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Computational tools for cellular scale biophysics

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Abstract

Mathematical models are indispensable for disentangling the interactions through which biological components work together to generate the forces and flows that position, mix, and distribute proteins, nutrients, and organelles within the cell. To illuminate the ever more specific questions studied at the edge of biological inquiry, such models inevitably become more complex. Solving, simulating, and learning from these more realistic models requires the development of new analytic techniques, numerical methods, and scalable software. In this review, we discuss some recent developments in tools for understanding how large numbers of cytoskeletal filaments, driven by molecular motors and interacting with the cytoplasm and other structures in their environment, generate fluid flows, instabilities, and material deformations which help drive crucial cellular processes.

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The intracellular world is rich with phenomena that occur only for sufficiently large and dense systems. One fascinating example is the emergence of cytoplasmic streaming in the *Drosophila melanogaster* oocyte. Recent theoretical and computational work, combined with experiment, has shown that kinesin motors carrying cargo along cortex-bound microtubules can generate a *swirling instability*, spontaneously aligning those microtubules and thus providing an ordered scaffolding on which the motors can drag cargo which entrains the cytoplasm and drives a cell-spanning vortex. This dramatic instability occurs only when microtubules are sufficiently *dense* [1,2], and for cells as large as the oocyte, such densities require thousands of microtubules. Simulations that achieve such scale are challenging, and those which fail provide information that is *qualitatively* wrong. This generality is famously discussed by the physicist P.W. Anderson in his 1972 article *More is Different* [3].

Here we discuss some extant and new computational tools for simulating the interactions of cytoskeletal filaments with the cytoplasm in which they are embedded and the molecular motors that push, pull, and crosslink them. These tools are often more general, and we will highlight other interesting use cases, e.g. the simulation of dense suspensions of swimming bacteria. These tools fall into two primary categories: discrete simulations, which model individual components and their interactions, and coarse-grained models, which reduce the complexity of discrete systems while offering analytical ingress and simulational efficiency.

