Spatial Microbial Dynamics

Anushri Arora* Tetsuhiro Harimoto Tal Danino
Itsik Pe'er†

Abstract

The specific growth of bacteria in immune-deficient necrotic tumor cores, coupled with advancements in engineering living cells, makes bacteria an attractive cancer therapy. However, precise understanding of spatial-temporal colonization and interaction between bacteria and tumors is not well understood. The focus of this work thus lies in computationally inferring underlying population distributions of bacteria and cancer cells, and curating an interpretative state-space model which infers global and local parameters for the competitive dynamics involved in such a system.

1 Introduction

A recent and novel utilization of microbiome research is development of engineered bacteria as therapy for cancer[9;17]. This approach relies on engineering bacteria with desired functions to grow in necrotic tumor cores and recombinantly produce anti-cancer payload[2;34;43;21;22].

Microbiome dynamics has been successfully modeled based on competitive/cooperative bacterial interactions using the Lotka-Volterra formulation[10;30;6;7;38;41], and its stochastic and spatial extensions[3;32;11;23;20;10;30;6;7;38;41]. Spatial ecology, on the other hand, often relies on point estimates. In particular, Ripley's K function formalizes local density[13;19;12;25;31] with diverse applications[33;39;29] and extensions[16;14].

Deep Neural Networks (DNNs) emerged as transformative across application domains[36;1;8;26;37]. DNNs are able to effectively learn non-linear mappings between predictors & targets through parameter optimization. State-space models have recently come in the limelight due to their interpretative temporal structure & ability to incorporate known statistical prior's during model formulation & inference[4].Such state-space models when integrated with DNNs result in better parametric model formulation[28;42;35;24].

In this paper we devise a deep state state-space simulation framework which can effectively learn both global & local parameters that govern underlying system dynamics (stochastic Lotka Volterra) from images of GFP expressing bacteria invading artificially created tumor micro-environments.

*anushri.arora@columbia.edu
†itsik@cs.columbia.edu

2 Methods

2.1 Data Analysis & Spatial Point Interactions

Input to our models are videos[22] of GFP expressing bacteria invading a multicellular spheroid environment. The videos capture the proliferation & colonization of bacteria within these spheroids, where over time necrotic tumor cores are observed. We extract individual frames from these videos (Fig 1.) with dimensions of 2048×2048 (light blue:bacteria & dark blue:necrotic tumor core) which are subsequently used to study global system dynamics using the state space model described in the following section.

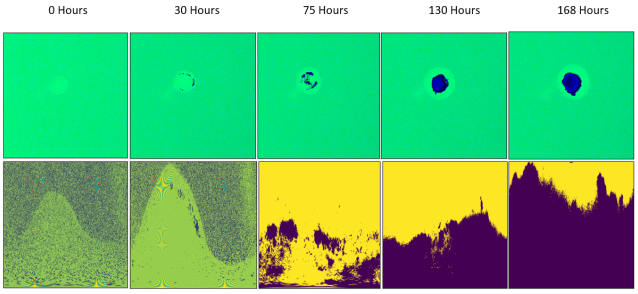


Figure 1: Top:Original Images, Bottom:Polar Images $[(x, y) = (\theta, r)]$

Thereafter we depict dynamics of each point interaction in this system with Ripley's K function estimated using the radius dimension of polar images.

Lastly we learn an effective parameterization of the underlying data distribution in the polar space. This is achieved through a Mixture Density-RNN[40;15], which learns the parameters for a family of individual distributions (two Gaussian's in our case) using the log likelihood of the input. This description encourages learning a robust model which can handle temporally abrupt distribution changes via a mixture term which quantifies the proportion of each individual distribution. We also ensure the mean of each Gaussian is positive using the LogSoftmax activation, since no negative values are seen in our data.

2.2 State Space Model

We use the Hidden Markov formulation (Fig 2) to characterize the suspected Lotka-Volterra dynamics by a chain of latent random variables z_t derived from noisy image sequences x_t. Our framework can mathematically be visualized through Eqn 1.

$$\mathbf{p(x, z)} = \prod_{\mathbf{i=0}}^{\mathbf{168}} \mathbf{p}_\theta(\mathbf{x_i}|\mathbf{z_i}).\mathbf{p}(\mathbf{z_i}) \tag{1}$$

We encode our observations into a lower dimensional (256) latent space via a Convolutional Variational Auto-Encoder[27], thus capturing relevant spatial features while restricting our latent space via known priors. Subsequently, a well studied Variational Inference mechanism[4;5] is adopted to jointly learn model parameters & underlying data distributions as shown in Eqn 2, 3 (Generative Model) & Eqn 4 (Inference Model). Additionally, multiple experiments are performed to test the efficacy of varied transition networks in the latent space.

