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ABSTRACT

303 | ASTRONOMY & ASTROPHYSIS (AS) / BIOPHYSICS (BP)

309 | BIOPHYSICS (BP)

Developing a DNA-Based Single-Molecule Imaging Toolkit for Mechanobiology Across Time and Space

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ABSTRACT

Mechanical forces at cell interfaces regulate adhesion and signaling, yet their key physical variables—force magnitude, spatial distribution, loading history, and force duration—remain difficult to measure in living systems. We are developing a DNA-based single-molecule imaging toolkit that makes these signals quantifiable across time and space, combining spatial force mapping with time-resolved single-bond mechanics.

Our approach integrates modular DNA tension probes with high-sensitivity fluorescence microscopy to convert piconewton forces into digital optical readouts. Dual-threshold DNA hairpins enable force stratification and time-domain reconstruction, reporting both loading rate and force duration from the same molecular linkage. At the ensemble level, multicolor imaging yields spatial force landscapes within adhesion zones. At the single-molecule level, sparse labeling produces discrete step-like trajectories that reveal the loading and holding dynamics of individual receptor–ligand interactions under endogenous cellular forces.

We apply this toolkit to integrin adhesions and immune receptors. Extending the platform to the T cell receptor (TCR), we achieved single-molecule imaging of TCR–pMHC mechanics in living synapses, resolving stereotyped two-step activation traces and extracting per-bond loading rates (~1 pN/s) and high-force dwell times on the order of seconds, providing a quantitative "time code" for antigen recognition. Together, this toolkit enables mechanobiology measurements that are simultaneously quantitative, spatially resolved, and time-resolved, opening a route to systematic mechanical phenotyping across receptors and cellular states.

KEYWORDS

Mechanical forces, single-molecule imaging, loading rate, force duration

Quantitative Biophysics of Mechanically Regulated Transcription Enabled by a Microfluidic-Optical Intelligent Laboratory

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ABSTRACT

Mechanical cues regulate cellular behavior across multiple spatial and temporal scales, yet the quantitative links between external perturbations, nuclear mechanics, chromatin reorganization, and transcriptional dynamics remain insufficiently resolved. In this work, we present a microfluidic-optical intelligent laboratory for the quantitative biophysics of mechanically regulated transcription. The system integrates valve-controlled microfluidic manipulation, programmable biochemical and mechanical microenvironment regulation, live-cell optical imaging, and automated high-content data analysis into a unified experimental framework. Using this platform, dynamic external stimuli can be precisely imposed on living cells while cellular morphology, nuclear deformation, chromatin structural responses, and transcription-related signaling dynamics are monitored in real time.

Our approach is designed to investigate how mechanical inputs are converted into intracellular physical signals and how these signals propagate through nuclear envelope deformation, nuclear pore dynamics, and chromatin reorganization to influence transcriptional regulation. In particular, the platform enables quantitative analysis of force-dependent changes in nuclear transport behavior, oscillatory signaling activity, and downstream transcriptional responses at both the single-cell and population levels. By combining controlled perturbation with continuous optical readout, the system supports reproducible, high-resolution, and scalable studies of mechanotransduction beyond conventional endpoint assays.

This work establishes an integrated methodology for studying mechanically regulated transcription from a quantitative biophysics perspective. The significance of the platform lies not only in improving experimental controllability and throughput, but also in providing a systematic route to connect programmable microenvironmental inputs with measurable physical determinants of gene regulation. It offers a versatile technical foundation for mechanobiology, cell-state transition analysis, and broader investigations of dynamic cellular behavior in complex microenvironments.

KEYWORDS

mechanotransduction, transcription dynamics, microfluidic platform, live-cell imaging, quantitative biophysics

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What Counts as an "Improvement" in Photometric Redshift? – Statistical Insights from Machine Learning and Morpho-*z*

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ABSTRACT

Current and upcoming large-scale sky surveys rely on accurate photometric redshift (photo-*z*) estimation to study the properties of dark energy through cosmological probes. Despite significant efforts to improve point estimates and construct well-characterised photometric redshift probability distribution functions (PDFs), the literature lacks a clear and quantitative definition of what represents "improvement" in photo-z PDF, or how this "improvement" relates to its point estimate performance. This work showcases the various ongoing research approaches by the astrophysics group in Universiti Sains Malaysia (USM) in tackling this issue: we critically analysed the impact on redshift point estimates, probability density functions (PDFs), and distributions by varying the number of photometric bands, enhancing existing machine learning methodologies and including various galaxy morphological parameters, which leads to the production of morphological redshifts (morpho-*z*). Working on large galaxy and quasar samples from surveys like the Sloan Digital Sky Survey (SDSS), we employed a comprehensive list of evaluation metrics which targets specific components of point estimates, PDFs, and distributions to analyse how improvement in one performance aspect influences the others. In general, we found that while the improvement in both point estimates and PDFs agree globally, individually they do not always translate proportionally, and we will highlight how the enhancements in one metric may not lead to similar improvements in the other metric under specific conditions. In this work, we will also discuss the impacts of the galaxy fundamental plane and missing data on photometric redshift performance, summarising our insights on this topic.

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KEYWORDS
Photometric redshift, morphological redshift, machine learning, galaxy morphology, statistical methods

MAPPING THE EARLY PROCESSES OF STAR FORMATION WITH ALMA

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ABSTRACT:
Stars like our Sun are continually forming throughout our home galaxy, the Milky Way. The Atacama Large Millimeter/submillimeter Array (ALMA), located in the Atacama Desert of northern Chile, is currently the most powerful radio interferometric array on Earth. With its unprecedented sensitivity and resolution, ALMA allows us to observe star-forming regions in extraordinary detail. In this talk, I will present our ALMA observations that reveal the earliest stages of star formation with exceptional clarity. In particular, I will discuss our findings on accretion disks and jets around forming stars and explore the physical mechanisms that govern their formation. These accretion disks are expected to evolve into protoplanetary disks, where planets eventually form.

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First Detection of a Linear Structure in the Midplane of the Young HH 211 Protostellar Disk: A Spiral Arm? *The Astrophysical Letter*, 951, L2, 10.3847/2041-8213/acdbca, 2023, C.-F. Lee, K.-S. Jhan, & A. Moraghan.

Magnetocentrifugal Origin for Protostellar Jets Validated through Detection of Radial Flow at the Jet Base. *The Astrophysical Letter*, 927, L27, 10.3847/2041-8213/ac59c0, 2022, C.-F. Lee, Z.-Y. Li, H. Shang, & N. Hirano.

KEYWORDS
Star formation, Star-forming regions, Jets, Accretion Disks.

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The E-Cadherin–β-Catenin Linkage as a Mechanochemical Rheostat at Adherens Junctions

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ABSTRACT

Adherens junctions (AJs) are essential cell-cell adhesion complexes whose function is dynamically regulated by mechanical forces. However, how forces directly control the central E-cadherin–β-catenin linkage has remained unknown. Here, using single-molecule force spectroscopy and a genetically encoded tension sensor, we reveal that this linkage operates as a mechano-chemical rheostat. The wild-type complex ruptures primarily at ~5 pN under force. Phosphorylation of specific serine residues on the E-cadherin tail enhances mechanical stability, raising rupture forces to ~15 pN, whereas phosphorylation of a critical tyrosine on β-catenin antagonizes this stabilization, reducing rupture forces below 5 pN. These force-dependent behaviors arise from multi-step partial detachment and cooperative unfolding of β-catenin's ARM domains. Crucially, we demonstrate that physiological forces of ~5 pN act on this complex in living cells, directly validating the in vitro measurements. Our findings establish how force and phosphorylation converge to regulate cadherin–β-catenin interactions, with direct implications for tissue mechanics and homeostasis.