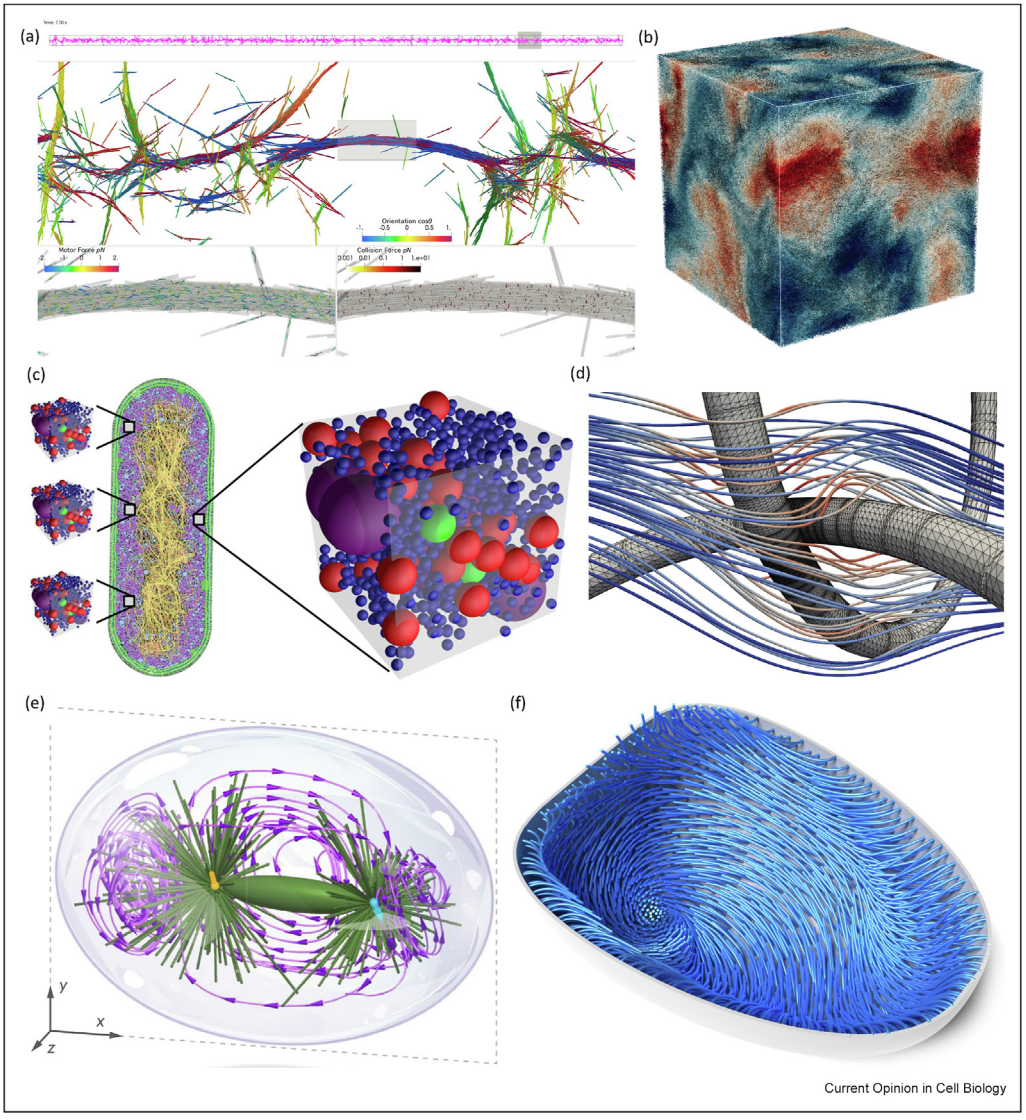
Discrete simulation methods

Specialized software packages applicable at different length scales with various capabilities exist for simulating the cytoskeleton. Our group works on mesoscale cellular processes, above the length- and time scales on which molecular dynamics are informative. At the smallest such scale, CyLaKS (Cytoskeleton Lattice-based Kinetic Simulator) [4] provides detailed simulations of motor and crosslinker kinetics [5]. At a slightly larger scale, MEDYAN (MEchanochemical DYnamics of Active Networks) [6] simulates detailed reaction dynamics related to actin, and is especially useful for examining how chemical changes affect mechanical properties [7]. Cytosim [8] implements growing and shrinking flexible filaments, a wide range of motor and cross-linker models, and is relevant to both actin and microtubule problems over a wide range of length scales [9].

For large/dense systems, steric interactions and intracellular flows can dominate the dynamics. The packages above neglect hydrodynamic interactions and prevent overlaps using repulsive Lennard-Jones [10] or WCA [11] potentials, thus requiring small timesteps at high densities. The specialized software package *aLENS* (a Living ENsemble Simulator) [12,13], models cytoskeletal filaments as rigid spherocylinders moving under steric, Brownian, and cross-linking forces (active or passive), and drag or hydrodynamic forces. To resolve

collisions *aLENS* utilizes a *complementarity constraint* incorporated into the dynamics formulation [14,15]. An iteration at each timestep ensures no overlap between colliding particles while simultaneously calculating the equal and opposite forces (Newton's Third Law) that prevent such overlaps. This method avoids repulsive potentials, improving efficiency by permitting larger timesteps. *aLENS* is highly optimized for performance on multi-node parallel architectures. Figure 1(a) gives an example *aLENS* simulation [13] where Kinesin-like multimeric motor proteins bundle microtubules [16]. When binding together microtubules of opposite polarity, the motors drive internal polarity sorting and, eventually, bundle fracture. This approach can be applied to other canonical problems in biological active matter. Figure 1(b) shows the simulation of, at a late time, $15M$ microswimmers interacting via hydrodynamics and collisions [15]. The collective flow generated by the swimmers transports and reorients them, leading to the kinds of dynamic system-scale flow structures observed in experiments [17,18] and predicted by early theories [19–21]. Current research

Figure 1



Simulations of discrete biological components. Using *aLENS*, **(a)** shows the evolution of an ensemble of microtubules, which have been contracted and sorted by model multimeric kinesin motors [13]. The entire ensemble, with MTs colored in pink, is shown at the top. A zoom of the gray-shaded region is shown in the main panel, with MTs colored by orientation, and yet further zoomed-in views at the bottom show forces due to motors and collisions; **(b)** shows an *aSENS* simulation of 15 million model microswimmers, colored by their velocity (blue slow, red fast). Panel **(c)** shows a colloidal model of finite-sized molecules (purple: ribosomes, green: ternary complexes, blue: proteins) interacting [26]. Panel **(d)** shows streamlines of the resolved flow past very nearly touching slender filaments. Using *SkellySim*, **(e)** shows cytoplasmic streamlines (purple) as a spindle complex is pulled upon by cortically-bound dynein motors [39]; **(f)** shows conformations of motor-loaded microtubules in an idealized oocyte, after formation of an intracellular twister [2].

