Learning Cilia Orientation in DiffTaiChi

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Abstract

Here, I investigated cilia behavior in a multi-scale way with a two-pronged approach. On one hand, an analysis of current literature and computational models of cilia kinematics were investigated, and on the other hand a computational model of cilia kinematics was built in a differentiable physics simulator using DiffTaiChi. This work is motivated by "biobot" research [1]. An instantiation of biobots is *anthrobots*, which are small aggregates of human epithelial cells (extracted from their natural place in the human lung tract) which are covered in cilia and use the cilia to move around. The long-term goal of anthrobot research is to develop an engineering pipeline that can build anthrobots to perform behaviors like drug delivery or human tissue repair. Here, I give a brief overview of cilia dynamics across many spatial scales and use DiffTaiChi to simulate anthrobots, modeling the cilia as sinusoidal actuators in simulation.

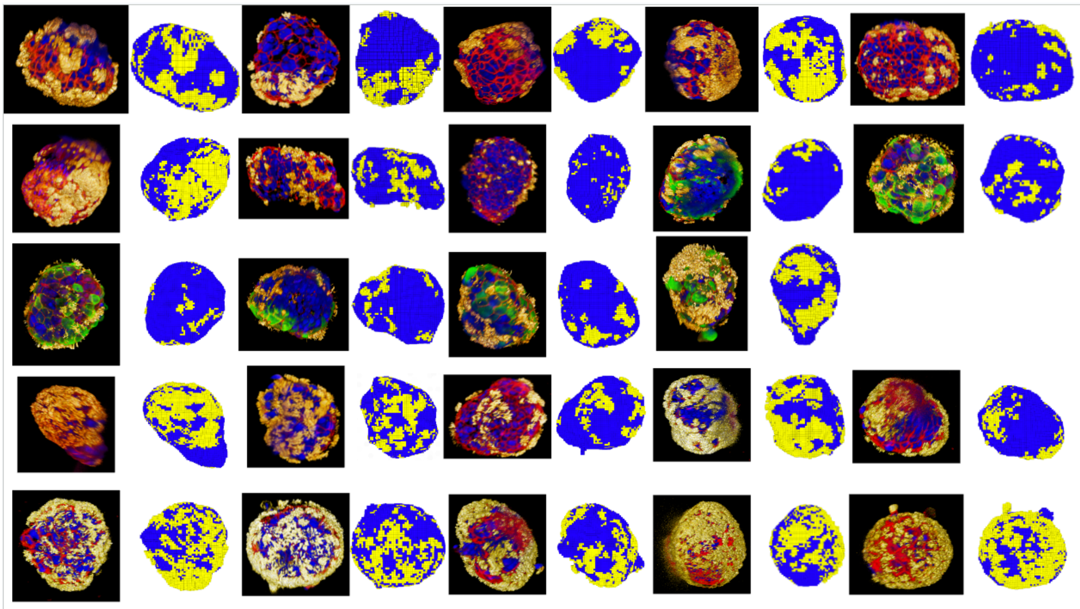

Fig. 1 Dataset of anthrobots with known cilia distributions. Yellow voxels are *ciliated* cells, and blue voxels are unciliated cells. For each pair, the left visualizes the raw imaging data and the right shows the voxel model of the anthrobot.

Background

"Biobots" are a relatively new field of research concerning the engineering of robots made of biological building blocks (i.e. cells). Biobots utilize the multitude of existing cell functions produced by evolution to exhibit novel behavior not found in naturally occurring organisms. Biobots are constructed by extracting cells from their natural *in vivo* environment (for example from *Xenopus laevis* frogs ("xenobots") [2] or human epithelial cells ("anthrobots") [1]) and reassembling them into synthetic morphologies. Biobot morphologies in the current literature have been discovered by evolutionary algorithms, where many biobots are simulated *in silico* and selected for their ability to e.g. locomote; this new phenomena has been coined "AI-designed organisms" (ADOs). Evolutionary algorithms are very computationally expensive, redundantly simulating a large population of biobots for many generations, suggesting a potential need for new ADO methodologies. Here I attempt a new method untried in the current ADO literature using backpropagation to discover the locomotive aspect of a biobot's morphology: motile cilia and their aggregate orientation on a biobot.