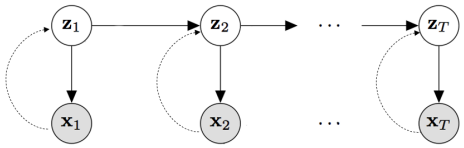


Figure 2: Graphical Model Architecture

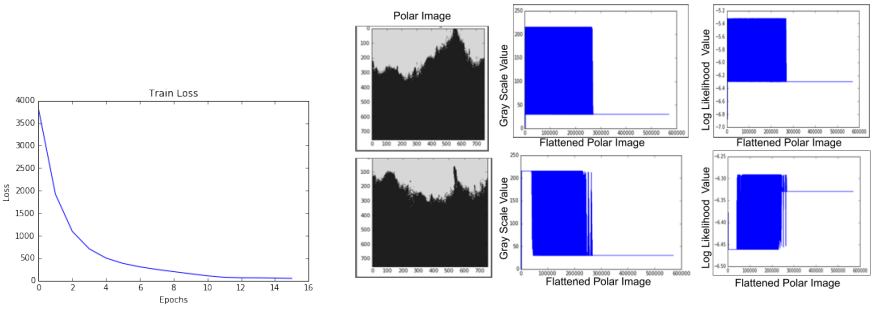
$$\mathbf{p(z_{i+1}|z_i)} = \mathbf{N}(\mu_\phi(\mathbf{z_i}),\, \mathbf{\Sigma^2_\phi}) \qquad (2)$$

$$\mathbf{p(x_t)} \sim \mathbf{N}(\mu_\psi(\mathbf{z_i}),\, \mathbf{\Sigma^2_\psi}) \qquad (3)$$

$$\mathbf{p(z_i|x_i)} = \mathbf{N}(\mu_\theta,\, \mathbf{\Sigma^2_\theta}) \qquad (4)$$

3 Results

a) Data Analysis & Point Interactions: We train our Mixture Density RNN over 15 epochs (Fig 3a) with a batch size of 16 for our LSTM cell. We test our model by checking the log-likelihood of flattened test images using the learnt distribution parameters. It can be seen the model is able to accurately represent images with both single & bi-modal peaks (Fig 3b).



(a) MD-RNN Training (b) Testing Flattened Images

Figure 3: Mixture Density - RNN.

Next, we estimate the uni-variate K function, conditioned on the maximum radius value using the MCMC estimation. As shown in Fig 4, due to limited

point events in early time steps, a stable & small K value is recorded. Thereafter, during the competitive phase, a linear trend in local point interactions is noted (time step 30 to 95). Ultimately a saturated K value is observed, once colonization & necrotic growth is complete. We hence conclude these findings to be consistent with our approximated competition equations.

b) State-Space Model: We train our state-space model for 25 epochs & test every 5 epochs by reconstructing 3 random images from our test set as shown in each column of Fig 5. We vary our network with linear, LSTM and convolutional transitions in the latent space and note similar performance between the linear and convolutional system.

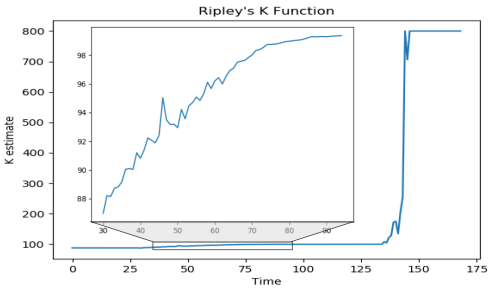


Figure 4: K function

We conclude our linear & convolutional model show similar performance in accordance with the linear approximation of our Lotka Volterra formulation.

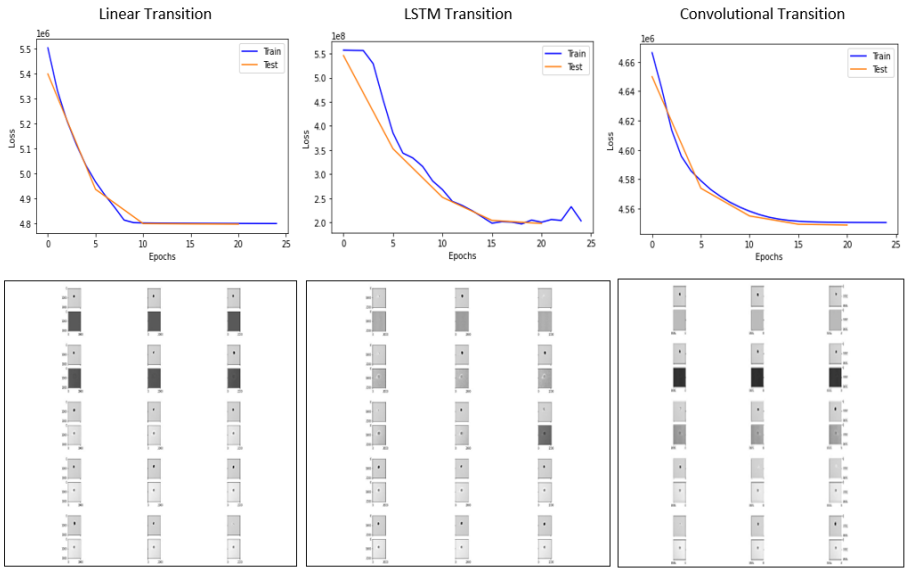


Figure 5: Top Row: Train, Bottom Row: Each row represents 3 images from test set - Original vs Reconstructed respectively