seeks to understand the fully nonlinear and statistical nature of these complex systems. To enable such large simulations, *aLENS* was built from the ground up with scalability in mind. Other performant and scalable software packages, designed for different purposes, are worth highlighting. HOOMD [22,23] supports simulations of hard particles on thousands of graphical processing units (GPUs), and is widely used for molecular dynamics and materials science, but has yet to find broad purchase in cellular biophysics. The very recently released code PolyHoop [24] implements a vertex-type [25] model with flexible boundaries for simulating soft particles and cellular tissues in two dimensions and scales to millions of deformable particles.

Many-particle colloidal simulations can provide a platform for detailed analyses that reveal non-trivial couplings between chemistry, transport, and diffusion in the crowded intracellular environment. An example of such a model is the work by Maheshwari et al. [26]. They examined an apparent paradox: faster-growing cells must synthesize proteins faster, yet they are more crowded, and so diffusion is slower, which should reduce ribosomal efficiency. Their model integrated chemical kinetics with colloidal simulations of ribosomes, ternary complexes, and a physiological number of proteins (see Figure 1(c)), to reveal how proximity and reaction dynamics combine to increase ribosomal efficiency with crowding, overcoming the reduced diffusivity.

Other software is required when the flows generated by long and deformed filaments are important. Approaches built on *slender-body theory* [27,28] and boundary integral methods [29] simplify the dynamics of thin filaments and obviate the need to discretize volumetrically, but nevertheless result in partial differential equations (PDEs) that are nonlinear and high-order (thus, numerically stiff), and nonlocal due to their long-ranged hydrodynamic interactions. Various implementations thereof have been used to examine a variety of intracellular problems, including actin network rheology and bundling [30], and ciliary coordination in reef coral larvae [31]. Our group has also built an open-source software package for this regime: *SkellySim* [32], which simulates cytoskeletal filaments that move the cytoplasm surrounding them as they grow, catastrophe, bend and buckle under load, and push or pull on bodies to which they are attached. Like *aLENS*, *SkellySim* is built for scalability, combining fast algorithms that exploit the special structure of low Reynolds number flows [33–35] and implicit time-stepping schemes to simulate thousands of interacting filaments, at or near the scales important for many cellular problems. When filaments are very nearly touching, fluid flows can be surprisingly stormy [36], and methods built on slender-body theory are less accurate in these cases. Recent advances [37,38] can resolve these complex flows in limited circumstances, see Figure 1(d), but are not yet integrated into efficient codes for cytoskeletal dynamics.

Figure 1(e) shows an application of *SkellySim* to study spindle positioning in the *C. elegans* single-cell embryo [39]. This preamble to cell division has long been studied, testing differing conceptions of what intracellular forces control positioning [40]. This simulation shows the flows produced by the pulling of cortically-bound force generators and is the latest in a lineage of related simulations [41,42] investigating different models of how molecular motors or microtubule polymerization might position the spindle. This numerical study is coupled to detailed biophysical experiments that measure cytoplasmic flows and use laser cutting of microtubules to discern the nature of forces underlying the spindle's motion. All results were consistent with microtubules being pulled by cortically-bound force generators, presumably dynein, and experimentally derived flow fields are remarkably similar to *SkellySim* simulations.

A fundamentally different application of *SkellySim* investigated the origin of large-scale cytoplasmic flows observed in the *Drosophila* oocyte [2]. Figure 1(f) shows (in cut-away view) the collective deformation of ∼3000 model microtubules anchored to the periphery of a geometrically idealized mid-stage oocyte [2], with each subjected to a length-distributed 'follower-force' modeling kinsein-1 motors carrying cargo up along the microtubule. This motion produces both an upwards cytoplasmic flow and a downwards compressive force upon the microtubules. Their consequent bending or buckling [43] generates large-scale hydrodynamic flows that entrain the microtubules together, and collective alignment of moving cargos then drives a global rotational flow (a "twister"). A prior study [44] identified bending and alignment for 100 microtubules in a half-space, but simulation of the full closed-geometry oocyte requires considerable scale-up.