KEYWORDS

Adherens junctions, E-Cadherin–β-Catenin complex, Mechanical forces, phosphorylation, Magnetic Tweezers

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Single-Molecule Mechanical Insights into Telomere Structures, Dynamics, and Protein Interactions

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ABSTRACT

Our group uses single-molecule magnetic tweezers to investigate the mechanical principles governing nucleic acid function and protein–nucleic acid interactions at telomeres, with a focus on systems of biological and therapeutic relevance. To explore telomere biology, we developed a "rescue-rope" strategy that enables mechanical manipulation of DNA structures with free ends, such as the telomeric 3′ overhang. Using this approach, we identified and characterized a mechanically stable yet rarely formed antiparallel triplex structure at the human telomere. We further examined the dynamics of the shelterin proteins TRF1 and TRF2, revealing that single human telomeres are compacted into heterogeneous loops and that TRF1 modulates telomeric DNA fork movement by transiently pausing strand separation with a binding energy of 11 k_BT. To advance telomere length (TL) as a clinical biomarker, we developed a single-molecule terminal restriction fragment (smTRF) assay that provides absolute TL distributions with base-pair precision. This method was validated across cancer cell lines and a cohort of 48 individuals, yielding detailed TL profiles that distinguish alternative lengthening of telomeres (ALT) from telomerase-positive cells and correlate with age. In parallel, we dissected the catalytic mechanism of a mini hammerhead ribozyme targeting RNA, uncovering a conformational ensemble comprising five distinct mechanical conformers. Our data demonstrate that magnesium ions selectively stabilize the catalytically active conformer, supporting a concerted mechanism of conformational selection. Collectively, our work establishes single-molecule mechanics as a powerful platform for uncovering fundamental mechanisms in RNA catalysis and genome maintenance, with direct implications for therapeutic development and clinical diagnostics.

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KEYWORDS
Single-molecule magnetic tweezers, telomere dynamics, protein-DNA interactions, mechanical conformers, RNA catalysis

Physics of cellular chirality

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ABSTRACT

Chirality is a fundamental and highly conserved feature in biology, playing a critical role in development from the cellular level to tissues and organisms. This work presents a two-tiered mechanics modeling approach to understand how chiral symmetry is broken and propagated across scales. First, we investigate the origins of single-cell chirality by constructing a torsional clutch-filament model for a single radial fiber. The model reveals that chiral symmetry breaking arises from the competition between active, counter-clockwise rotation driven by growing actin filaments and the passive release of accumulated elastic energy, which favors clockwise rotation. The balance between these opposing mechanisms determines the net cellular swirling direction, a prediction that aligns with recent experimental observations. Then, we develop a generalized mechanics model of chiral polarized particles to explore how individual cellular chirality translates into collective chiral patterns in cell populations. Simulations on ring-shaped and rectangular substrates show that cells with identical chirality can self-organize into distinct supracellular patterns. Notably, we find that both excessively strong and weak individual chirality hinder pattern formation. Furthermore, the influence distance of substrate boundaries depends on cell–cell interaction strength: weaker interactions reduce this influence, while overly strong interactions lead to cell stacking and prevent chiral ordering. Our study highlights the coordinated roles of boundary conditions, single-cell chirality, and cell–cell interactions in governing chiral dynamics in cell populations, providing mechanistic insights into the link between cellular and tissue/organism-level chirality.

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KEYWORDS

Chirality; Mechanics model

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Single-molecule mechanical insights into nucleosome regulation by histone variants

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ABSTRACT

Chromatin serves as a crucial platform for gene regulation, wherein histone variants play a pivotal role. As the largest histone H2A variant, macroH2A possesses unique linker and macro domains, exerting significant regulatory effects on multiple biological processes, including X chromosome inactivation, embryonic development, cellular metabolism, and tumorigenesis. By utilizing an in vitro nucleosome assembly system combined with high-resolution magnetic tweezers, we discovered that macroH2A facilitates the binding of FACT and drastically reduces nucleosome stability, thereby mediating the eviction of macroH2A from the nucleosome. Furthermore, we identified Serine 139 (Ser139) of macroH2A as a critical residue that regulates the interaction between FACT and macroH2A.Additionally, focusing on the histone variant H3.3, we provided, for the first time, novel mechanistic insights into how H3.3 and its Ser31 phosphorylation regulate nucleosome dynamics and transcriptional responses. We also established that this mechanism plays an important role in macrophage immune response pathways.

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KEYWORDS

Nucleosome, histone variants, magnetic tweezers

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Understanding Endocytosis and Intracellular Transport with Multidimensional Single Particle Tracking

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ABSTRACT

Understanding the characteristic motions of functionalized nanoparticles is crucial to understand their interactions with cells. A multi-dimensional single particle tracking technique has been developed to fully disclose the 3D translational and rotational motions of anisotropic imaging probes, as well as relevant biomolecular information, in live cells. Using plasmonic gold nanorods as probe in our recent studies, we have visualized the live endocytic and intracellular transport events of nanoparticle cargos with unprecedented details in live cells. These experiments have led to new insights on the working mechanisms of molecular motors (dynamin in clathrin mediated endocytosis and kinesin/dynein in microtubule-based intracellular transport).

REFERENCE STYLE

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KEYWORDS

Single Particle Tracking; Molecular Motor; Rotational Dynamics

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NEW OPPORTUNITY FOR MOLECULAR SIMULATIONS, WHERE AI MEETS PHYSICS

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ABSTRACT

In this talk, we will discuss on recent progress made on the development of AI assisted molecular dynamics simulation package, SPONGE, and its application to various molecular systems including studies on chemical reactions and protein related modeling tasks. In protein and protein complex structure prediction, we introduce GRASP, which efficiently and flexibly incorporates the different forms of information obtained through relatively high throughput experiment, such as XL, CL, CSP, and DMS. GRASP significantly improves AI model's capability of structure prediction. We also developed a *probabilistic tokenization model* for metastable protein structures, ProTokens. By unifying 1-dimensional and 3-dimensional representations of protein structures, ProTokens also enable sequence and all-atom protein structure design via various generative models. We demonstrate that generative pretraining over ProToken vocabulary allows scalable foundation models to perceive, process and explore the microscopic and dynamical structures as well as functions of biomolecules through this sequence-structure-function-literature multi-mode model. We finally show how these various simulation methods and packages can be conveniently executed through the help of an AI agent.

KEYWORDS:

Molecular simulation, structure prediction, AI agent.

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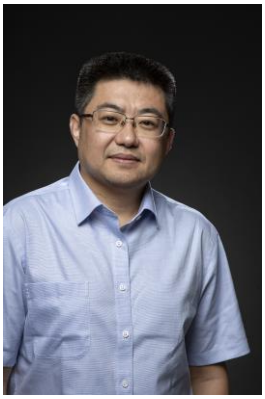

Yi Qin Gao

Yi Qin Gao received his bachelor's degree from Chemistry Department of Sichuan University in 1993, a master's degree from Institute of Chemistry, Chinese Academy of Sciences in 1996, and a PhD degree from California Institute of Technology in 2001. Between 2001 and 2004, he was a postdoc at Caltech and then Harvard. In 2004, he became an assistant professor in Chemistry Department, Texas A&M University. Since 2010, he has been a Professor in College of Chemistry & Molecular Engineering, Peking University. He joined BIOPIC as a PI in 2013. He is a New Cornerstone Fellow, the associate dean of School of Science of Peking University, and an associate editor of the ACS journal JCTC.

