Using protein-DNA chimeras to detect and count small numbers of molecules

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Quantification of specific molecules is central to many fields, including biology, where differences in the number of low abundance proteins can bring about profoundly different cellular consequences. We describe general methods to detect and quantify small numbers of specific molecules. We redirected self-splicing protein inteins to create "tadpoles", chimeric molecules comprised of a protein head covalently coupled to an oligonucleotide tail. We made different classes of tadpoles that bind specific targets, including *Bacillus anthracis* protective antigen and the enzyme cofactor biotin. We measured bound target by quantifying DNA tails by T7 RNA polymerase runoff transcription and by real-time PCR. Assays based on these reagents had dynamic ranges of more than 11 orders of magnitude and distinguished numbers of molecules different by as little as 10%. At their low limits, they detected as few as 6400 protective antigen molecules, 600 biotin molecules, and 150 biotinylated protein molecules. In crudely fractionated human serum, they detected as few as 32,000 protective antigen molecules. Tapdoles enable simple and sensitive measurements of the number of molecules. By hybridization of their nucleic acid tails, they may open paths to new materials and nanostructures.