Coarse-grained models

Coarse-grained models reduce many-component systems to continuum PDEs — approximations which are easy to simulate and amenable to mathematical analyses, yielding information — such as parametric conditions for instability — not directly accessible from discrete simulations. Such models have been used extensively to understand 'active matter', including the behavior of purified cellular components and extracts [53]. They are also used to understand cellular biophysics across a wide range of scales [54], including describing the dynamics of the spindle and other cytoskeletal assemblies [55–61], the dynamics of passive and active microtubule beds [62,1,63], actively fluctuating suspensions [64,65], phase coordination in active assemblies [66–68], and tissue-scale organization and morphogenesis [69–72].

Discrete simulations of active particles (i.e. Figure 1(a-c)) are well complemented by continuum models, together revealing their basic behaviors and fundamental instabilities [19–21,57,58]. One class is "micro-macro" models using a Fokker–Planck equation to evolve the distribution of particle positions $\mathbf{x}$ and orientations $\mathbf{p}$. A mean-field fluid flow transports and rotates the particles, and is itself determined by the Stokes equation forced by the macroscopic stresses created by microscopic particle activity. These theories are expensive to simulate since $\mathbf{x}$ (3D) and $\mathbf{p}$ (2D) are independent variables, giving 5 + 1 dimensional PDEs. Averaging out the orientational degrees of freedom leads to lower-dimensional 'moment-closure' models evolving, for example, the particle concentration c, the polarity vector $\langle \mathbf{p} \rangle$, and the concentration-weighted nematic tensor $D = \langle \mathbf{pp} \rangle$. Their evolution equations depend upon yet higher-order moments, like $\langle \mathbf{pppp} \rangle$, which must be approximated in terms of lower-order moments ('closed'). Common phenomenological closure schemes fail to preserve mathematical structure found in the original kinetic theory, particularly an H-theorem relating configurational entropy production to active stresses and dissipation. It was recently shown that 'generalized Bingham closures' exactly preserve these entropy identities [73]. First used for passive suspensions [74,75] (and later for active apolar suspensions [56]), we extended such closures to polar active suspensions (e.g. swimmers) [46], and developed very fast and accurate methods, appropriate for large-scale simulation, for determining them [45,46]. Figure 2(a) shows a simulation of an apolar active suspension on a 512^3 grid over long times. Such high resolutions are infeasible with a kinetic theory, and enable the study of coherent flow structures and their statistical structure [45,46]. Figure 2(b) shows the active power generated by an active suspension, comparing different closures. The generalized Bingham closure accurately reproduces much of the dynamics found in the kinetic theory, while the isotropic and quadratic closures fail to do so, in some cases dramatically.

