SRS Pharmacokinetic Tomography

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Conflict of Interest

Conor Evans holds patents on technologies related to Coherent Raman Imaging that have been licensed to both Leica and Zeiss

Acknowledgments

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Pharmacokinetics

- A central concern in drug development is that a drug reaches its intended target
- Challenging for topical and transdermal administration
- Radiographic methods (e.g. MARG) give uptake, but not dynamics
- Modifications to drugs for tracking (e.g. fluorescence) often fundamentally alter pharmacokinetics
- Ideally, would aim to follow drug uptake in subjects, not model systems

Our goal is to overcome this limitation and create quantitative optical imaging methods

Coherent Raman Scattering (CRS) Microscopy

Imaging based on intrinsic vibrational contrast

Two Colors: ω_p "Pump"

ω_s "Stokes"

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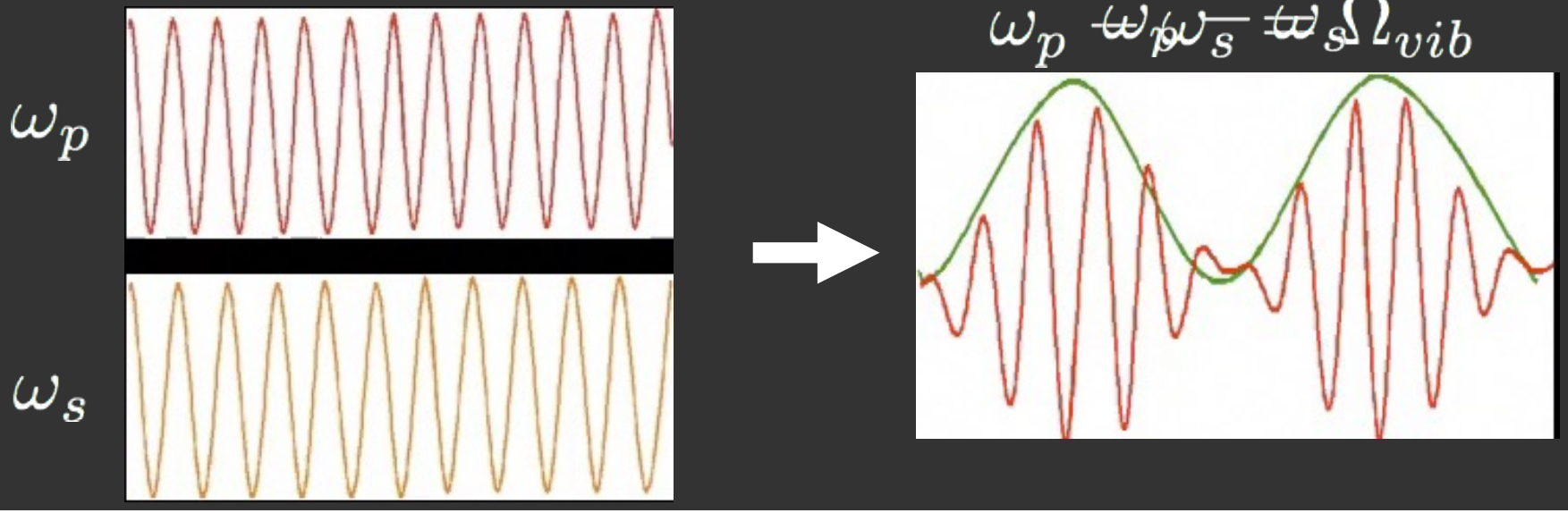
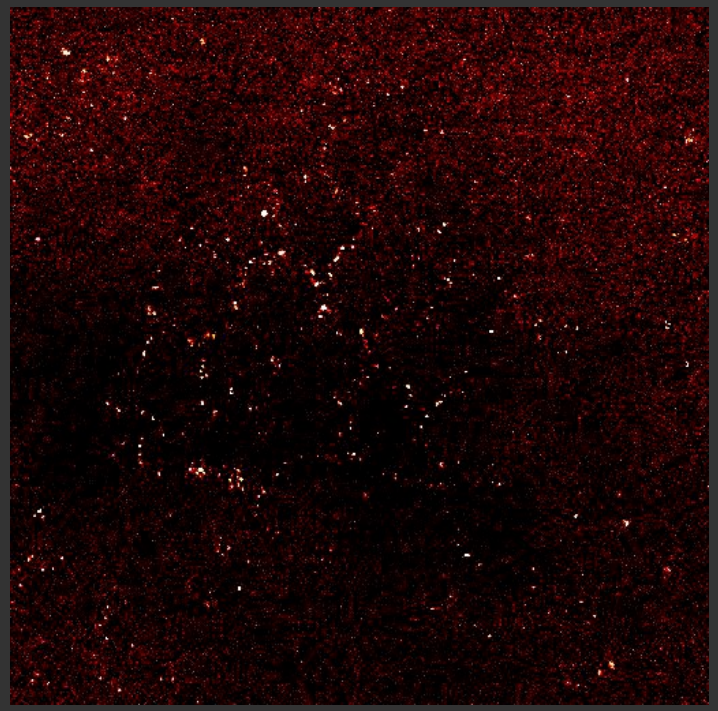
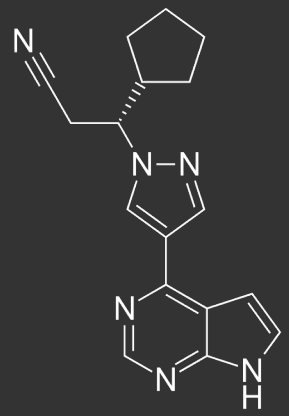


