phosphatidylcholine and sphingomyelin species in the cell membrane, leading to a deformation of the erythrocytes. We found a clear discrimination between NAS patients and healthy with 8% false negative and 11% false positive among healthy controls. The ESR might then be a low-cost and efficient test to detect shape-altered erythrocytes.

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BPS2025 - Surface remodeling and inversion of matrix-cell interaction underlies community recognition and dispersal in biofilms

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Biofilms are ubiquitous surface-associated bacterial communities embedded in an extracellular matrix. While it is commonly assumed that biofilm-dwelling cells are glued together by the matrix, this simplistic view fails to explain many observations, including the ability of biofilms to exclude other species and non-matrix-producing clonemates and the swift dispersion to a planktonic state upon starvation. Here, we investigated cell-matrix interactions in *Vibrio cholerae* (*Vc*), the causative agent of cholera. We combined genetics, microscopy, simulation, and biochemical tools to make the surprising, counter-intuitive discovery that native *Vc* cell surfaces are repulsive to *Vibrio* polysaccharide (VPS), the main matrix component in *Vc* biofilm, leading to spontaneous depletion aggregation during growth. Our findings challenge the common belief in the field that exopolysaccharides act as a glue to adhere biofilm-dwelling cells together. Downregulation of VPS and surface trimming by a polysaccharide lyase cause surface remodeling as biofilms age, shifting the nature of cell matrix interactions from attractive to repulsive and facilitating cell dispersal as aggregated groups. Furthermore, we experimentally show that this concept may generalize to certain other biofilm forming species and exopolysaccharides. Indeed, we demonstrated the generality of our new conceptual model in another model biofilm-former, *Pseudomonas aeruginosa*. Our results suggest a new conceptual model in understanding the intricate matrix-cell interaction as the major driver for biofilm development and a potential drug target.

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BPS2025 - Multi-scale modeling to predict cancer cell mechanics and migration based on transcriptional state and microenvironment

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Cancer is a disease characterized by increasing heterogeneity as it progresses. Single-cell RNA sequencing has shed light on the variety of states that cancer cells can adopt, but connecting transcriptional signatures to functional outcomes remains a major challenge. Here, we have taken a multi-scale modeling approach to connect heterogeneous cytoskeletal gene expression programs exhibited by breast cancer cells to biochemical signaling networks and extracellular matrix conditions that regulate the cellular mechanical state. Our model, G-BoHyM-3D, comprises three key components: transcriptomic data, Boolean-hybrid-modular model (BoHyM), and 3D stochastic cell simulations. We identified multiple signaling nodes that connect various extracellular and gene expression signals to key cytoskeletal proteins. The signaling network is solved using a Boolean hybrid modular (BoHyM) approach specifically developed to deal with the distinct timescales and complexities of biochemical signaling processes. This integrated framework accurately predicted differences in cell migration behavior of MDA-MB-231 breast cancer cells based on single-cell transcriptional differences. Further development will offer a versatile and user-modifiable tool for investigating how both extracellular and intracellular signaling mechanisms regulate cellular cytoskeleton components, which in turn influence cell-substrate interactions, force generation, invasion, migration, and emergent phenomena, such as collective rotational and invasive cell migration.

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BPS2025 - Mechanical strain causes heritable mutations

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Understanding the causes of mutations has major implications for designing therapies. It is well known that solid tumors are more genetically diverse than liquid tumors, but while changes to a cell's genetics can be caused by at least one physical stressor, namely radiation, whether mechanical stresses or strains can also alter a cell's genetics is unclear. Heritable loss of chromosomes is prevalent during solid tumor initiation, and here we show rare but heritable losses in cells in tumoroids—particularly when confined by 3D stiff matrix that limits growth and variation in size. Stiffness increases mitotic aberrations including micronuclei and chromosome loss detected using live cell chromosome reporters (ChReporters). Colonies of rare ChReporter-negative cells (0.1%–1%) within cancer tumoroids are consistent with Luria-Delbruck's theory of heritable genetic changes that also predicts higher inter-tumoroid variance versus Poisson statistics. Knockdown of myosin-II, a well-known mechanosensor, perturbs the spindle and increases chromosomal loss and variance without affecting tumoroid growth, suggesting myosin-II plays a role in genome stability and expanding its functions to tumor suppressor. Consistent with our experimental findings, pan-cancer analysis of clinical data shows a correlation between increased chromosomal changes and elevated collagen-I expression, with genetic variance also increasing proportionally to the mean. Hence, stiffening of the extracellular matrix during cancer's initial progression suppresses growth but causes genetic diversification and drives mechano-evolution.

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BPS2025 - Illuminating mechanotransduction in breast cancer metastasis using optogenetic vinculin and SPECTR—a simple and sensitive method to visualize vinculin conformational changes

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Cancer cell invasion from the primary tumor along aligned collagen fibers is a well-documented phenomenon, driven by cell mechanosensation via focal adhesions. At the heart of this process is vinculin, a mechanosensitive adhesion protein that facilitates force transmission between integrins and actin. We propose that stretch-induced activation of vinculin regulates the directional migration of invasive cells along collagen. To test this hypothesis, we have engineered vinculin analogs for live cells that report vinculin's conformation and control its activity with light. To visualize the exposure of hidden binding sites in vinculin, we inserted a short peptide that is revealed only in the open, ''stretched'' conformation. This exposed tag can bind a small fluorescent protein, allowing us to quantify the open conformation through simple colocalization of vinculin and the fluorescent marker. This technique (SPECTR, short peptide exposure for conformation tracking) relies simply on direct excitation and colocalization of bright fluorophores. Additionally, to photo-manipulate vinculin's force transmission capabilities, we inserted the photo-responsive LOV domain into surface loops, where LOV could allosterically impact vinculin's actin binding site. Our studies of cell motility on micropatterned substrates that mimic aligned collagen will be presented.

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BPS2025 - Optimization of therapeutic T cells through biophysical modeling

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Despite recent experimental progress in characterizing cell migration mechanics, our understanding of the mechanisms governing rapid cell movement remains limited. To effectively limit tumor growth, antitumoral T cells need to rapidly migrate to find and kill cancer cells. To investigate the upper limits of cell speed, we developed a new hybrid stochastic-mean field model of bleb-based cell motility. We first examined the potential for adhesion-free bleb-based migration and show that cells migrate inefficiently in the absence of adhesion-based forces, i.e., cell swimming. While no cortical contractility oscillations are needed for cells to swim in viscoelastic media, high-to-low cortical contractility oscillations are necessary for cell swimming in viscous media. This involves a high cortical contractility phase with multiple bleb