Articles and Perspectives focused on Big Data are flagged.

EDITORIAL
Interdisciplinary innovations are key to effective use of quantitative biological information
J. Lippincott-Schwartz 3893

PERSPECTIVES
Biosecurity in the age of Big Data: a conversation with the FBI
K. G. Kozminski 3894–3897

Analyzing the dynamics of cell cycle processes from fixed samples through ergodic principles
R. J. Wheeler 3898–3903

The role of functional data in interpreting the effects of genetic variation
D. L. Young and S. Fields 3904–3908

Big Data in Caenorhabditis elegans: quo vadis?
H. Hutter and D. Moerman 3909–3914

Forces, fluctuations, and self-organization in the nucleus
T. Pederson, M. C. King, and J. F. Marko 3915–3919

Single-cell phenomics in budding yeast
Y. Ohya, Y. Kimori, H. Okada, and S. Ohnuki 3920–3925

Reproducible quantitative proteotype data matrices for systems biology
H. L. Röst, L. Malmström, and R. Aebersold 3926–3931

Quantitative nature of overexpression experiments
H. Moriya 3932–3939

BRIEF REPORT
A Highlights from MBoC Selection

Single-cell analysis of circadian dynamics in tissue explants

Studying signaling dynamics in single cells in vivo is critical to understanding how cells act and interact in 3D environments. Experimental and computational tools to quantify a circadian reporter in single cells in intact tissues for >1 wk are used to analyze the period, amplitude, and synchrony of circadian rhythms in vivo.
ARTICLES

Cell Biology of Disease

Microenvironment rigidity modulates responses to the HER2 receptor tyrosine kinase inhibitor lapatinib via YAP and TAZ transcription factors
Chun-Han Lin, F. A. Pelissier, Hui Zhang, J. Lakins, V. M. Weaver, C. Park, and M. A. LaBarge

The relative contributions of the molecular and physical characteristics of tissue microenvironments to cell responses to receptor tyrosine kinase inhibitors are not well understood. Polymer-based tissue culture substrata were used to isolate and study the contribution of matrix elastic modulus. YAP and TAZ, transcriptional coactivators and mechanotransducers of the Hippo pathway, are essential for mediating elastic modulus-dependent resistance to the HER2-targeted anticancer drug, lapatinib.

Cell Cycle

A comprehensive model to predict mitotic division in budding yeasts

A mechanistic in silico model predicts mitotic events and effects of perturbation in budding yeasts belonging to Ascomycota and Basidiomycota. The model identifies distinct pathways based on the population of cytoplasmic microtubules and cortical dyneins as determinants of nuclear and spindle positioning in these phyla.

Experimental testing of a new integrated model of the budding yeast START transition

Mathematical modeling of the cell cycle has unveiled recurrent features and emergent behaviors of cellular networks. Constructing new mutants and performing experimental tests during development of a new model of the budding yeast cell cycle yields a more efficient modeling process and results in several testable hypotheses.

Basic mechanism for biorientation of mitotic chromosomes is provided by the kinetochore geometry and indiscriminate turnover of kinetochore microtubules
A. V. Zaytsev and E. L. Grishchuk

A mathematical model is used to analyze the impact of the indiscriminate kinetochore microtubule turnover and the back-to-back kinetochore geometry on chromosome biorientation during mitosis. The authors show that mammalian kinetochore operates in a near-optimal regime, whereby these two features provide a significant error-correction activity.

Cytoskeleton

Physical limits on kinesin-5–mediated chromosome congression in the smallest mitotic spindles
K. M. McCoy, E. S. Tubman, A. Claas, D. Tank, S. A. Clancy, E. T. O’Toole, J. Berman, and D. J. Odde

Kinesin-5 mediates chromosome congression in Candida albicans via length-dependent depolymerase activity, which organizes chromosomes at the spindle equator to overcome fundamental thermal limits at the nanoscale and maintains spindle dimensions regardless of cell size.

Membrane Trafficking

Expression, sorting, and segregation of Golgi proteins during germ cell differentiation in the testis

A total of 1318 proteins characterized in the male germ cell Golgi apparatus reveal a new germ cell–specific Golgi marker and a new pan-Golgi marker for all cells. The localization of these and other Golgi proteins reveals differential expression linked to mitosis, meiosis, acrosome formation, and postacrosome Golgi migration and destination in the late spermatid.

A Highlights from MBoC Selection

Diffusion of GPI-anchored proteins is influenced by the activity of dynamic cortical actin

Membrane proteins that couple to cortical actin show temperature-independent diffusion. The loss of this coupling and perturbation of cortical actomyosin dynamics render the diffusion temperature dependent. The findings suggest that active fluctuations arising from dynamic actin filaments at the cortex can drive diffusion on the cell membrane.
Methods

Joint modeling of cell and nuclear shape variation
G. R. Johnson, T. E. Buck, D. P. Sullivan, G. K. Rohde, and R. F. Murphy

It is shown for the first time that cell shape can be accurately predicted from nuclear shape (and vice versa) for three different cell lines. This correlation is reduced by altering protein C1QBP or various drugs. In addition, a generative model is given for the kinetics of shape change. The software is available in the open-source CellOrganizer system.