Drug Uptake Dynamics in the Stratum Corneum

SRS Microscopy
Nitrile Stretch: 2250 cm-1
100% resonant signal
120 min



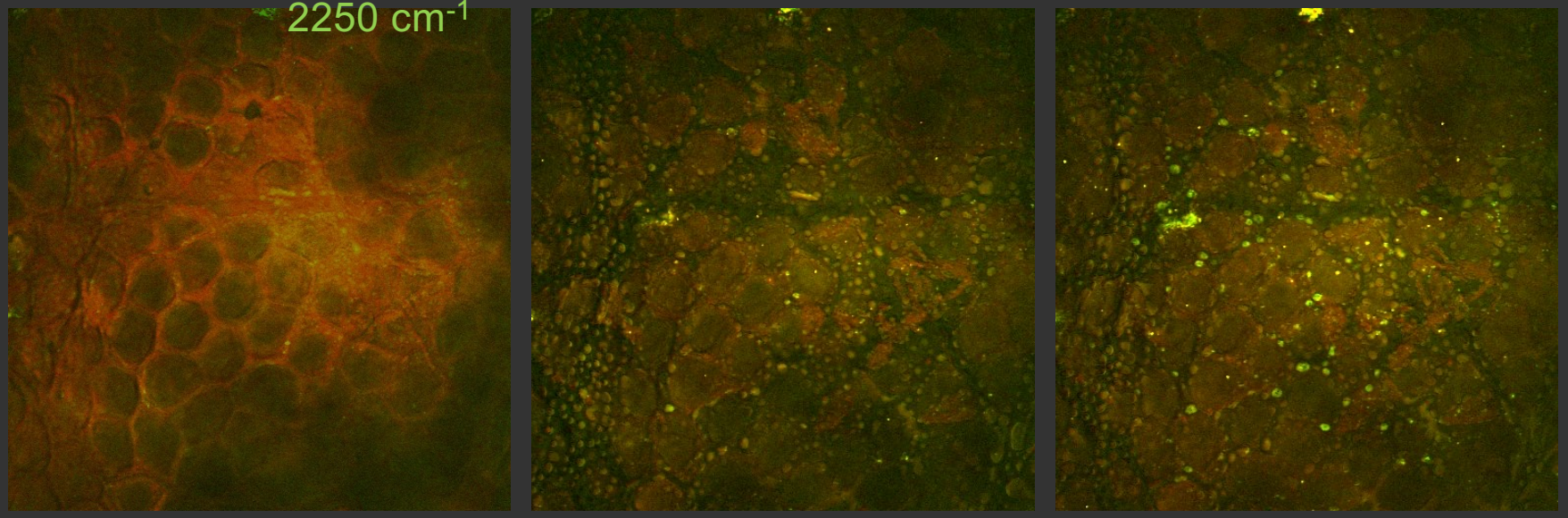


Direct visualization of Rux depositing on the surface of skin without background signal

Drug Uptake Dynamics in the Stratum Corneum

Red: Lipid 2845 cm^{-1}
2250 cm^{-1}

Green: Nitrile



15 min **70 min** **120 min**

Observe the formation of “particles” at the lipid junctions between corneocytes (Drug in EtOH, drug in delivery gel)

Observing deposition/metamorphosis occurring at the hydrophobic lipid interface

Towards a General Method for SRS PK Tomography

Few drugs have a single unique peak in the silent region
The majority of drugs do not have any unique spectral bands

But almost every drug has a unique Raman spectrum

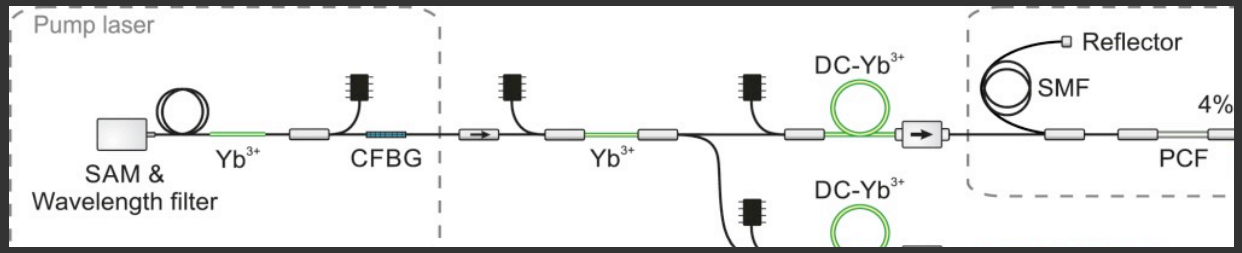
Identifying and quantifying drugs requires a means of acquiring spectral data