Cilia are small mictrotubule complexes protruding from many eukaryotic cells' surfaces which perform many functions for the cell. The cilia types we are concerned with here are *motile* cilia. Motile cilia *in vivo* are generally considered to direct fluid flow for organisms; for example, they clear fluid in mammal airways [3]. On an anthrobot, cilia are unevenly spatially distributed (Fig 1), and it's hypothesized that this spatial distribution contributes to the organism-level movement trajectory expressed by the anthrobot.

Here, I hypothesize that another key cilia-scale factor contributes to anthrobot movement: cilia *orientation*. This hypothesis is motivated primarily by a paper published by Juan Ramires-San et. al. in 2020, which details the multi-scale dynamics of cilia orientation and how they ultimately contribute to fluid flow in airways. When you look at the function of cilia arrays across a cell or across a cluster of cells, there are spatial correlations which emerge as aggregate forces on the environment of these cells (Fig 3D). Cilia exert directional forces on their environment (Fig 3C), which manifest functionally as directing fluid flow in human airways and as locomotive forces in anthrobots (Fig 3E). Cilia orientation is known to be shaped by the environment of the cell during development [4], so a possible application of this research is to be able to shape cilia orientation in the development of anthrobots (e.g. by manually directing fluid flow over anthrobots during their development).

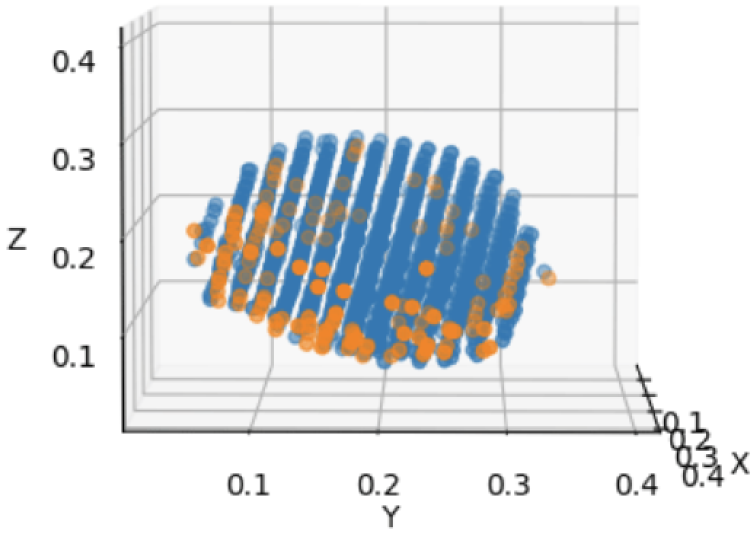

Fig. 2 3D visualization of an anthrobot from DiffTaiChi, visualized with Matplotlib. Blue particles represent the anthrobot body, orange particles are actuated cilia.

TaiChiLang is a differentiable programming language embedded within Python, and it is compiled using Just-In-Time (JIT) compilation to transform Python code into GPU-accelerated code. Physics engines have been built using TaiChiLang, one of which is DiffTaiChi [5]. The anthrobots were simulated in DiffTaiChi, where particles are either actuated or non-actuated. At each timestep of the simulation, a sinusoidal force is applied to actuated particles, meant to simulate sinusoidal cilia kinematics.

Methods

Figure 1 shows the dataset I used from previous work done by Caitlin Grasso, another PhD student in Josh Bongard's lab at UVM who modeled anthrobots in another physics engine which was non-differentiable (VoxCraft). Also in Figure 1 the known anthrobot morphologies and known cilia distributions are shown. Further, the movement trajectories of these anthrobots were also known; they were collected from overhead videos of the anthrobots by tracking the centroids of each anthrobot over time. These trajectories were used as a fitness function for the simulated anthrobots. What is not known currently is the *orientation* of the cilia [3]. The goal of simulation is to learn the parameters for the cilia actuation which gives rise to the particular anthrobot trajectories, and we hope these parameters discovered in simulation have a direct correspondence to true cilia orientation. DiffTaiChi is a differentiable physics simulator, so the actuator parameters can be learned by backpropagation.