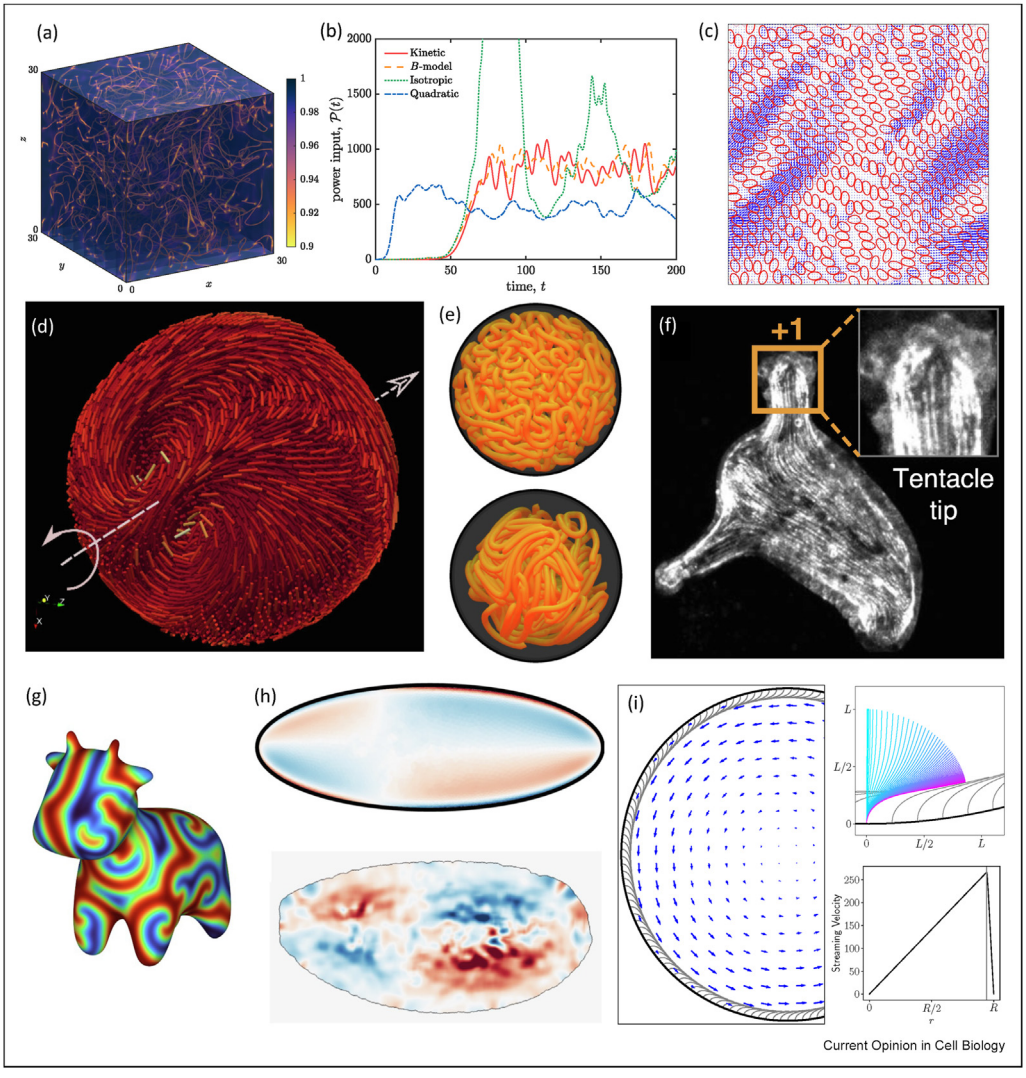
Such efficient models can be embedded into richer settings. Figure 2(c-e) shows examples. Motivated by thinking about the internal states of interacting cells, panel (c) shows a simulation of 1,000 immersed droplets, each filled with an active suspension [47]. The organization of activity within the drop drives both interior and exterior fluid flows through which the drops communicate. In these aggregates, the internal state of each droplet is not fixed but emerges from its interactions with others, which altogether determines the dynamics of the aggregate. Thinking of the aggregate as composed of machines – droplets – each composed of yet smaller machines – the active constituents of the suspension – reminds us of Leibniz's sentiment defining "an organism or a natural machine, as a machine each of whose parts is a machine…." It is challenging to scale such simulations to thousands of droplets. To do so, we combine our fast closure methods [45] with a highly accurate overset grid method [76] in each drop. Droplet–droplet interactions are computed using a boundary integral method that handles very nearly touching drops [77]. With high accuracy within drops and not having to discretize between drops, we can use far fewer total degrees of freedom compared to commonly used methods like phase-field methods (which have been used to study single/several active drops [78,79]) or the Immersed Boundary method [80], which converges especially slowly for these kinds of PDEs [81,82] (but has been used to simulate the deformations of model red blood cells in passive liquid crystals [83]). Such many-drop simulations are not yet practical in 3D but examining the behavior of single drops, or a few, is becoming so. Figure 2(d) shows a Lattice-Boltzmann simulation of a chiral liquid crystal inside a drop [48], which self-propels, driven by the rotational motion of surface topological defects. Figure 2(e) shows the initial and final configurations of a flexible, passive polymer immersed in an active suspension [49] (using the Bingham closure). Fluid activity organizes the polymer, and vice versa, yielding space-time correlated motions, as has been observed for chromatin [84] and in modeling chromatin as an active polymer in a passive fluid [85].