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Traversing the biophysics of amino acid sequence space

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ABSTRACT
During their function, proteins often exhibit dynamics ranging from picoseconds to many seconds. During their evolution, the dynamics of amino acid sequences of proteins ranges from days to millions of years. Bridging the gap between these two processes is a core challenge in the life sciences. Proteins display remarkable performance in catalysis and energy transduction. However, many energy, chemical manufacturing, and biotechnology applications remain practically unfeasible. A general underlying challenge is to gain enhanced predictive power over amino acid sequences that result in proteins with the properties needed for a variety of applications. However, sequence space seems hopelessly large, while the fitness landscape of sequence space is largely unprobed. Approaches to overcome these challenges will be presented in which proteins with computationally derived sequences are experimentally studied using spectroscopic methods, including Fourier transform infrared spectroscopy. The resulting data provide unexpected insights into limitations of current structure prediction approaches and general patterns of molecular evolution.

KEYWORDS
Protein engineering; sequence space, molecular evolution; structure prediction, infrared spectroscopy.

Neo-Gibbsian Statistical Energetics with Applications to Nonequilibrium Cells

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ABSTRACT

Generalization through novel interpretations of the inner logic of the century-old Gibbs' statistical thermodynamics is presented. A universal energetics hidden within Gibbs' thermodynamics is discovered; the neo-Gibbsian energetics is applicable to equilibrium and nonequilibrium. By shifting the current paradigm, it 1) introduces equilibrium as a statistical concept via Legendre-Fenchel duality symmetry between empirical measurements of extensive variables and their conjugates as entropic forces [1]; 2) identifies thermodynamic limit concisely as $k_B \to 0$ rather than N, $V \to \infty$; and 3) formalizes a mesoscopic energetics ($k_B \neq 0$) that predates the characterization of systems with fluctuations by information entropy. Duality symmetry breaking [2] captures nonequilibrium with an irreversible thermodynamic potential representing dissipation. Isothermal, isobaric, grand ensemble, a century-old conundrum, is shown to exist; an open chemical system under different chemical potentials provides the energetic foundation for living cells.

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KEYWORDS

Entropy, thermodynamics, nonequilibrium, Gibbs' theory, Legendre-Fenchel transform

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HOW TO EMPOWER AI APPLICATIONS TO PROTEIN SCIENCES USING INFRARED STRUCTURAL BIOLOGY?

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ABSTRACT [*major heading style: Bold 12 pt, UPPERCASE*]
The AI Applications of AlphaFold to Protein Sciences have experienced explosive growth since 2021. As of the latest updates in early 2026, the AlphaFold Protein Structure Database (AFDB), hosts over 260 million predicted protein structures. Which of these AlphaFold generated proteins structures are reliable to empower further explorations of protein functions, and which ones have serious errors? In this talk, I will address two questions: (1) how to use infrared structural biology to enhance protein structures from X-ray crystallography by providing protonation states of functionally important ionizable residues? (2) How to use infrared structural biology to enhance AlphaFold protein structures by providing experimental screening and testing to assess the accuracies of AlphaFold predicted protein structures? The XieLab has been developing infrared structural biology through advancing experimental techniques, developing Vibrational Structural Markers (VSM) for translating signature infrared signals to specific protein structures, and broadening the awareness and applications of infrared structural biology in proteins. In addition, Dr. Xie founded an Advanced Infrared Biology Research Facility at Oklahoma State University through NSF, NIH, and OSU funding, providing a range of advanced FTIR technologies to external users.

KEYWORDS
Protein sciences, AlphaFold, infrared structural biology, advanced FTIR Technologies, Vibrational Structural Markers.

Mechanical Dynamics of a Slipknotted Protein: Force-Induced Hierarchical Kinetic Locking States and Misfolded Traps

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ABSTRACT
Protein slipknot topology achieves a subtle balance among local stability, global structural dynamics, and folding accessibility. Although early theoretical simulations predicted that slipknotted proteins would exhibit anomalous catch-bonds behavior under mechanical force due to topological tightening, the force-dependent kinetics arising from this topology have remained experimentally unexplored. In this work, using single-molecule magnetic tweezers, we provide the first experimental evidence of multiple hierarchical kinetically locked states in a 3_1 slipknotted protein AFV3-109. Our data show that under a constant force of 10 pN, the most stable locked state reduces the unfolding rate by five orders of magnitude, providing strong evidence that topological constraints can generate a remarkably high energy barrier. Through modifying the sequence of the protein, we modulated the locking probability. Additionally, we found that AFV3-109 can be trapped in a misfolded state with less stability. These findings provide a new perspective for understanding the mechanical stability of slipknotted proteins in biological processes such as folding, degradation, and translocation.

KEYWORDS
Slipknotted Protein, Magnetic Tweezers, Kinetic Locking, MisfoldedTraps

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Single-particle tracking, kinetic simulation, and rational engineering of high performance artificial molecular motors

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ABSTRACT

Engineering artificial molecular motors which show high performance comparable to motor proteins is an important challenge for their applications. DNA is not only a fundamental molecule of living organisms but also a versatile building block used to engineer a variety of artificial molecular motors. DNA-gold nanoparticle (DNA-AuNP) motor is one of the fastest nanoscale artificial motors ever reported. DNA-AuNP motor operates as a burnt-bridge Brownian rachet (BBR) driven by RNA hydrolysis catalyzed by RNase H, and shows super-diffusion on RNA-modified 2D surface. However, its speed was 2~3 nm/s, still much lower than those of motor proteins. We recently resolved elementary processes of motion (pauses and steps) of the DNA-AuNP motor using high-speed/high-precision single-particle tracking. Furthermore, we developed a geometry-based kinetic simulation and revealed elementary chemical reaction processes that cause pauses, steps, and bottlenecks in motion. Then, we rationally engineered DNA-AuNP motor which shows high speed (30 nm/s) and long run-length (3 μm) simultaneously, performance comparable to a motor protein processive chitinase. Here we discuss the results above and our efforts to achieve perfect unidirectionality in motion with a DNA-gold nanorod motor and an RNA-modified 1D DNA nanotube rail, and to estimate force and efficiency of these artificial molecular motors.

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KEYWORDS

Molecular motors, Brownian ratchet, Optical microscopy, DNA nanotechnology

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Cellular sensing of Ligand Distribution in the Microenvironment

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ABSTRACT

The distribution of ligands within the cellular microenvironment plays a crucial role in regulating various cellular functions, including adhesion, migration, and differentiation. However, the mechanisms by which cells sense ligand distribution at the interface at micro- and nanoscale, as well as at the molecular level, remain largely unexplored. Using material approaches, we developed a series of material models simulating ligand distribution in extracellular matrix, ranging from the micrometer to the molecular scale, to isolate and examine specific ligand distribution information. From the perspectives of cellular force transmission and signal transduction, we investigate the mechanisms underlying cell behavior. We discovered that cells sense mechanical signals at the interface through a molecular chain composed of focal adhesions, actin cytoskeleton, and nuclear lamina, which regulates chromatin remodeling and the activity of YAP/TAZ transcriptional regulators, thus participating in gene transcription processes. Ligand distribution at the interface influences integrin spacing and mobility, modulating the assembly of molecular chains and the generation of intracellular traction forces. This allows cells to adapt to diverse interface structures through various adhesion mechanisms, such as pseudopodia or stress fibers. Moreover, stress fibers not only match changes in interface morphology but also leverage traction forces to remodel the interface, optimizing the cell-environment interface interaction. In summary, ligand distribution and cellular adaptation regulate intracellular traction forces through force balance, thereby influencing cellular behaviors and functions.