BUT

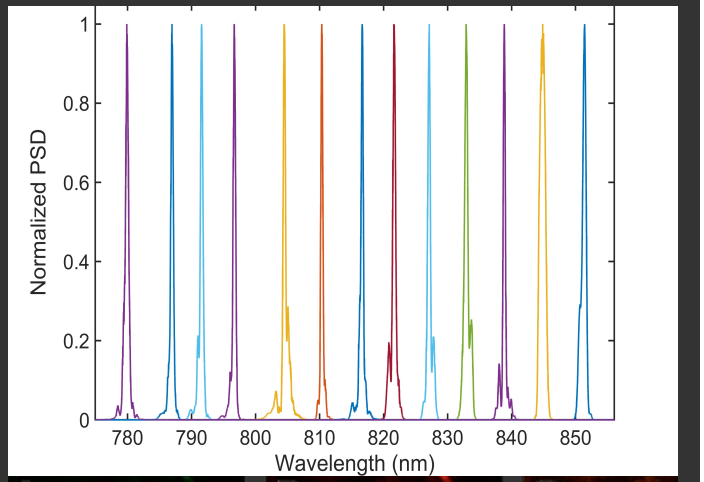
- Hyperspectral acquisition must be FAST (< 5s per spectral image)
- Hyperspectral acquisition must be broad – across the ENTIRE Raman spectrum

New Fiber Laser for Imaging

- All fiber-OPO offers stable dual output and rapid (<5ms) wavelength tuning from 500 – 3200 cm^{-1} via changing the pump laser repetition rate – *electronic adjustment*
- *5 ms per wavelength jump*
- >100 mW output powers for both pump and Stokes beams
- 19” RU enclosure for direct mounting & compactness