I started with known cilia distributions of anthrobots collected from previous work [1] (Fig 1). The epithelial cells which make up the anthrobot were immunostained with a-tubulin, a cilia marker, for imaging. The images were analyzed and translated into a standard format for simulation or processing. The anthrobots shown in Fig 1 are at a relatively high resolution; I down-sampled the voxels by one half to make simulation faster. In DiffTaiChi, the atomic units of simulation are called *particles*, so I will refer to the constituent anthrobot units as particles as opposed to voxels.

At a high level, a differentiable physics simulation works by progressing particles in simulation over many timesteps, using physical parameters (e.g. gravity, mass, particle force interactions, etc.) to update the particles' properties (e.g. position, velocity) at each timestep. Some particles are *actuated*, which means they can exert a kind of "intrinsic" force at each timestep which is determined by an actuation function. Actuated particles in this simulation exert forces which are sinusoidal over time to mimic the sinusoidal beating of cilia. The computation necessary to carry out these particle progressions at each timestep is differentiable by a method called *automatic differentiation*, which is a method to differentiate *any* computable function. By tracking the simulation state over all timesteps, a very long differentiable computation is recorded, which can be used to backpropagate a fitness function computed at the end of the simulation. During backpropagation, the parameters of the sinusoidal actuation functions (e.g. amplitude) are updated to produce a higher fitness function; in this case, a higher average particle displacement (to encourage anthrobot motility).

One approximately spherical anthrobot was tested with varying simulation parameters. The relevant parameters were: number of timesteps, gravity, number of sin waves in the actuation function, actuation strength, actuation omega (proportional to actuation frequency), and the mass of the particles.

The actuation function is the following:

$$A_{ij} = \sum_{j}^{n_{waves}} w_{ij} \sin\left(\omega * t * dt + \frac{2\pi}{n_{waves} * j}\right)$$

where i specifies the actuated particle in simulation, j range the number of sin waves being summed (in this case $n_{waves} = 4$), ω is the angular frequency of the actuation (corresponding to the cilia beat frequency). The value of ω was set to 40 for all simulations here. Ultimately w_{ij} were the parameters optimized by backpropagation.

These simulations were carried out on a GeForce GTX 1080 GPU. Each epoch took about 1 second. In some of the best simulations, after 600 epochs (10 minutes training time) the anthrobot moved about 15% of its body length over 1000 timesteps. This is approximately the right order of magnitude for this type of movement; the bottom of Figure 3E shows an anthrobot moving about 30-40% of its body length over 30 seconds. Further work might be done on larger-scale computing infrastructure.

Downsampling the biobots to a smaller size (15x15x15 particles instead of 30x30x30 particles) helped on two fronts: memory capacity and simulation dynamics. Memory capacity is obvious: it takes less memory to simulate fewer particles over all 1000 timesteps. When it came to simulation dynamics, the larger 30x30x30 biobots tended to be very *heavy* due to the significant amount of un-actuated particles in the body and with the burden of motility resting on a relatively small proportion of actuated particles. By downsampling, the proportion of actuated particles rose from to 2.2% to 9% of all particles.

The code for these simulations can be found at https://github.com/kambielawski/cilia-diff.

Discussion

The ultimate goal of this research is to inform the artificial development of self-motile biobots. There is existing research into artificially stimulating the orientation of epithelial cilia [4] [6]. By combining this project's inquiry into learning which cilia orientation distributions give rise to what macro-scale behavior, we can start to guide the real-world development of motile anthrobots.

Various roadblocks and limitations were encountered during physical simulation in DiffTaiChi. Gradients vanishing or exploding during training, particles falling apart from each other (due, apparently, to actuation forces being stronger than the forces binding particles together), and running out of memory were common occurrences. Having only one GPU on a home workstation was limiting in terms of GPU memory. But this fact *does* point to the potential of this method for biobot simulation: a single GeForce GTX 1080 can produce a semi-motile anthrobot in just 10 minutes of wall-clock training.