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Photo-tunable hydrogels reveal cellular sensing of rapid rigidity changes through the accumulation of mechanical signaling molecules, *Cell Stem Cell*, 32, 1, 121–136, 2025, J.P. Yang, P. Wang, Y. Zhang, M. Zhang, Q. Sun, H.Y. Chen, L. Dong, Z.Q. Chu, B. Xue, W.D. Hoff, C.S. Zhao, W. Wang, Q. Wei, Y. Cao.

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KEYWORDS
Cell mechanosensing, ligand distribution, mechanotransduction

MECHANICAL REGULATION OF BLOOD CLOTTING IN VASCULAR SYSTEMS

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Bloodworks Research Institute, Seatle, Washington, USA.

ABSTRACT

Our vascular system is constantly subjected to forces generated by blood flow. To prevent hemorrhage, blood vessels must sense injury and initiate clotting with precise spatial and temporal control while maintaining perfusion. Understanding how these processes are regulated is critical not only for treating bleeding and thrombotic disorders, but also for engineering functional vascularized tissues.

von Willebrand factor (VWF) serves as a key mechanosensor that responds to hydrodynamic forces to regulate platelet adhesion and aggregation during clot formation. Using single-molecule fluorescence imaging, microfluidic flow assays, and engineered vascular systems, we define how local force profiles activate VWF at sites of vascular injury and promote rapid deactivation downstream. We further examine how force-activated VWF engages platelet receptors and coagulation components to coordinate hemostasis and thrombosis under flow. Together, these studies reveal mechanisms by which mechanical forces regulate blood clotting in the vasculature. These insights have implications for understanding thrombotic disease, treating bleeding disorders, and developing therapies for tissue repair and vascularization.

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KEYWORDS
Mechanical regulation, blood clotting, single-molecule imaging, von Willebrand factor, flow.

Long-range transport of biomolecular condensates by Marangoni effect

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ABSTRACT

The spatiotemporal organization of biomolecular condensates is essential for establishing cell polarity. While classical models elegantly attribute condensate segregation to bulk cytoplasmic streaming and localized dissolution-recondensation cycles, the precise physical forces specifically propelling their long-range directed transport remain elusive. Here, we reveal that Marangoni effect acts as a fundamental engine for condensate motility. Using microfluidic reconstitution and quantitative biophysics, we demonstrate that biochemical gradients—such as interface modulating protein MEG-3—generate local interfacial tension gradients across condensate surfaces, directly converting chemical potential into mechanical propulsion. By bridging in vitro measurements with in vivo tracking of Caenorhabditis elegans P-granules through a parameter-free theoretical framework, we quantitatively predict and map intracellular transport landscape engaging Marangoni effect. Ultimately, we establish the Marangoni effect as a general principle of intracellular transport emerges from phase separation. Complementing diffusion and motor proteins, it provides a powerful physical paradigm for understanding cellular spatial organization.

KEYWORDS

Biomolecular condensates; Marangoni effect

THE INTERACTION OF ACCRETING SUPERMASSIVE BLACK HOLES WITH THEIR ENVIRONMENT AT Z~0

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ABSTRACT

Supermassive black holes (SMBH) that are found in the centres of most galaxies comply with scaling relationships that imply hand-in-hand growth of the SMBH with its galaxy bulge, which in turn implies that the SMBH play a significant role in regulating galaxy assembly. Black holes grow via coalescence as a consequence of their host galaxies merging or due to accretion. Our current broad understanding is that the SMBHs influence star formation via the consequences of accretion, which enables them to impact their environments out to spatial scales that are well beyond their gravitational sphere of influence. However, the exact mechanisms and the circumstances under which positive and negative feedback dominate are not understood. I will describe a multi-frequency investigation of the imprints if any at very nearby redshifts of this feedback between the accretion around the SMBH and star formation in the host galaxy that would result in the SMBH and galaxy growing hand in hand (S7). Galaxies with accreting SMBH at very nearby redshifts not only have imaging with good spatial resolution that enable the search for connections between the host galaxy properties and radio jet properties, but Integral Field Unit spectroscopy of these objects enables unraveling the outflows due to the accreting SMBH and their circumnuclear star formation. I will present a few follow-up results from this study on the properties of the sample, accretion triggered by a merger, and a a possible connection between inner star formation and accretion.

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Probing the Physics of Narrow-line Regions in Active Galaxies. IV. Full Data Release of the Siding Spring Southern Seyfert Spectroscopic Snapshot Survey (S7),

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Astrophysical Journal Suppl, 232, 11, 2017. A. Thomas, M. Dopita, P. Shastri, R. Davies, et al.

Probing the Physics of Narrow-line Regions in Active Galaxies. IV. Full Data Release of the Siding Spring Southern Seyfert Spectroscopic Snapshot Survey (S7), *Astrophysical Journal Suppl,* 232, 11, 2017. A. Thomas, M. Dopita, P. Shastri, R. Davies, et al.

KEYWORDS
supermassive black holes, black hole accretion, AGN feedback, galaxy assembly, SMBH scaling relationships

Topological Control of Biomolecular Condensates: DNA Supercoiling‑Driven Compaction and Activity-Induced Gelation

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ABSTRACT

Biomolecular condensates and polymer-rich cellular assemblies are dynamically tuned between liquid-like, compact, and gel-like states, but the generic physical mechanisms regulating these transitions remain unclear. Here, coarse-grained simulations identify topology as a unifying control principle across two representative systems. In DNA–protein condensates formed by bridging-induced phase separation, incorporating DNA torsional elasticity shows that supercoiling drives twist-to-writhe conversion and produces a compact "DNA corset" architecture consisting of a dense bridged core wrapped by surface plectonemes. Increasing superhelical density progressively reduces condensate size, whereas torsional relaxation restores expansion; this response is reversible for short DNA but becomes hysteretic for longer chains, revealing topological memory. In a complementary nonequilibrium model of rigid rings mixed with active–passive semiflexible polymers, self-propulsion increases effective chain stiffness and transport, enhances polymer–ring threading, and drives an otherwise non-percolating mixture across a threading-percolation threshold into a system-spanning topological gel. The critical activity decreases with intrinsic chain stiffness, threading lifetimes peak near the transition, and ring diffusion arrests as topological connectivity saturates. Together, these results show that bond-free topological constraints—encoded by supercoiling or threading—can regulate condensate compaction, gelation, and mechanical memory without requiring stronger attractive interactions. More broadly, our findings suggest that DNA topology and active processes may cooperate to control the material state of chromatin-associated condensates and other polymer-rich biomolecular assemblies.

REFERENCE STYLE

Supercoils Stabilize a "DNA Corset" Condensate with Torsion-Dependent Hysteretic Compaction, JACS Au 2026, 6, 2, 1390–1399, X.F. Wei, W. Zhuang.

KEYWORDS

biomolecular condensates, bridging-induced phase separation, DNA supercoiling.

Topological Control of Biomolecular Condensates: DNA Supercoiling‑Driven Compaction and Activity-Induced Gelation

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ABSTRACT

Biomolecular condensates and polymer-rich cellular assemblies are dynamically tuned between liquid-like, compact, and gel-like states, but the generic physical mechanisms regulating these transitions remain unclear. Here, coarse-grained simulations identify topology as a unifying control principle across two representative systems. In DNA–protein condensates formed by bridging-induced phase separation, incorporating DNA torsional elasticity shows that supercoiling drives twist-to-writhe conversion and produces a compact "DNA corset" architecture consisting of a dense bridged core wrapped by surface plectonemes. Increasing superhelical density progressively reduces condensate size, whereas torsional relaxation restores expansion; this response is reversible for short DNA but becomes hysteretic for longer chains, revealing topological memory. In a complementary nonequilibrium model of rigid rings mixed with active–passive semiflexible polymers, self-propulsion increases effective chain stiffness and transport, enhances polymer–ring threading, and drives an otherwise non-percolating mixture across a threading-percolation threshold into a system-spanning topological gel. The critical activity decreases with intrinsic chain stiffness, threading lifetimes peak near the transition, and ring diffusion arrests as topological connectivity saturates. Together, these results show that bond-free topological constraints—encoded by supercoiling or threading—can regulate condensate compaction, gelation, and mechanical memory without requiring stronger attractive interactions. More broadly, our findings suggest that DNA topology and active processes may cooperate to control the material state of chromatin-associated condensates and other polymer-rich biomolecular assemblies.

