Multiscale Simulations of Morphogenesis

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Introduction

Developmental, physiological and pathological processes in life sciences involve components spanning a wide range of length scales, from biomolecules to organs, as well as time scales, from nanoseconds to days. Experimental techniques can only partially elucidate the complex interplay among these spatial and temporal scales, providing many opportunities for computational research to complement experiments. Computational methods based on interacting particles, so-called particle-methods, provide a simple yet robust and unifying framework capable of studying phenomena spanning from the molecular level to tissue and organism scale.

Using particle-methods, we investigate a set of biological problems which are relevant to morphogenesis and span a wide range of temporal and spatial scales (Fig. 1). At the molecular scale, we study glycocalyx dynamics and nanoparticle transport through the cell membrane. At the mesoscale, we present stochastic and deterministic reaction-diffusion systems and address cell level dynamics including signaling, growth and migration. At the macroscale, we report on a model for tumor growth and tumor induced sprouting angiogenesis.

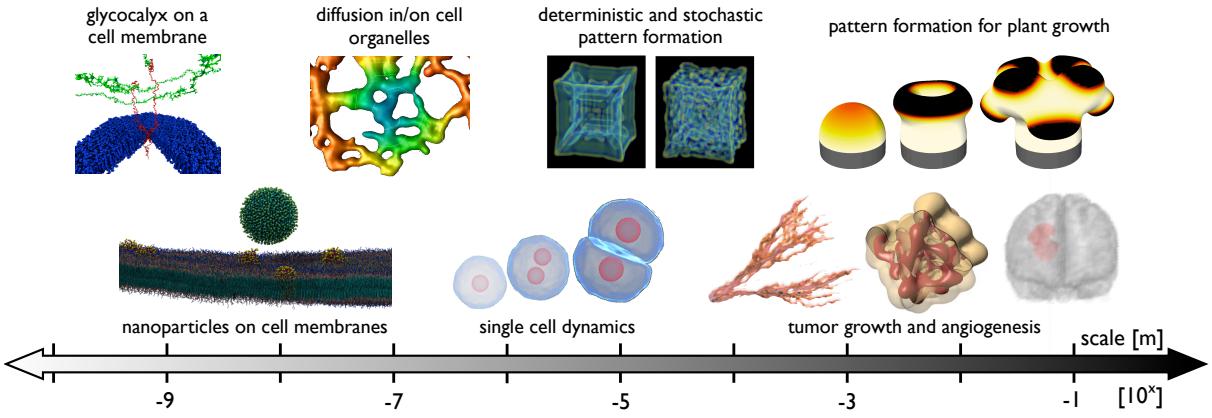

Figure 1: Simulations spanning multiple scales

Methods

Particle methods subdivide a complex system into discrete elements, the so-called particles. The unit of discretization can range from atoms to groups of cells. In the problems we study, the system size usually ranges from hundreds to millions of particles. For such large systems, it is not possible to obtain analytical solutions for the equations of motion; therefore, the system dynamics is solved numerically using computational approaches. The particle-environment and particle-particle interactions are defined through mathematical formulations that reproduce the key physical features of the system [1].

We developed multiple methods to solve those equations efficiently and accurately. We heavily rely on high performance computing to distribute the workload among thousands of processors, resulting in critical acceleration of the simulations. The computational techniques and related life science problems are the following: all-atom molecular dynamics (AA-MD) for glycocalyx, coarse-grained

molecular dynamics (CG-MD) for membrane permeation of nanoparticles, sub-cellular element model (SEM) for single cell dynamics and cell migration, continuum particle method (CPM) for morphogenesis and angiogenesis, and stochastic simulation algorithms (SSA) for pattern forming reaction diffusion systems and tumor growth.

The AA-MD and CG-MD simulations share the core theoretical background [2]. Both consist of solving the Newtonian equations of motion that govern the time evolution of a many-body system. The main difference is that in AA-MD, each particle represents an atom, while in CG-MD, each particle represents a cluster of atoms or a molecule. Coarse graining is needed to reach larger time scales inherent to relevant medical phenomena such as cellular uptake of nano-medicine.

The SEM simulations are used to model whole cells. In the SEM approach, each cell is modeled as an aggregate of soft sphere objects interacting through short range potentials. Here, the particles discretize a sub-volume of the cell's cytoskeleton and are parametrized to reproduce the overall viscosity and mechanical response of tissue [3].

The CPM simulations solve partial differential equations by discretizing them using particles with overlapping kernel functions. Particles methods can be used to handle complex, deforming shapes and model their dynamics [4,5]. Furthermore, these methods can be coupled to particles representing discrete entities like single molecules or cells [6].

SSA is used to model stochastic effects in systems of chemical kinetics when the number of molecules is low. In its classic formulation, SSA can only treat a single reaction event per time step. This can be computationally expensive for large systems as appear in reaction-diffusion systems. τ-leaping can accelerate such processes by firing several reactions per time step. In the context of reaction-diffusion processes, accelerated techniques like spatial τ-leaping and hybrid τ-leaping have been developed [7].

Applications

The flexibility of the particle-methods framework amongst spatial and temporal scales enables the *in silico* analysis of a plethora of biologically relevant systems in areas where *in vivo* investigations can be intrusive, cumbersome, expensive or even potentially life-threatening.

The use of molecular dynamics techniques allows zooming at the molecular scale, where we have developed the first atomistic model of the glycocalyx, based on structural knowledge and homology modeling. We study its conformation and orientation under blood flow induced shear and the forces mediated by it on the supporting lipid bilayer. The permeability of nanoparticles through phospholipids bilayers is investigated using coarse-grained molecular representations.

At the cellular level, we employ the SEM to capture the viscoelastic properties of interacting cells. The method has been extended to account for growth, proliferation, migration and cell-cell mediated signaling. We apply the extended method to investigate the influence of mechanical stimuli on organ growth. In particular, we study phenomena observed experimentally in fruit fly wing disk development and sepal growth. Furthermore, we study cell migration and signaling in the context of cancer cell invasion and *in vitro* wound healing experiments.

CPM simulations are employed to study phenomena at different spatial scales. We investigate reaction-diffusion processes both inside and on surfaces as observed on the endoplasmic reticulum [8]. At larger scales, we couple pattern forming reaction-diffusion systems to tissue deformation and growth models. The methods are applied to study organogenesis, tumor formation and plant growth [1,4]. In the context of tumor induced angiogenesis, we couple the CPM to discrete particles representing single migrating tip cells. The extracellular matrix and growth factors are modeled as a continuum and govern the migration path of tip cells [6].

Finally, we use stochastic spatial and hybrid τ-leaping to simulate pattern forming reaction diffusion equations of morphogenesis [7]. Tumor growth via dissemination and proliferation of cells as in glioma is modeled using stochastic differential evolution with Brownian motion [1].

Conclusion

Morphogenesis consists of a multitude of biophysical and chemical processes, spanning a broad range of length and time scales. Each of these processes operates locally at their own time scale, but collectively contribute towards the emergence of morphogenesis. Under the unifying framework of particle methods, a rigorously validated and physically sound modeling of the aforementioned processes can be achieved. Unlike grid-based methods, particle methods are local and free from shape restrictions. They can easily provide a basis for hierarchical coarse graining using a bottom-up approach in order to robustly calibrate and assess their predictive capabilities. At the same time each application can still be decoupled and refined independently if needed.

We envisage that our massively parallel computational tools for multiscale modeling of morphogenesis will continue to benefit from advances in high performance computing. This will enable the study of more detailed and complete systems. We take on the challenge of coupling and calibrating such processes with relevant examples being in the field of drug delivery and tumor growth.

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