Solving PDEs on complex and evolving surfaces is a rapidly developing area within computational biophysics. As motivation, Figure 2(f) shows an image of the well-aligned actin fibers in a hydra, with a +1 defect highlighted at the tip of one of its tentacles [50,86]. The hydra has a complex morphology, and the properties of active matter on surfaces depend on both surface curvature and topology [87–89] – spherical cow approximations are insufficient. Methods for solving PDEs on general surfaces (e.g. Refs. [51,90]) should enable the high-fidelity solution of active matter problems on non-spherical cows (see Figure 2(g)) and specialized solvers for prototype surfaces permit rapid parameter sweeps and optimization [91,92]. Luckily, some biological geometries are nice, like the early *Drosophila* embryo, shown in Figure 2(h). In the work of Hernández-López et al. [52], a contractile actomyosin gel (with oscillatory contractility controlled by the cell cycle) is coupled to the cytosol. This two-phase model explains the spreading out of duplicating nuclei within the embryo during its early development.

Continuum models have seen little use in biological problems with long biopolymers (e.g. Figure 1(e/f)). In Ref. [62], we developed the Brinkman-Elasticae (BE) model, an anisotropic porous-media model that treats well-aligned collections of filaments as a continuum, encoding filament density as a parameter; see also [93–95] for related work. In Ref. [1], we developed an active version, ala Figure 1(f), to study

the generation of streaming flows in the oocyte. Using this active BE model in a cylindrical oocyte (Figure 2(i)) — the problem's natural 'spherical cow' — reduces the dynamics to a one-dimensional PDE, the analysis of which identifies the source of the swirling instability: a density-dependent self-reinforcing feedback wherein deformed microtubules drive azimuthal flows that further deform the microtubules around them [1]. This model can also be solved quickly. In Ref. [1], we computed a phase diagram over 1,000,000 sets of parameters in less than 12 CPU hours, which is in remarkable agreement with that found using *SkellySim* [2], which took over 3,000,000 CPU hours for 54 sets of parameters. Such fast scans of phase space can put bounds on experimentally hard-to-measure parameters, e.g. the density of cortex-bound microtubules and the number of operational kinesins [1].

Figure 2



Simulations of active systems using continuum models. **(a)** visualizes the nematic order parameter, from a simulation of an apolar active suspension using the generalized Bingham closure ('B-model') [45]. **(b)** shows that the B-model reproduces the average dynamics of the kinetic theory better than common ad-hoc closure models [46]. Panels **(c–e)** show simulations which utilize a continuum active fluid theory as a component: **(c)** shows the large-scale instability and flow generated by 1,000 'active drops' [47]; **(d)** shows a 3D Lattice-Boltzmann simulation of an 'active cholesteric drop' [48]; **(e)** shows the dynamics of a passive polymer immersed in an apolar active suspension [49]. Panel **(f)** shows well-aligned actin fibers on a hydra, with a +1 defect at the tentacle tip [50]. Panel **(g)** shows the solution of a Ginzburg–Landau equation on a non-spherical cow [51]. Panel **(h)** shows the vorticity, both measured (lower) and modeled (upper), in a developing *Drosophila* embryo [52]. Panel **(i)** shows the dynamics (time moving from cyan to magenta) of the microtubule bed, and the resulting steady-state flow, in the *Drosophila* oocyte, as modeled by the Brinkman-Elasticae model with a driving 'follower-force' representing the action of cargo-carrying kinesins [1].

Future perspective

The tools discussed here greatly expand the range and scale of computationally addressable biological problems; We anticipate continued improvements in algorithms, implementation, and computer speed. As for our own plans, we are moving towards large-scale simulations of the spindle and the nucleus; We are making *aLENS* more general, supporting a greater variety of motor and cross-linker models, fiber turnover and flexibility, and hydrodynamic interactions. This may eventually yield a merger of *aLENS* and *SkellySim*, allowing for full hydrodynamic simulations of dynamic, flexible filaments with robust treatment of contacts and near-contacts. This requires new mathematics to formulate algorithms (building on a body of recent developments [96,97,38]) and significant software engineering to make them efficient. Such a code would be especially useful for tackling phenomenon arising in actomyosin gels, such as the deformations recently observed *in vitro* [98]. For our PDE models, we are developing spatially adaptive solvers for evolving and/or complex domains, allowing us to model cells of complex morphology (i.e. neurons).

Perhaps as important, many of the tools described here are open-source software packages. These tools also need to be easier to install, use, and analyze, objectives we have worked towards while developing *aLENS* and *SkellySim*. The number of questions addressable through such tools is far greater than the number that their developers can possibly ask for themselves.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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