

# Designing better biosensors from first principles

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## Abstract:

Biosensors and microfluidics have yet to collectively meet necessary and desired benchmarks of high sensitivity, specificity, reproducibility, multiplexing and speed. Notably, scaling in multiplexed sandwich assays faces compounding cross-reactivity [1], while the trade-off between time-to-result and sensitivity remains stifling. Here, we will discuss conceptual frameworks and practical designs that transcend these limitations. Firstly, the colocalization-by-linkage assay on microparticles (CLAMP) enables scalable multiplexing on barcoded microparticles with standard flow cytometry readout [2,3]. Thousands of proteins can be detected in 20  $\mu$ l with a turnaround of  $\sim$ 3 h only. Secondly, the microfluidic sieve detector (MFSD) rapidly ‘sieves’ hundreds of microliters of sample in 1 min, and detects individual proteins digitally following partitioning and enzymatic amplification [4]. The MFSD enables very rapid ( $< 5$  min) and ultrasensitive (zeptomolar) assays with 7 OM dynamic range and low CVs ( $<15\%$ ) suitable for quantification; it can also detect nucleic acids (isothermally) more sensitively and faster than PCR. While classical mass action and transport theory apply, insight is gained from a proposed stochastic Brownian agent dynamics (SBAD) model with flow. We believe the MFSD sets a new standard for assays, and together with the CLAMP, and with SBAD, highlight the potential for new biosensing approaches and principles.

## Keywords:

sandwich assays, multiplexing, digital assays, microfluidic sieve, stochastic Brownian agent dynamics.

## References:

- [1] D. Juncker *et al.* Cross-reactivity in antibody microarrays and multiplexed sandwich assays: shedding light on the dark side of multiplexing, *Curr. Op. Chem. Biol.* 18, 29-37 (2012) doi:10.1016/j.cbpa.2013.11.012.
- [2] M. Dagher, M.Kleinman, A. Ng, and D. Juncker, Ensemble multicolour FRET model enables barcoding at extreme FRET levels, *Nature Nanotechnology*, 13, 925-932 (2018). doi:10.1038/s41565-018-0205-0
- [3] M. Dagher, *et al.*, nELISA: A high-throughput, high-plex platform enables quantitative profiling of the inflammatory secretome, *Nature Methods*, 22, 2375–2385 (2025). doi: 10.1038/s41592-025-02861-6
- [4] G.Kim, M. L. Shen A. Ng, D. Juncker, Microfluidic sieve and detector for rapid ultrasensitive assays with single-molecule sensitivity, *bioRxiv*, 2025.10.30.685461 (2025). doi: 10.1101/2025.10.30.685461