REFERENCE STYLE

Supercoils Stabilize a "DNA Corset" Condensate with Torsion-Dependent Hysteretic Compaction, JACS Au 2026, 6, 2, 1390–1399, X.F. Wei, W. Zhuang.

KEYWORDS

biomolecular condensates, bridging-induced phase separation, DNA supercoiling.

Unraveling Design Principles of Chromatic Acclimation and Energy Transport in Purple Bacteria

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ABSTRACT

Purple bacteria convert solar energy to biochemical energy with high quantum efficiency across a wide range of environments. Under low-light conditions, many species increase the number of antenna complexes and switch their primary antenna complex from light-harvesting complex 2 (LH2) to a blue-shifted variant, LH3. The effects of these organizational and molecular changes on the dynamics of solar energy conversion have remained unclear. Here, we integrated cryogenic electron microscopy (cryoEM), ultrafast absorption and fluorescence spectroscopy, and quantum dynamics simulations to compare the structural and spectral properties of antenna complexes and native membranes from *Rbl. acidophilus* strain 7750 grown under different light conditions. Our analyses revealed that hydrogen bonding dynamically tunes the transition energy, introducing a previously unreported excited-state energy equilibrium between bacteriochlorophyll rings in LH3. This energy redistribution opened new inter-complex pathways, enabling 68% faster energy transport to maintain high conversion efficiency despite the increased antenna size. Collectively, these results establish organizational and molecular modifications as tunable knobs to optimize not only absorption but also transport for robust light harvesting under the fluctuating sunlight intrinsic to natural environments.

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KEYWORDS

Energy transfer, Photosynthesis, Femtosecond spectroscopy, Antenna network

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DYNAMICS AND MECHANISM OF A DUAL FUNCTION CraCRY PROTEIN

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ABSTRACT

The cryptochrome/photolyase family (CPF) is a group of structurally similar flavoproteins with distinct functions. The function of photolyases (PLs) is to repair DNA lesion caused by ultraviolet radiation. Cryptochromes (CRYs) exhibit various functions, serving as blue-light photoreceptors in plants and insects, regulating their growth and development. Most CRYs do not possess DNA repair functions. However, a recently discovered animal-like cryptochrome named CraCRY in *Chlamydomonas reinhardtii* functions as both cryptochrome and (6-4) photolyase, which can repair a type of DNA lesion caused by ultraviolet light, (6-4) photoproduct (6-4PP). The molecular mechanism by which CraCRY utilizes blue light energy to repair DNA lesion and form the initial signaling state remains unclear. Here, we used ultrafast spectroscopy and single-molecule methods to elucidate the dynamics and molecular mechanism of CraCRY. We elucidate the entire repair photocycle with femtosecond resolution and the structural conformation of initial signaling with single-molecule detection. We also reveal the actual redox state for simultaneously maintaining the two functions, which is a hot debate of the key cofactor issue in the field.

REFERENCE STYLE

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KEYWORDS

DNA repair, Signal transduction, Photolyase and cryptochrome, Femtosecond spectroscopy, Single-molecule detection,

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Traversing the biophysics of amino acid sequence space

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ABSTRACT
During their function, proteins often exhibit dynamics ranging from picoseconds to many seconds. During their evolution, the dynamics of amino acid sequences of proteins ranges from days to millions of years. Bridging the gap between these two processes is a core challenge in the life sciences. Proteins display remarkable performance in catalysis and energy transduction. However, many energy, chemical manufacturing, and biotechnology applications remain practically unfeasible. A general underlying challenge is to gain enhanced predictive power over amino acid sequences that result in proteins with the properties needed for a variety of applications. However, sequence space seems hopelessly large, while the fitness landscape of sequence space is largely unprobed. Approaches to overcome these challenges will be presented in which proteins with computationally derived sequences are experimentally studied using spectroscopic methods, including Fourier transform infrared spectroscopy. The resulting data provide unexpected insights into limitations of current structure prediction approaches and general patterns of molecular evolution.

KEYWORDS
Protein engineering; sequence space, molecular evolution; structure prediction, infrared spectroscopy.

Marangoni effect as a general principle for intracellular transport

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[6]School of Physics, Peking University, Beijing 100871, China

ABSTRACT

The establishment of cell polarity is a fundamental symmetry-breaking event that relies on the precise spatiotemporal organization of intracellular matter. Organization and distribution of biomolecular condensates is essential for establishing cell polarity. In *Caenorhabditis elegans* embryos—a canonical model for asymmetric cell division and germline specification—cell polarity is tightly coupled to the spatial organization of P granules. Although classical frameworks attribute condensate segregation to bulk cytoplasmic streaming and localized dissolution–recondensation cycles, the physical forces that drive their rapid, long-range directional transport remain poorly defined. Here we identify the Marangoni effect as a fundamental engine of condensate motility. Through microfluidic reconstitution and quantitative biophysical measurements, we show that biochemical gradients—exemplified by the interfacial regulator MEG-3—establish local gradients in interfacial tension across condensate surfaces, thereby converting chemical potential differences into mechanical propulsion. By integrating *in vitro* measurements with *in vivo* tracking of P granules in *Caenorhabditis elegans* within a parameter-free theoretical framework, we quantitatively predict and map the intracellular transport landscape governed by Marangoni-driven flows. Together, these results establish the Marangoni effect as a general physical principle for intracellular transport emerging from phase separation. Complementing diffusion and motor-driven processes, this mechanism provides a unified framework for understanding the spatial organization of living matter.

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KEYWORDS

Biomolecular condensate, Cell polarity, Marangoni effect, Biophysics

THE GRAVITATIONAL-WAVE UNIVERSE: FROM COMPACT MERGERS TO COSMOLOGY

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ABSTRACT
Gravitational-wave astronomy is maturing into a precision tool for astrophysics and cosmology. Results from the LVK O4 run reveal a diverse population of merging compact objects, including asymmetric-mass and mass-gap events that challenge standard stellar evolution models. Neutron star mergers continue to illuminate r-process nucleosynthesis and the nuclear equation of state. Crucially, GW standard sirens now provide independent measurements of the Hubble constant, offering a fresh perspective on the long-standing Hubble tension. The stochastic background detected by Pulsar Timing Arrays further constrains supermassive black hole binary populations and early-Universe cosmology. We summarize the current landscape of results and discuss how next-generation detectors such as Einstein Telescope and LISA will transform our view of the gravitational-wave Universe across cosmic time.

REFERENCE STYLE
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KEYWORDS
Gravitational waves, black hole mergers, cosmology, neutron star physics, stochastic Gravitational-wave background

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Ringing Black Holes

In this talk I will discuss one of the frontiers of both theory and data analysis in gravitational wave astronomy - understanding the ringing of black holes and probing them from real data. I will review past efforts started from Chandrasekhar, Detweiler, et al in analyzing modes of black holes and explain what we currently understand in both linear and nonlinear wave properties, as well as the corresponding detection aspect. At last, I will show a few pressing problems and where we will be heading.

