

# **Carbon Nanotube Based Biosensors Using Corona Phase Molecular Recognition (CoPhMoRe): Development and Applications**

By

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## **Technical Summary**

Molecular recognition sites that specifically bind a target molecule are essential for clinical research, disease diagnosis, and therapeutic development. To this end, a promising technique developed by the Strano laboratory at MIT is Corona Phase Molecular Recognition (CoPhMoRe), which uses amphiphilic polymers or macromolecules adsorbed onto a nanoparticle surface to generate a synthetic recognition site. The underlying nanoparticle, which can also function as the sensor transducer, pins the polymer to a specific 3D conformation using non-covalent interactions, resulting in a binding pocket analogous to the antigen binding domain of a natural antibody. While CoPhMoRe has proven considerable versatile in recognizing small organic molecules such as vitamins, neurotransmitters, pharmaceutical drugs and steroid hormones, the recognition of large molecules such as viral proteins has been less explored. Macromolecular analytes introduce a much wider set of potential interactions, requiring refined analysis and new insights into mechanisms. This thesis focuses on (i) constructing CoPhMoRe sites for protein analytes, (ii) exploring new methods and mechanistic understanding to inform CoPhMoRe recognitions and also (iii) translating CoPhMoRe phases to interfaces that can be incorporated into biosensors for specific applications.

Towards Aim (i), this thesis has developed CoPhMoRe sites for protein based disease biomarkers, including interleukin-6, nucleocapsid and spike proteins of SARS-CoV-2, enabling rapid and label-free near-IR fluorescence detection of target analytes with dose dependent responses in complex environments. Towards Aim (ii), this thesis investigates new methods and analyses for CoPhMoRe characterization, such as the expansion of the Molecular Probe Absorption (MPA) technique. This technique measures the accessible surface area of a CoPhMoRe based sensor by using a fluorescent molecule as a probe that quenches upon interacting with the corona phase. Further advances involve instrumentation and mathematical models to analyze the chiroptical properties of corona phases, facilitating the CoPhMoRe handedness determination at the single molecule level with circularly polarized excitation sources. Towards Aim (iii), this thesis explores form factor advancements to broaden the utility of CoPhMoRe sensors. It includes profiling cellular immune heterogeneity by integrating the optical nanosensor arrays into microfluidics to interrogate chemical species efflux from individual cells in real-time using Nanosensor Chemical Cytometry (NCC). Furthermore, nanosensors are encapsulated into stable hydrogels for integration into acoustic tags to track hormone levels in marine animals.

Together, the successful development of CoPhMoRe nanosensors opens new pathways for synthetic molecular recognition that enables the detection of biological macromolecules, and holds great promise for life science applications.

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