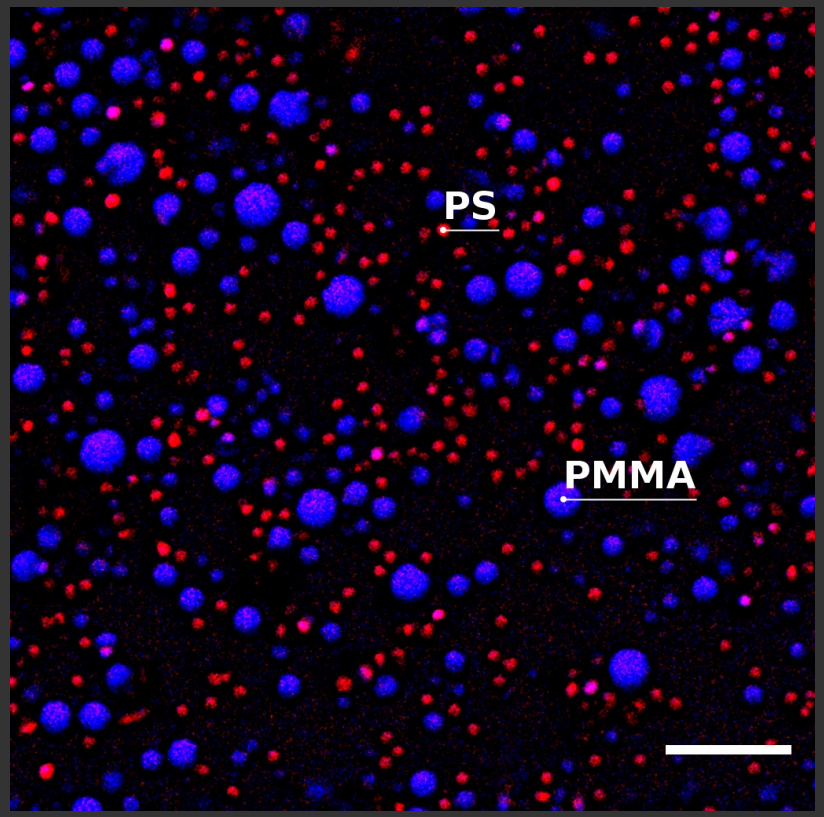


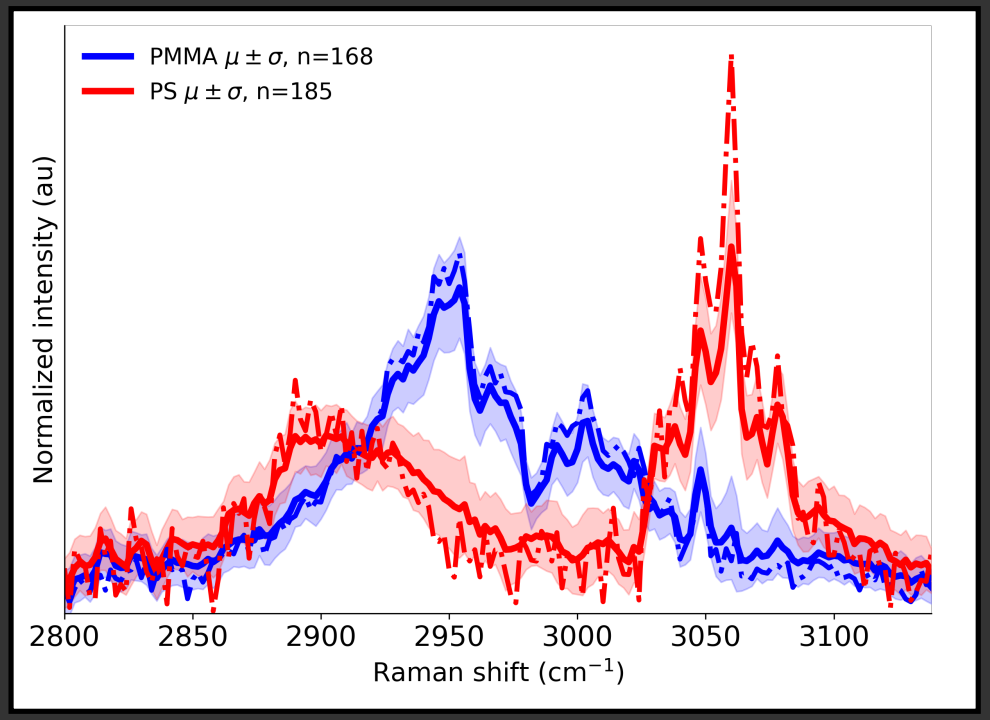
Maximilian Brinkmann, *et al.*, "Portable all-fiber dual-output widely tunable light source for coherent Raman imaging," Biomed. Opt. Express 10, 4437-4449 (2019)



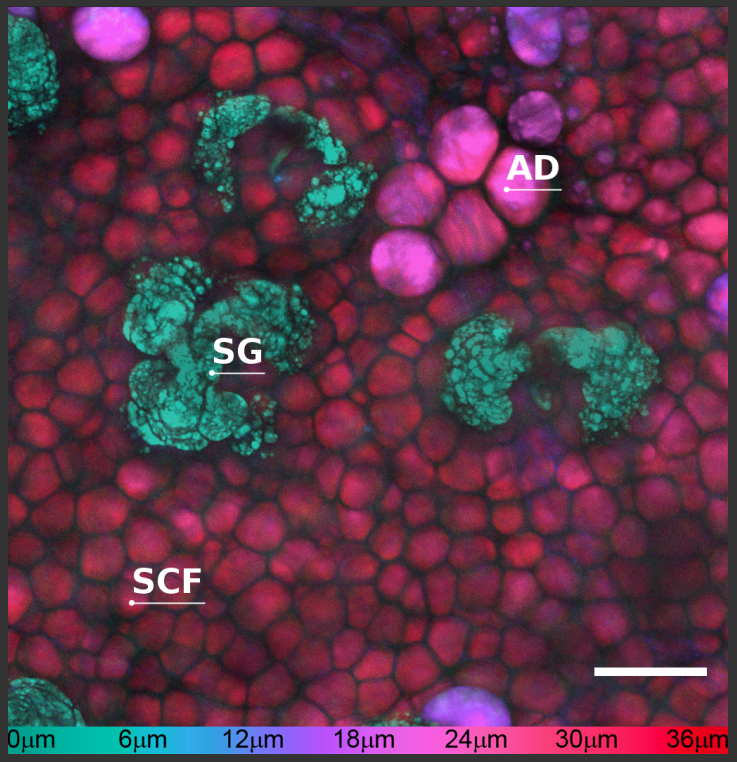
Images of human sebaceous gland from 30 m thin skin tissue sections. (a) CARS image obtained by tuning to 2845 cm^{-1} (symmetric CH_2). (b) CARS image obtained by tuning to 2934 cm^{-1} (asymmetric CH_3). (c) Merged two-color image from (a) and (b) revealing heterogeneous distributions of lipids (green/yellow) and proteins (orange/red).