Title of the paper

COSMIC RAY FEEDBACK IN THE UNIVERSE: FERMI BUBBLES AND ODD RADIO CIRCLES

H.-Y. K. Yang[1,*], M. Ruszkowski[2], E. Zweibel[3], P.-H. Tseng[4], H.-Y. Schive[4], C.-Y. Chen[4], T. Chiueh[4], G.-H. Li[1], O. Piana[5], Y.-H. Lin[6]

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[2]Department of Astronomy, University of Michigan, USA.
[3]Department of Astronomy, University of Wisconsin-Madison, USA.
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[5]Department of Physics, Informatics & Mathematics, University of Modena & Reggio Emilia
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ABSTRACT [*major heading style: Bold 12 pt, UPPERCASE*]
Relativistic jets emanating from active galactic nuclei (AGNs) play a pivotal role as a feedback mechanism in the Universe, and the cosmic rays (CRs) carried by AGN jets can have profound influence on galaxy properties and the circumgalactic medium. Consequently, self-consistent modeling of CR propagation, spectral evolution, and emission mechanisms is imperative for understanding the thermal and non-thermal emissions of galaxies. We employ advanced 3D CR-magnetohydrodynamic simulations to elucidate that the multi-wavelength observations of the Fermi and eRosita bubbles within the Milky Way can be accounted for by past activity of Sgr A*. We investigate the feasibility of generating symmetric bubbles through the interaction of oblique AGN jets with the dense Galactic disk. We posit that, when viewed head-on, AGN jet-inflated bubbles may provide a plausible explanation for the recently identified enigmatic odd radio circles (ORCs). We further test this AGN bubble scenario of ORC formation using semi-analytical models and show that the predicted number of ORCs is consistent with that found by existing surveys. These works advance our understanding of CR jet feedback and their influence on various astrophysical phenomena within our cosmic neighborhood.

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AGN Jet-inflated Bubbles as Possible Origin of Odd Radio Circles, ApJ, 974, 269, 2024, Y. H. Lin, H.-Y. K. Yang

KEYWORDS
Cosmic rays, active galactic nuclei, hydrodynamics, numerical simulations

Site-specific Functionality Tuning the Excited-State Dynamics of Thio-nucleobases

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ABSTRACT

A small chemical modification of the nucleobase structure can significantly enhance the photoactivity of DNA/RNA, which may incur DNA/RNA damage, thus holding promising applications in photochemotherapy treatment of cancers or pathogens. Thio-nucleobases have emerged as promising DNA/RNA-embedded biocompatible photosensitizers because sulfur substitution red-shifts absorption into the UVB/UVA region and enables efficient access to reactive triplet manifolds. However, their photophysical and photochemical performance is highly sensitive to the position and nature of additional functional groups. Here, by a combination of femtosecond and nanosecond time-resolved spectroscopic experiments and high-level *ab initio* calculations, we focus on disentangling the site-specific functionality tuning effect on the earliest events and excited state dynamics of a series of thio-nucleobases and thio-nucleosides.

Our findings: for 6-methylthioguanine (me6-TG), dual thionation/methylation reshapes the excited-state relaxation by introducing bifurcated singlet-state pathways and a unique photodissociation channel. Unlike conventional thiobases, the $^1n_N\pi^*$ state serves as the principal doorway for triplet formation, affording a substantial triplet yield while opening C–S bond cleavage to generate reactive thiyl-radical intermediates. For protonated 2-thiocytidine (2tCyt), acidic protonation weakens the ribose-induced acceleration of triplet decay: the $2tCydH^+$ lifetime approximately doubled relative to neutral 2tCyd, demonstrating that protonation can reconfigure triplet-state electronic structures and suppress rapid photoisomerization, offering a pH-responsive strategy for controlling thionucleoside photoreactivity. For 5-phenylethynyl-4-thiouridine (5ph-4TU), C5 π-extension synergizes with thionation to extend absorption into the visible/NIR two-photon regime. The phenylethynyl group suppresses C5–C6 twisting, raises the barrier to the S_2/S_1 conical intersection, and stabilizes a long-lived emissive $S_2(^1\pi\pi^*)$ state, while still enabling triplet formation and cytotoxic singlet-oxygen generation under two-photon NIR irradiation. Collectively, these studies establish site-specific functionalization as a powerful design principle for tuning conical intersections, intersystem crossing, radical generation, and two-photon photoactivity in thio-nucleobases, paving the way for the development of advanced photodynamic and photochemotherapy approaches.

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KEYWORDS

Excited state dynamics; Photoreactivity; Nucleobase; Electronic Structure; Conical intersection

Single-molecule magnetic tweezers reveal distinct dynamics and enhanced mechanical stability of ssDNA 3_1 and 5_2 knots

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Abstract

Nucleic acid knots play essential roles in diverse systems, ranging from RNA pseudoknots in the Zika virus to DNA knots in viral DNA ejection. However, the physical properties and potential functions of nucleic acid knots remain largely unexplored. We designed ssDNA sequences capable of forming 3_1 and 5_2 knots and characterized their mechanical responses and folding pathways using single-molecule magnetic tweezers. Experimental results reveal that the sequences designed for 5_2 knots can adopt three distinct conformation: hairpin, 3_1 knot, and 5_2 knot. Our results reveal that knotted topologies significantly enhance the mechanical stability of ssDNA structures from ~10 pN to > 30 pN, while the tightened 3_1 and 5_2 knot absorb 16-18 nt and 25-30 nt, respectively. Furthermore, biochemical assays demonstrate that the ssDNA knot provides superior resistance against Exonuclease T5 digestion compared to unknotted structures. This study highlights the potential of topological engineering for enhancing the biostability of nucleic acid structures and provides a framework for exploring the functional applications of ssDNA knot.

