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Spotlights on Recent *JACS* Publications

GROUP II INTRON SPLICING MECHANISM REVEALED

In their original form, eukaryotic messenger RNAs include both coding (exons) and noncoding segments (introns). Some organisms excise those introns via a ribonucleoprotein complex called the spliceosome, while in other organisms the introns act as RNA enzymes to splice themselves out. Such self-splicing molecules are called group II intron ribozymes, and they require two magnesium ions to function. But precisely what role those ions play has been unclear. Recently, Alessandra Magistrato and colleagues have reported a plausible reaction mechanism (DOI: 10.1021/jacs.6b01363).

The researchers use classical and quantum-classical molecular dynamics simulations to nail down the first step in intron excision: the cleaving of the RNA phosphodiester bond at the 5′ end of the intron. Their simulations suggest that group II introns function via a dissociative mechanism in which magnesium ions stabilize the transition state and the nucleophile releases its proton to bulk water. That is in sharp contrast to protein-based nucleases, in which magnesium ions serve as Lewis acids to activate water directly. "The novel reaction path elucidated here might be an evolutionary ancestor of the more efficient two-metal-ion mechanism found in enzymes," they suggest.

Jeffrey M. Perkel

NEW FLUORESCENT VOLTAGE INDICATORS MONITOR NEURONAL ACTIVITY

Many biological processes rely on the unequal distribution of ions across the plasma membrane of cells, which results in the creation of a transmembrane voltage (V_m). Traditional methods for monitoring V_m involve the use of electrodes, which are invasive and limited in throughput.

Now, researchers led by Evan Miller describe a new family of fluorescent voltage-sensitive organic dyes that can be used to measure V_m in neuronal cells with high spatial and temporal fidelity (DOI: 10.1021/jacs.6b05672). The new organic dyes—known as rhodamine voltage reportors (RhoVRs)—display excitation and emission profiles in the green to orange region of the visible spectrum. They use a new localization motif for cell membrane targeting and achieve increased sensitivity to small changes in V_m.

The team demonstrates that the new dyes can be used in conjunction with traditional optical tools, such as green fluorescent protein and calcium indicators, that are also used to monitor neuronal activity in mammalian cells. Broadly applicable optical methods for tracking V_m, such as RhoVRs, could lead to a better understanding of the role of V_m in health and disease.

Christine Herman, Ph.D.

CLEANEST CONFIRMATION OF MARCUS LAW

Oxidation–reduction reactions are characterized by the transfer of an electron from a donor molecule to an acceptor molecule. Conventional wisdom had dictated that the electron-transfer rate should have a linear relationship to the exergonicity, or change in free energy, of the reaction. But in 1956, Rudolph Marcus predicted an unexpected bell-shaped dependence of the reaction rate on the Gibbs free energy, whereby electron-transfer rates become slower with larger energy differences between the reactants and the products. The Marcus law has traditionally been confirmed by altering the chemical structures of donors and acceptors.

Now, Dmitry Matyushov and co-workers report a straightforward verification of Marcus theory, by characterizing the dependence of the electron-transfer rate on the medium temperature using a fullerene–porphyrin dyad (DOI: 10.1021/jacs.6b04777). Without modification of the chemical structure, electron transfer in this system also demonstrates bell-shaped dependence when plotted against inverse temperature. The authors explain that this unusual temperature dependence is because of the strong decrease in the energy required for solvent reorganization with increasing temperature.

Alexander Hellemans

HOW DNA BENDS TO THE GROOVE

The double-helix—the classic structural model of DNA—is not static: the molecule also bends, and that capability plays a key role in many biological processes, including gene expression, protein–DNA binding, and DNA repair. B-DNA, the most common form of DNA, has a major groove and a minor groove, and it tends to bend preferentially in the direction of one of these grooves. Ning Ma and Arjan van der Vaart reveal new insights into the bending of DNA in a computational study (DOI: 10.1021/jacs.6b05136).

To understand what governs the directionality of the bending of DNA, the authors carry out free energy simulations for eight DNA sequences of 12 base pairs. They find that sequences with four to six consecutive adenines, known as A-tracts, tend to bend toward the minor groove, whereas non-A-tracts are more likely to bend toward the major groove. Additionally, based on the team's computational analysis of structures from the Protein Data Bank, protein–DNA complexes favor bending toward the major groove. The work suggests that differences in groove hydration may influence DNA bending, shedding light on how this biologically important phenomenon is controlled.

Deirdre Lockwood, Ph.D.

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