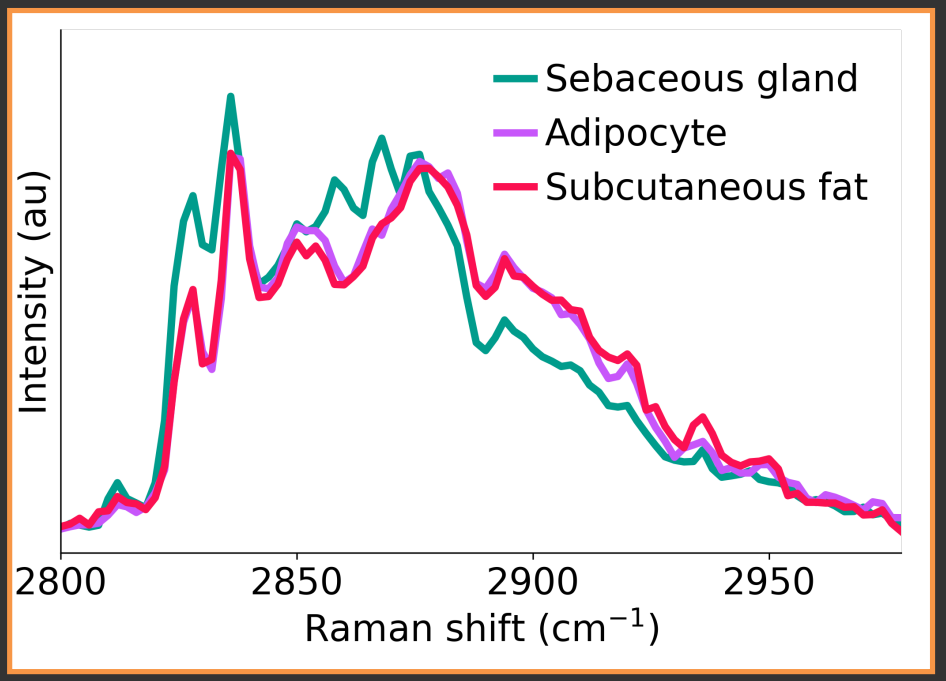
Hands-Off HyperSpectral SRS



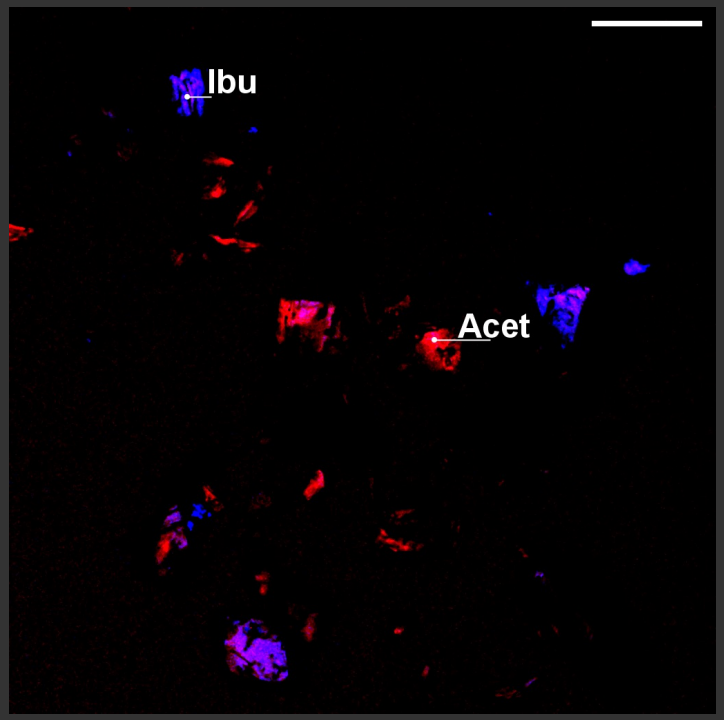


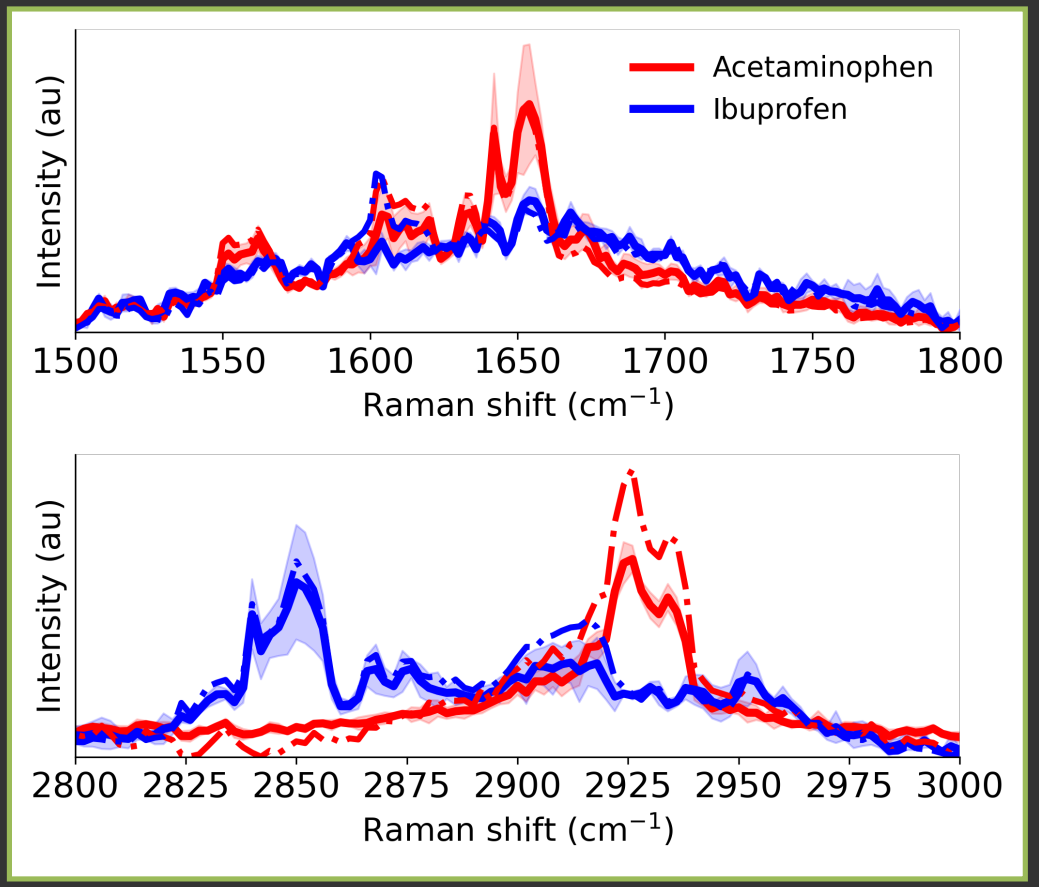
Hands-Off HyperSpectral SRS





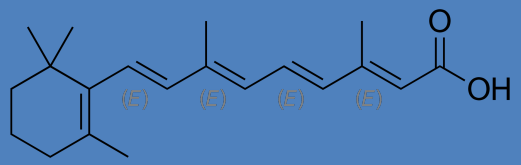
Multi-Window Hyperspectral SRS