For future work, a more careful consideration of biobot physics may be carried out along with a more thorough sweep through the DiffTaiChi parameters. Here, a crude and serendipitous parameter search guided by a weak intuition was carried out, whereas a more informed and careful parameter search along with higher computing power and greater memory capacity (specifically for longer timescale simulation) may offer greater insight. In pursuit of the ultimate goal of uncovering the relationship between cilia orientation and average forces exerted on cells' environments (whether in humans or in biobots), there may be other methods which work better than backpropagation. The sinusoidal nature of cilia corresponded well with the

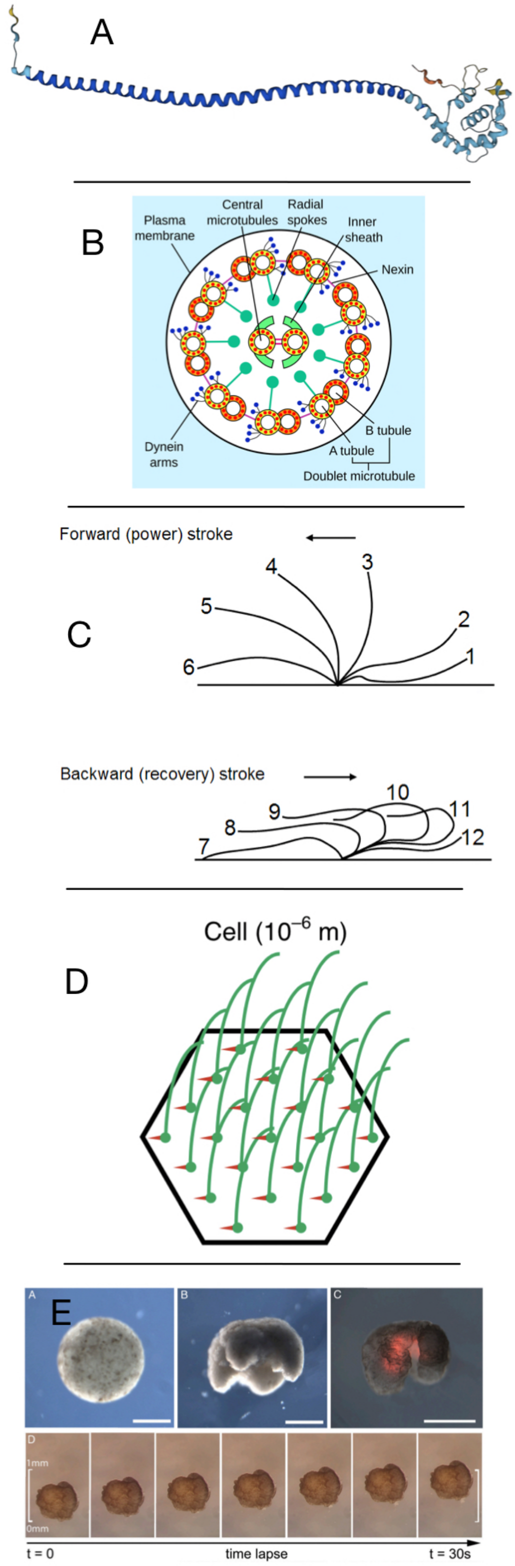

Fig. 3 Cilia over many scales. A (molecular scale): DNAH5 protein (central dynein arm kinematic component); B (protein complex scale): cross-section of a cilia; C (organelle): cilia kinematics; D (cell scale): aggregate cilia orientation on a cell; E (organism scale): anthrobots

easily implementable sinusoidal actuation in DiffTaiChi, but other methods may be better suited. New biological experiments might be carried out to approach the relationship from the other direction: by directing fluid flow over anthrobots during their development, we have a rough idea how cilia orientation will develop thanks to [4], and then we can draw connections by observing the anthrobot movement trajectory once it is fully developed.

The multi-scale cilia modeling investigation carried out here is highly preliminary. There is a vast cilia literature which went mostly untapped, DiffTaiChi is a relatively new method for AI-designed organisms and little computational resources were used, and again the search for proper simulation parameters was not systematic or well-informed. Despite these limitations, the results here do not rule out the further research and development of this method for uncovering cilia orientation in anthrobots, and in fact may be interpreted as quite promising. Further research may lead to differentiable physics engines becoming a primary tool for ADO engineers.

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