Results

I . ssDNA knot designed

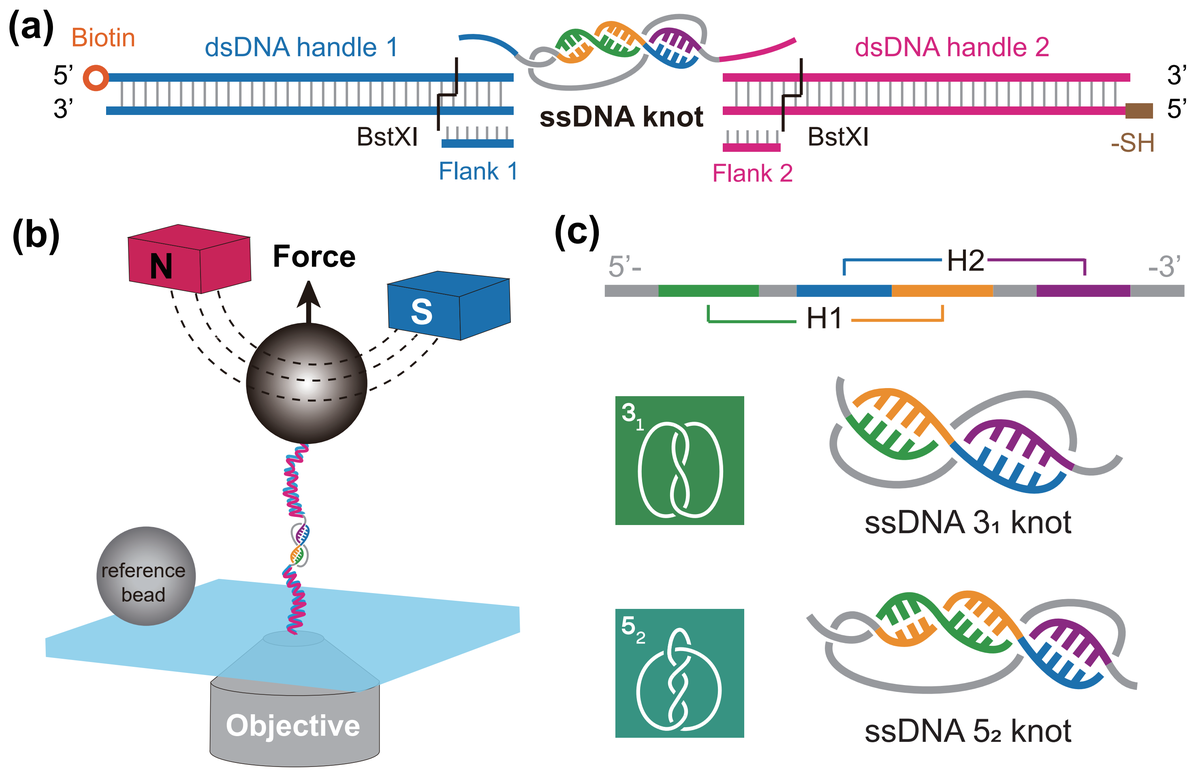

Figure 1. Design, construction, and experimental setup of ssDNA knots. (a) Assembly and ligation strategy for single-molecule ssDNA knot constructs. (b) Schematic of single-molecule magnetic tweezers for stretching ssDNA knots. (c) Design of ssDNA 3_1 and 5_2 knots based on the sequence cross-pairing method.

II . Mechanical stability characterization

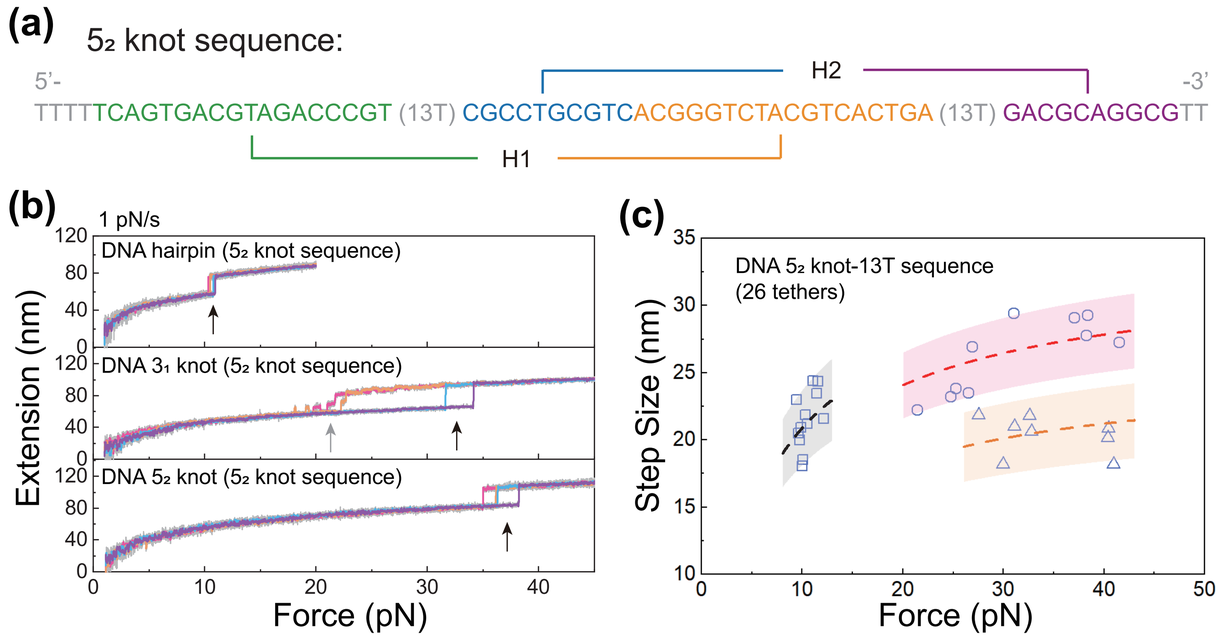

Figure 2. Mechanical stability characterization of the ssDNA 5_2 knot. (a) Sequence design of the ssDNA 5_2 knot. (b) Three representative, non-interconvertible force-extension curves observed in the magnetic tweezers stretching processes. (c) Statistical clustering based on transition forces and step sizes identifies three distinct topological structures.

III . Mechanical stability and folding pathway

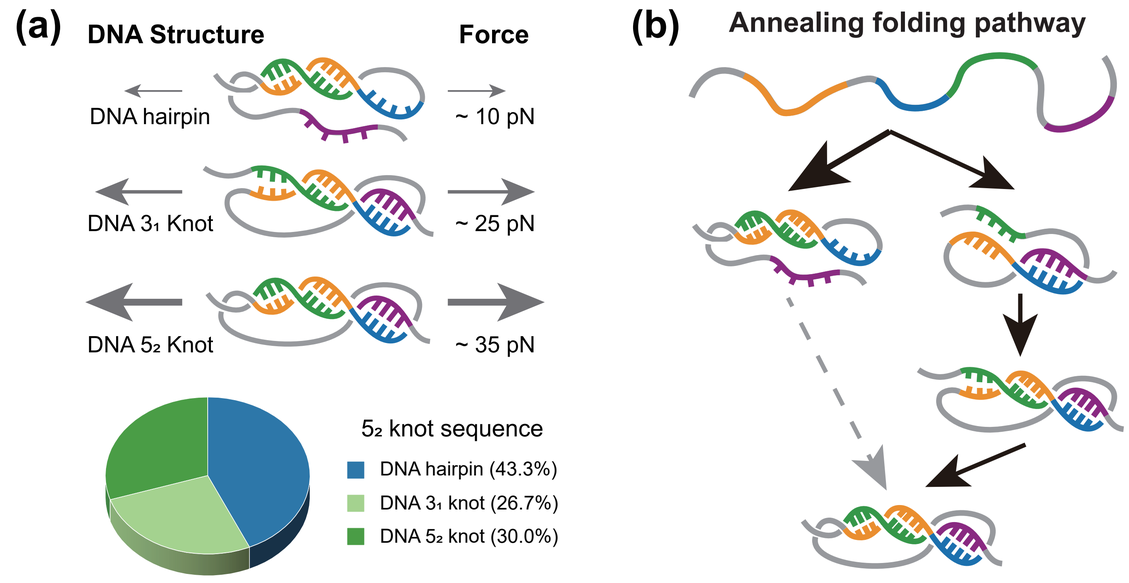

Figure 3. Impact of knot topology on structural stability and folding kinetics. (a) Positive correlation between mechanical stability and the crossing number of knots. (b) Population distribution of the three observed structures. (c) The multi-pathway hierarchical annealing folding model for ssDNA 5_2 knot.

IV . Exonuclease Resistance of ssDNA Knots

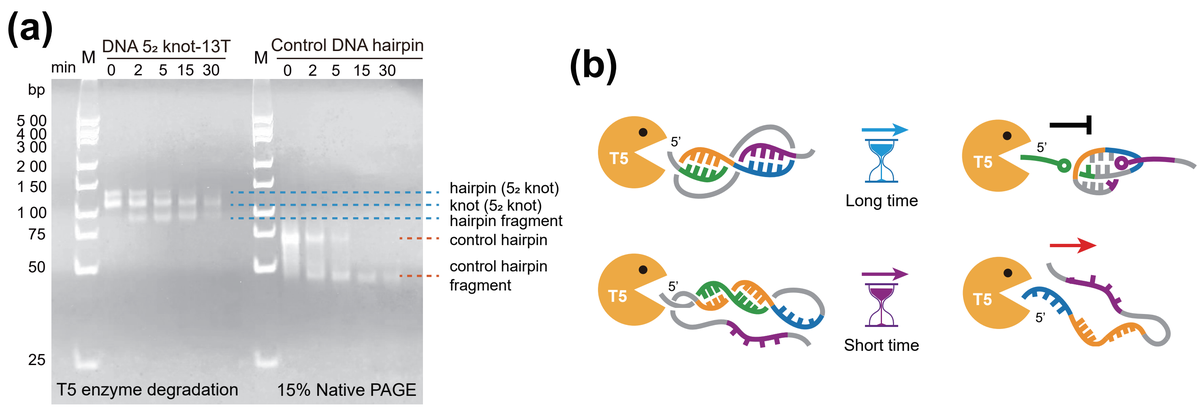

Figure 4. (a) Exonuclease resistance of ssDNA knots. (a) Electrophoretic comparison of T5 exonuclease resistance between the ssDNA knot and hairpin. (b) Knot topology acts as 'topological protection' to significantly enhance the resistance of nucleic acids against nucleic acid exonuclease degradation.

