Modular Microscopy Systems for Single Molecule Imaging

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Abstract

Single molecule approaches to understanding biological processes present many unique challenges for microscopy systems that conventional microscope platforms were not designed to meet. These challenges can be grouped into 3 broad categories: 1) a greater need for open and flexible access to optical pathways; 2) more stringent requirements for precise control over sample position; and 3) the paramount importance for stability in the overall system. To serve the important emerging needs of single molecule approaches, we have developed an *open*, *modular*, *flexible*, and *extensible* microscopy platform, which we call the RM21™. It is specifically designed to meet these challenges, while also making customization and innovation straightforward. Very importantly, we have leveraged our expertise in precise positioning in all aspects of this platform: the RM21™ is designed from the bottom up, with system stability firmly in mind, as well as full integration with an array of options for both micro- and nanopositioning stages. These design considerations enable precise and comprehensive control over sample positioning while maintaining overall system stability. We have also placed anchor points for cage-system mounting of widely available optomechanical components at convenient positions throughout this platform, supporting flexibility and ease of design, assembly, and alignment of desired final systems. Finally, we have developed and integrated both focal and 3-dimensional active drift-compensation systems to address the stability needs of single molecule experiments. We demonstrate how this platform can be configured to support several specific single molecule methods, and provide examples of how it can be extended to support others. We also use single molecule imaging to examine the sample positioning capabilities of these systems, as well as their stability with and without active drift compensation.