Probability-based particle detection that enables threshold-free and robust in vivo single-molecule tracking
C. S. Smith, S. Stallinga, K. A. Lidke, B. Rieger, and D. Grunwald

Any single-molecule study starts with finding those single-molecule signals in recorded images. Currently, parameters such as filter and thresholds are user set, and errors are unknown and not observed or controlled. A framework is presented in which expert knowledge and parameter tweaking are replaced with a probability-based hypothesis test.

Proteome-wide quantitative multiplexed profiling of protein expression: carbon-source dependency in Saccharomyces cerevisiae
J. A. Paulo, J. D. O’Connell, A. Gaun, and S. P. Gygi

A mass spectrometry–based tandem mass tag 9-plex strategy was used to determine alterations in relative protein abundance due to three carbon sources—glucose, galactose, and raffinose. More than 4700 proteins were quantified across all nine samples; 1003 demonstrated statistically significant differences in abundance in at least one condition.

Nuclear Functions

Structural organization of nuclear lamins A, C, B1, and B2 revealed by superresolution microscopy
T. Shimi, M. Kittisopikul, J. Tran, A. E. Goldman, S. A. Adam, Yixian Zheng, K. Jaqaman, and R. D. Goldman

Superresolution microscopy and computational image analysis demonstrate that the four nuclear lamin isoforms of mammalian cells are each organized into distinct meshwork structures sharing similar physical characteristics. Knockouts of single lamins alter the structure of the remaining lamins, suggesting interactions among the meshworks.

Signaling

Highlighted from MBoC Selection

Enhanced dimerization drives ligand-independent activity of mutant epidermal growth factor receptor in lung cancer
C. C. Valley, D. J. Arndt-Jovin, N. Karedla, M. P. Steinkamp, A. I. Chizhik, W. S. Hlavacek, B. S. Wilson, K. A. Lidke, and D. S. Lidke

Epidermal growth factor receptor kinase mutations drive oncogenesis, but the molecular mechanism of pathological signal initiation is poorly understood. Using high-resolution microscopy methods, the authors reveal that these kinase mutations induce structural changes in the receptor ectodomain that lead to enhanced, ligand-independent dimerization.

Modeling the roles of protein kinase Cβ and η in single-cell wound repair
W. R. Holmes, L. Liao, W. Bement, and L. Edelstein-Keshet

A mathematical model for the roles of PKCβ and η in Rho and Cdc42 zone formation in single-cell wounds explains qualitative and overall quantitative experimental observations, including a puzzling PKCη overexpression zone inversion.

Systems Biology

Orchestration of ErbB3 signaling through heterointeractions and homointeractions

ErbB receptors form homodimers and heterodimers between family members. To model ErbB2/ErbB3 signaling, single-particle tracking data are used to create a simulation space with overlapping receptor domains. Stochastic modeling of receptor dimerization and phosphorylation reveals the complexity of ErbB2-3 interactions.
Modulation of receptor dynamics by the regulator of G protein signaling Sst2
S. P. Venkatapurapu, J. B. Kelley, G. Dixit, M. Pena, B. Errede, H. G. Dohlman, and T. C. Elston
4124–4134
G protein–coupled receptor signaling is negatively regulated by both receptor internalization and regulator of G protein signaling (RGS) protein–stimulated inactivation of the G protein. The RGS protein can also positively regulate receptor signaling by binding to the receptor, thereby reducing receptor internalization.

Interlocked positive and negative feedback network motifs regulate β-catenin activity in the adherens junction pathway
D. J. Klinke, II, N. Horvath, V. Cuppett, Yueting Wu, Wentao Deng, and R. Kanj
4135–4148
Quantitative experiments and mathematical modeling show that the activity of β-catenin in the adherens junction pathway is regulated by interlocked network motifs consisting of a positive feedback loop, which restores the integrity of adherens junctions, and a negative feedback loop, which limits β-catenin–induced gene expression.

In vivo quantitative analysis of Talin turnover in response to force
G. K. Hákonardóttir, P. López-Ceballos, A. D. Herrera-Reyes, R. Das, D. Coombs, and G. Tanentzapf
4149–4162
Cell–ECM adhesion is regulated by mechanical force. Quantitative imaging and mathematical modeling are used to elucidate how the intracellular adhesion complex of integrin-based adhesions responds to force, revealing the molecular mechanisms that allow the adhesion complex to respond to force to stabilize cell–ECM adhesion over development.

Apolar and polar transitions drive the conversion between amoeboïd and mesenchymal shapes in melanoma cells
S. Cooper, A. Sadok, V. Bousgouni, and C. Bakal
4163–4170
Quantitative imaging of single living tumor cells invading three-dimensional collagen matrices is used in tandem with unsupervised computational analysis to characterize melanoma-cell shape space. Melanoma cells can switch between amoeboïd and mesenchymal forms via two different routes in shape space—an apolar and a polar route.

Theory

Dendritic spine geometry can localize GTPase signaling in neurons
S. A. Ramirez, S. Raghavachari, and D. J. Lew
4171–4181
The spread of Cdc42 activation at dendritic spines is modeled by means of reaction-diffusion equations solved on spine-like geometries. Excitable behavior arising from positive feedback in Cdc42 activation leads to traveling waves of Cdc42 activity. The narrow neck of the dendritic spine halts wave propagation, resulting in localized Cdc42 signaling.