Conclusion

- **Mechanical Stability & Topological Complexity: a positive correlation, hairpin (~ 11 pN) < 3_1 knot (~ 25 pN) < 5_2 knot (~ 35 pN).**
- **Hierarchical Folding Mechanism: hairpin and 3_1 knot serve as essential metastable intermediates and structural scaffolds for the folding of linear ssDNA into 5_2 knot.**
- **Exonuclease Resistance: ssDNA knots tighten into a compact, non-eliminable "knot core", providing 'topological protection' against enzymatic degradation.**

Reference

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Higher-Order Interactions and Water-Driven Fluctuations Affect Condensate Mechanics and Longevity

On the basis of simulation trajectories of five distinct IDP condensates we show that the same physical principle—cooperative, higher-order residue contacts acting as transient, multi-valent cross-links—affects both the static mechanical response the droplet. In this picture each protein segment can engage three or more partners simultaneously; the average number of such higher-order interactions per residue sets the instantaneous elastic modulus and surface tension without additional fit parameters. When explicit solvent is present the continual exchange of water molecules imports kinetic energy that repeatedly disrupts the residue interaction, maintaining the system near a steady state of residue interaction breaking and reformation and postponing the slow relaxation that would otherwise drive the condensate toward a gel like structure. Removing the solvent flux eliminates the energy input, causing the same universal aging behaviour observed in all systems studied. Thus a single, motif-based higher-order interaction model quantitatively links sequence, mechanics and lifetime by separating the roles of network connectivity and non-equilibrium energy supply, providing a minimal physical framework applicable to any phase-separated protein fluid.

HOLLOW CONDENSATES EMERGE FROM GELATION-INDUCED SPINODAL DECOMPOSITION VIA DISTINCT MOLECULAR TRIGGERS

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ABSTRACT

Recent studies have identified diverse hollow biomolecular condensates, characterized by biomolecule-depleted interiors surrounded by biomolecule-rich shells. Although several formation mechanisms have been proposed, a general thermodynamic and kinetic driving force remains elusive. Here, we investigate two distinct transcription factor-DNA systems—p53 and FOXA1—to elucidate the underlying mechanistic principles of hollow condensate formation. First, in a well-defined system where p53 and random sequence double-stranded DNA (Random DNA) form biomolecule-rich condensates, the introduction of dsDNA containing p53-binding motifs (p21 DNA) induces a morphological transition to hollow structures and a localized liquid-to-gel transition at the condensate periphery. A three-component phase-field model demonstrates that this peripheral gelation leads to the gradual depletion of protein and Random DNA from the condensate core, triggering spinodal decomposition and lumen formation. In parallel, we observed a spontaneous hollowing phenomenon in condensates formed by the FOXA1 protein and Random DNA. Over time, these solid condensates spontaneously transition into spherical shells, accompanied by the gradual expulsion of DNA from the condensates. We propose that this morphological transition is driven by the establishment of slow-scale protein-protein interactions, which outcompete and replace the initial protein-DNA interactions. This interaction rewiring leads to protein gelation, which acts as the mechanistic driver for hollowing. Together, these findings demonstrate that gelation-induced spinodal decomposition serves as a universal physical mechanism for lumen formation in multicomponent condensates.

REFERENCE STYLE

Hollow condensates emerge from gelation-induced spinodal decomposition, *Proceedings of the National Academy of Sciences of the United States of America*, 122, e2520491122, 2025, C. Li, L. Meng, Y. Tong, J. Lin, and Z. Qi.

KEYWORDS

biomolecular condensates, phase separation, hollow condensates, spinodal decomposition

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How Animals Sense the Geomagnetic Field to Navigate?

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ABSTRACT

The ability of animals to perceive guidance cues from Earth's magnetic field for orientation and navigation has been demonstrated by a wealth of ecological and behavioral experiments. This magnetic sense has evolved across a broad range of animal taxa, from invertebrates to vertebrates, exhibiting remarkable diversity. Yet the nature of this sensory modality remains fascinatingly unresolved. Previously, we discovered a putative magnetoreceptor (MagR), which forms a nanoscale biological compass with Cryptochrome (Cry)[1]. We also demonstrated the quantum biological principle of Cry-based magnetic sensing and expanded the classical radical pair model with our collaborators[2]. Later, we identified an evolutionarily conserved intermolecular electron transport (ET) pathway in the MagR/Cry complex, in which electrons travel stepwise along a flavin-tryptophan chain in Cry and further extend to iron-sulfur clusters in MagR via an ET bridge formed by a series of stepping-stone amino acids[3]. In this talk, I will explore a possible connection among these three models, discuss how intermolecular electron transfer modulates protein magnetism in the MagR/Cry complex, and address the fundamental question of how biological organisms recognize quantum information.

REFERENCE

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KEYWORDS

Magnetoreception, Animal navigation, Quantum compass, Biocompass

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Photoreceptors are proteins that transmit photochemical signals into chemical actions. The processes are generally characterized by ultrafast photoreceptions accompanying photochemical reactions, followed by slower processes involving protein conformational changes. I will present examples on the ultrafast regulation of an excited-state energy transfer regulation by the major light-harvesting complex of photosystem II (LHCII) in response to the rapid fluctuations of light intensity. To accomplish this goal, I will discuss a multistate density functional theory designed to model photochemical and charge transfer processes. In addition, I will illustrate a computation-aided design of an engineered terpenoid synthase enzyme.

Cells constantly encounter time-varying mechanical cues, yet most mechanobiology—and the canonical molecular clutch model—assumes static substrates. Using photo-responsive hydrogels to impose controlled stiffness oscillations, we uncover a frequency-dependent regime of mechanosensing in which cellular traction forces are markedly amplified: at specific driving frequencies, traction exceeds that on static matrices fourfold stiffer. This amplification arises from a mismatch in timescales—rapid adaptation of force generation versus slower deactivation of mechanotransduction proteins—leading to their accumulation and a sustained increase in effective clutch engagement. Extending these insights to function, we show that mesenchymal stem cells can migrate rapidly on soft substrates (<4 kPa) when stiffness is cycled quickly. Under dynamic conditions, traction builds progressively and drives a fast mechanical turnover of focal adhesions, bypassing the need for classical front–rear polarity and biochemical adhesion cycling characteristic of mesenchymal migration. A minimal theory that balances forces under periodic stiffness inputs quantitatively predicts both migration speed and shape evolution. Together, these results motivate a revised framework that couples instantaneous mechanosensing to delayed signaling kinetics, revealing how “mechanical rhythms” both amplify traction and unlock high-speed, polarity-independent migration on otherwise non-permissive soft matrices. The work suggests design principles for dynamic biomaterials and points to frequency as a tunable parameter for guiding cell behavior in tissue engineering and therapy.