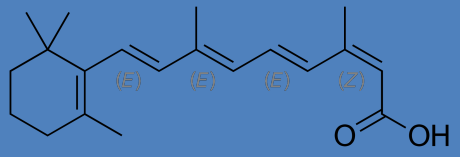


Distinguishing between different APIs

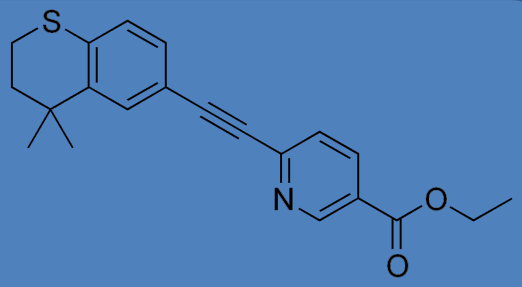
Tretinoin

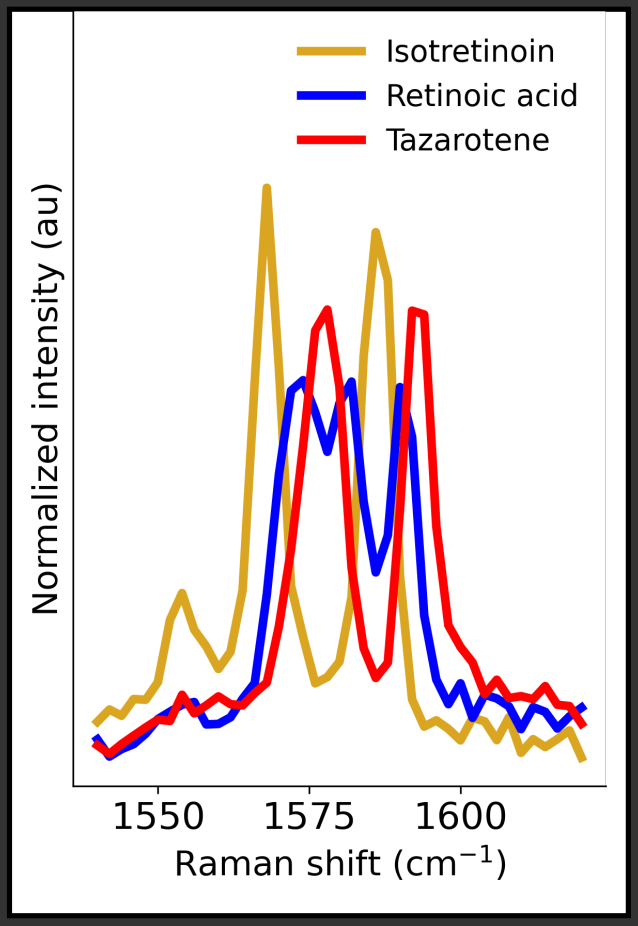


Isotretinoin



Tazarotene





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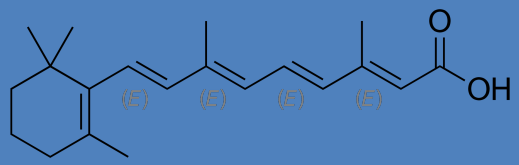

