utilize a machine learning model, based on the CVAE structure with an additional so called forward model to interpret images [3].

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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 [4].

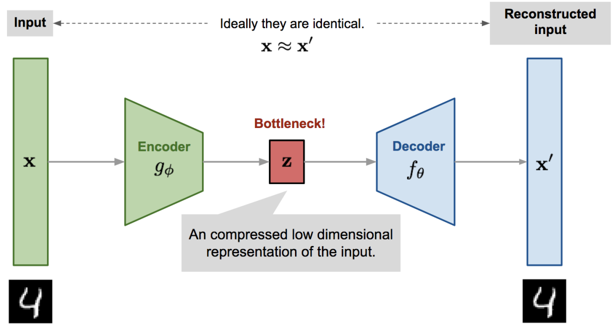

Input
Ideally they are identical.
$\mathbf{x} \approx \mathbf{x}'$
Reconstructed input
x
Encoder
g_ϕ
Bottleneck!
z
Decoder
f_θ
$\mathbf{x}'$
An compressed low dimensional representation of the input.

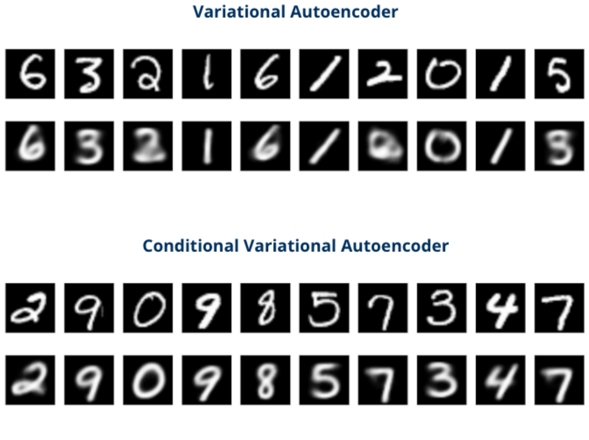
Figure 2: Autoencoder Architecture

To achieve this, we optimize parameters of encoder $g_\theta(x_n)$ encodes a high dimensional input X into a lower dimensional latent space z and the parameters of decoder $f_\phi(g_\theta(x_n))$ which reconstructs it into X', such that the reconstruction is 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 [5]. This makes it possible to sample the latent space to get samples that are a combination of two entities in 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 $q_\phi(X|z, c)$ [6].


Variational Autoencoder

Conditional Variational Autoencoder

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 $p_*(x^{[0:T]})$ [3] 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 $p_\theta(x^{t+1}|x^t, z)$.

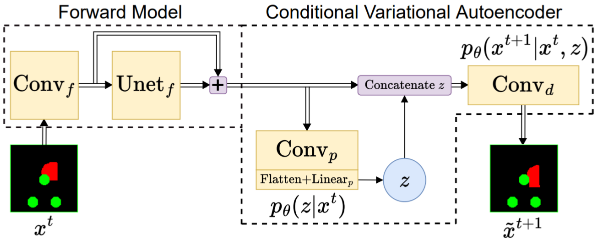


Figure 4: Model Architecture

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 train our own version of the model proposed by paper since, to our knowledge, a pre-trained model is not publically avaiable yet. We have modified the original code published by the authors to able to do this. Our code is also available on Github[1].

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

Dataset To generate training samples we have used Morpheus[2] [7] model for a Cellular-Potts. We generate random initial conditions with stationary walls and one cell and two cells. This gives us two datasets, each eith 800 training samples, 100 validation and test samples.

Training We 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.

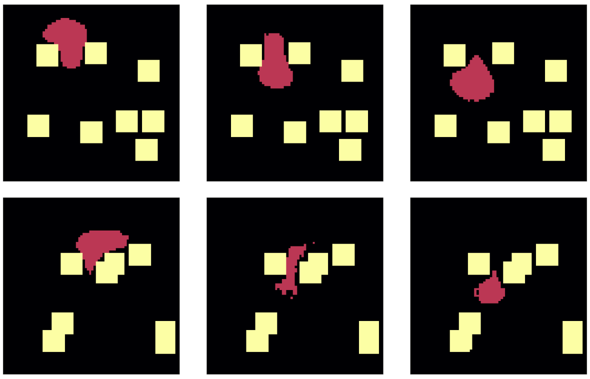


Figure 5: Neural Simulator: One Cell

The model is able to learn the expected dynamics of the cells. However we sometimes see gaps and holes in the cells, as well as some movement of the walls.

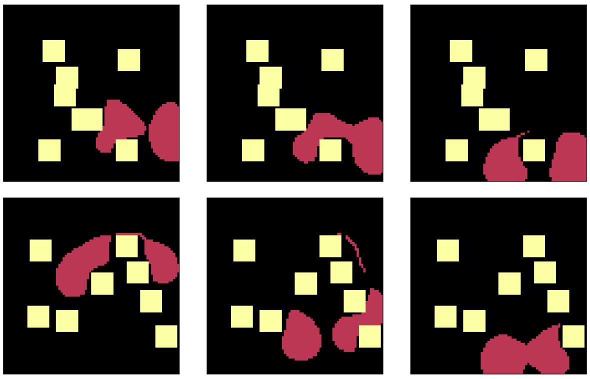


Figure 6: Neural Simulator: Two Cells

Similarly we see expected output from the two-cell model. We also see that the single-cell model is able to transfer to the two-cell cases.

Edge Cases We have also seen some edge cases where the model breaks down. Sometimes we can see gaps and holes in the cells, as well as some movement of the walls. Also, the cells sometimes lose volume and disappear.

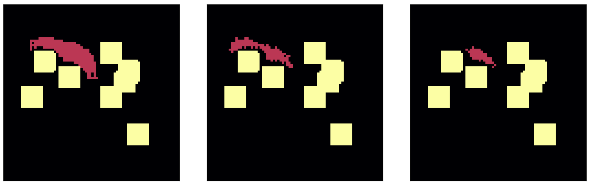


Figure 7: Neural Simulator: Edge Cases

4 Conclusion

Problem of predicting cell motility is non-trivial, many possible trajectories. Architectural choices are not just for image reasons. Edge Cases are rarely observable.

Applications to real biological data and use to infer idealized initial conditions. Explainability of model may help understand how behaviours are decided. Bypass the need for a mechanistic understanding of the system.

References

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