Docket #: S24-491

Enhanced Detection of Drug-Protein Interactions in Live Cells Using IR Spectroscopy

Stanford scientists in Prof. Steven Boxer's lab have invented a quantum cascade laser (QCL)-based IR spectrometer and assay for the sensitive detection of drug-protein interactions in live cells. This technology enhances the limits of detection for in-cell IR assays, allowing direct and non-perturbative measurement of small molecule-protein interactions using vibrational spectroscopy.

Most current methods for detecting drug binding to proteins mainly rely on in vitro techniques or indirect measurements through cellular physiological responses. These methods often fail to provide direct, quantitative insights into molecular interactions and can be limited by the need for fluorescent or chemiluminescent labels, which may perturb the binding process.

Stanford researchers have developed a QCL-based IR spectrometer capable of directly measuring vibrational probes in live cells, drastically improving the sensitivity and reducing the limit of detection for test nitrile compounds from 80 μM to 16 μM. This novel technology addresses the limitations of luminescence and fluorescence-based techniques by providing non-perturbative, direct measurements of small molecule-protein interactions with significantly enhanced sensitivity and signal-to-noise ratio. The use of nitrile vibrational probes offers precise information on binding sites, allowing for accurate and detailed analysis of drug-target interactions within their native cellular environments.

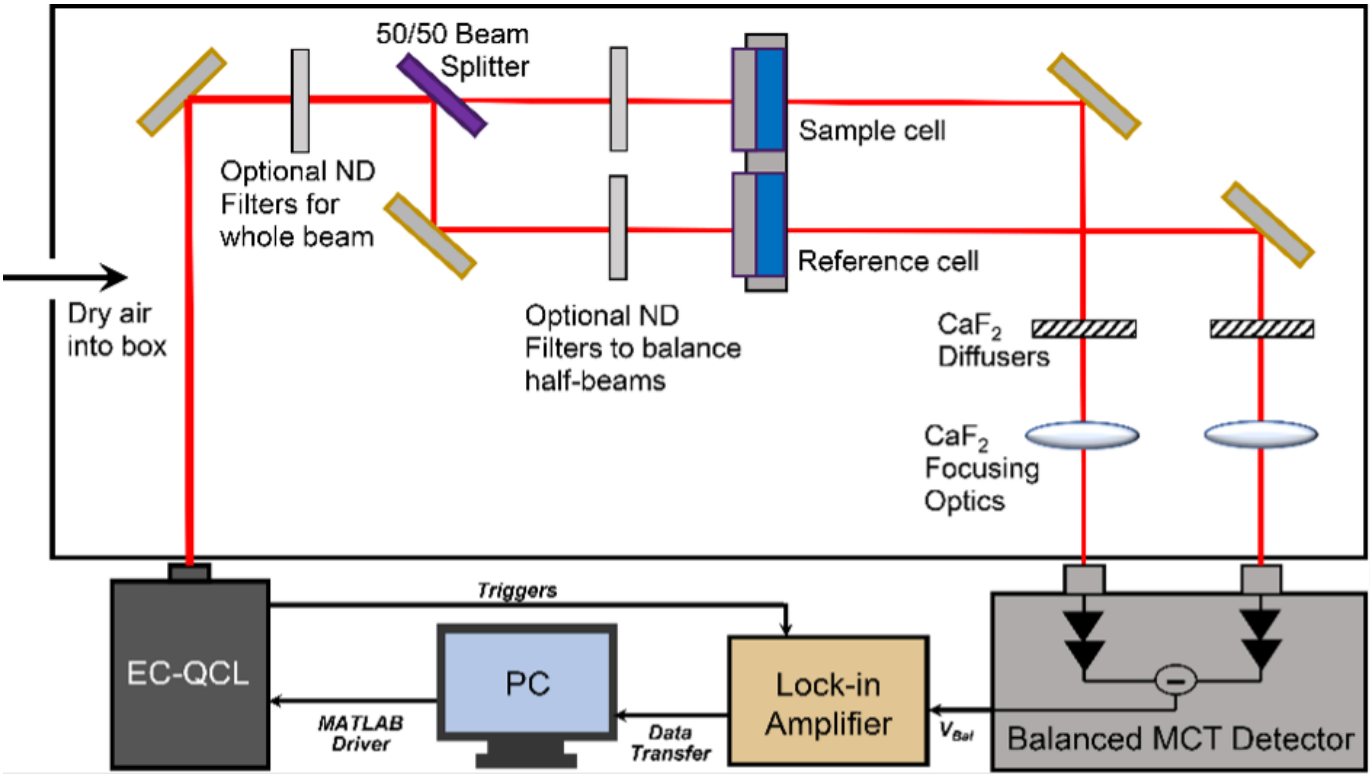


Figure Description: Instrument block diagram for the double-beam, QCL-based mid-IR spectrometer.

Stage of Development:
Proof of concept in bacterial cells

Applications

- Real-time drug-protein interaction analysis in live cells
- Early to mid-level drug development screening
- Study of small molecule binding to membrane proteins

Advantages

- **Five-fold higher sensitivity:** Reducing the detection limit of a nitrile test compound from 80 µM to 16 µM
- **Better signal-to-noise ratio**
- **In-cell detection:** Overcoming limitations of separative and in vitro methods
- **Direct, non-perturbative measurement:** No need for fluorescent labels

Publications

- Mukherjee, S., Fried, S. D. E., Hong, N. Y., Bagheri, N., Kozuch, J., Mathews, I. I., Kirsh, J. M., & Boxer, S. G. Covalent drug binding in live cells monitored by mid-infrared quantum cascade laser spectroscopy: Photoactive yellow protein as a model system. *Journal of the American Chemical Society*, 2025. https://doi.org/10.1021/jacs.5c14498

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