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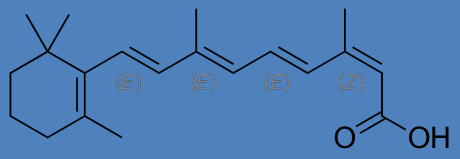
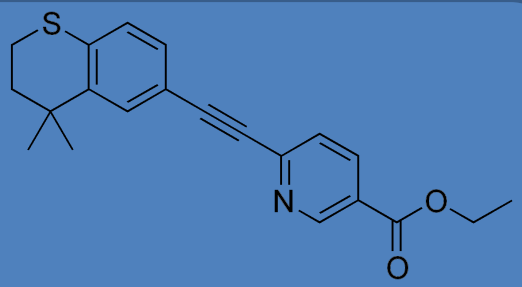
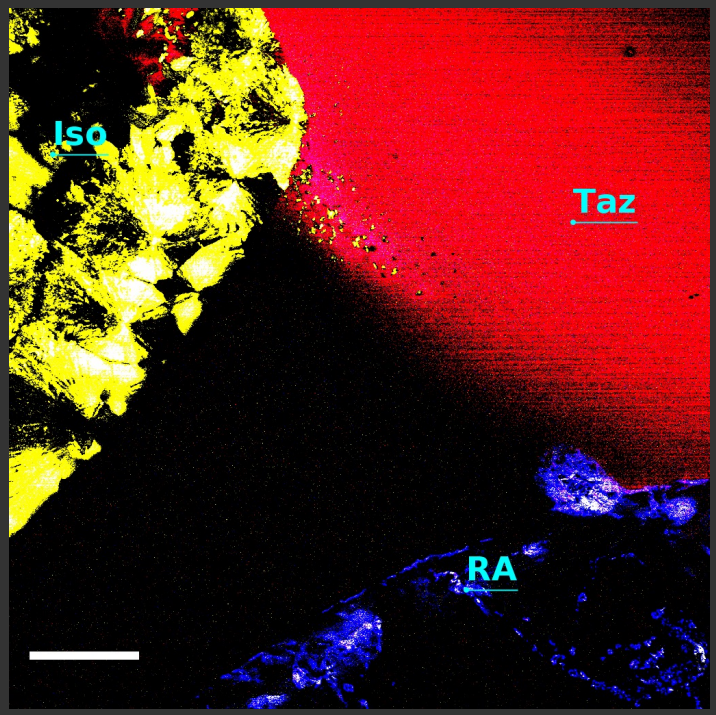


Tazarotene





Sparse Spectral Sampling SRS – S4RS

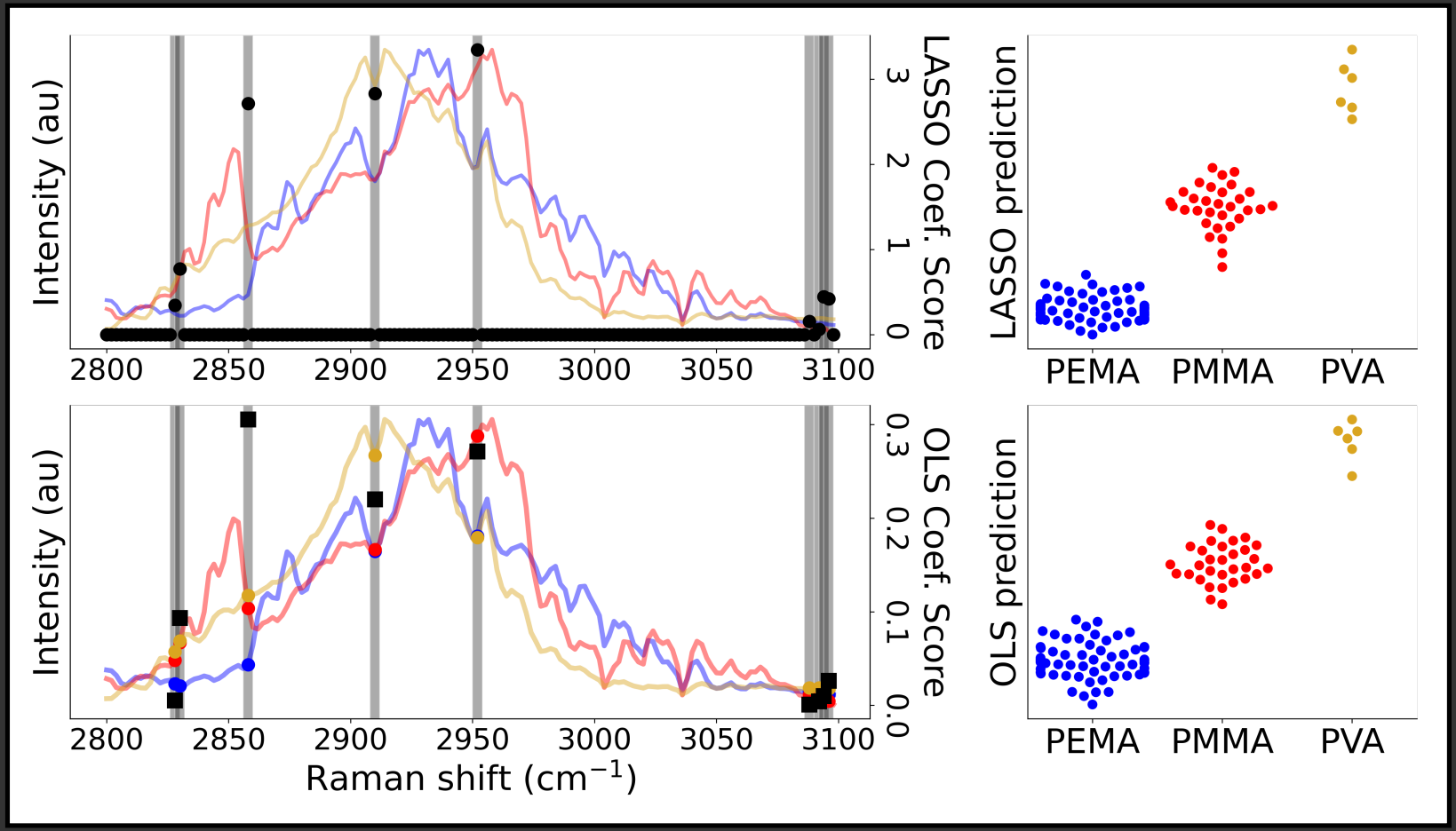
This hyperspectral approach enables multi-window rapid acquisition of Raman spectral data

BUT acquiring spectra is still too slow!!!

Can we instead *sample* the Raman spectrum so that we can distinguish and quantify specific molecules?

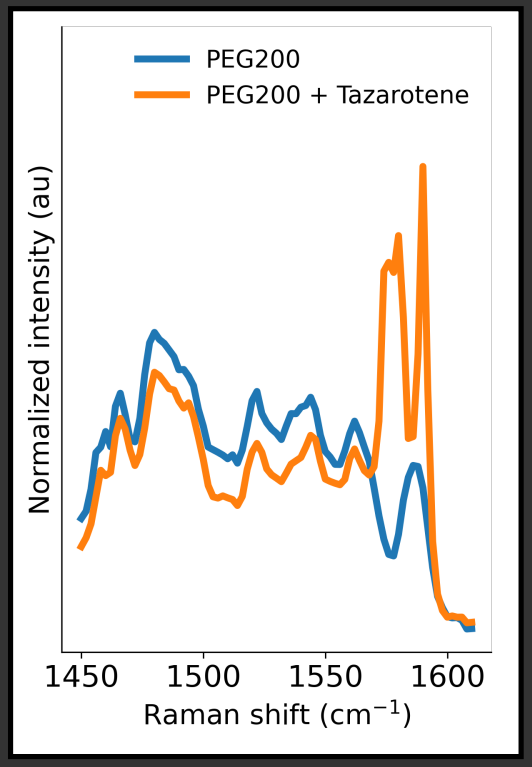
Sparse Spectral Sampling SRS

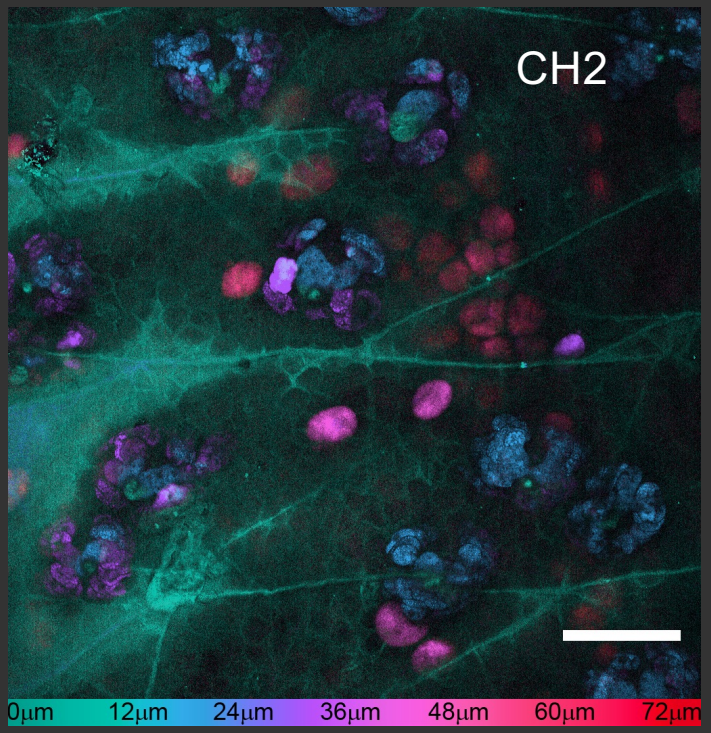
Sparse Spectral Sampling SRS – S4RS



Multicomponent PK Imaging with S4RS

Dynamically acquire S4RS data at specific Raman shifts
Allows selective imaging of: lipids, tazarotene, PEG200





Multicomponent PK Imaging with S4RS