A High Throughput Spectroscopic Dosimeter for Simultaneous Measurement of Singlet Oxygen and Photosensitizer during PDT Treatment

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Presentation Outline

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- **Background of PDT and production of singlet oxygen**
- **Historical perspective of singlet oxygen detection**
- **Design considerations for a high-throughput singlet oxygen luminescence spectrometer**
- **Data on system characterization and *in-vivo* study**
- **Summary and outlook**

Background

- **Photodynamic Therapy (PDT) is a promising modality for cancer treatment. Oxygen molecules in the metastable singlet delta state $O_2(^1\Delta)$ are key to cancer cell destruction.**

- **Currently, it is difficult, if not impossible, to predict the response of an individual to PDT. This has inhibited the acceptance of PDT for clinical uses.**

- **A real-time dosimeter for singlet oxygen would be a valuable tool both for PDT researchers and clinicians.**

- **A singlet oxygen dosimeter for cw mode PDT remains largely unavailable**

Production of Singlet Oxygen

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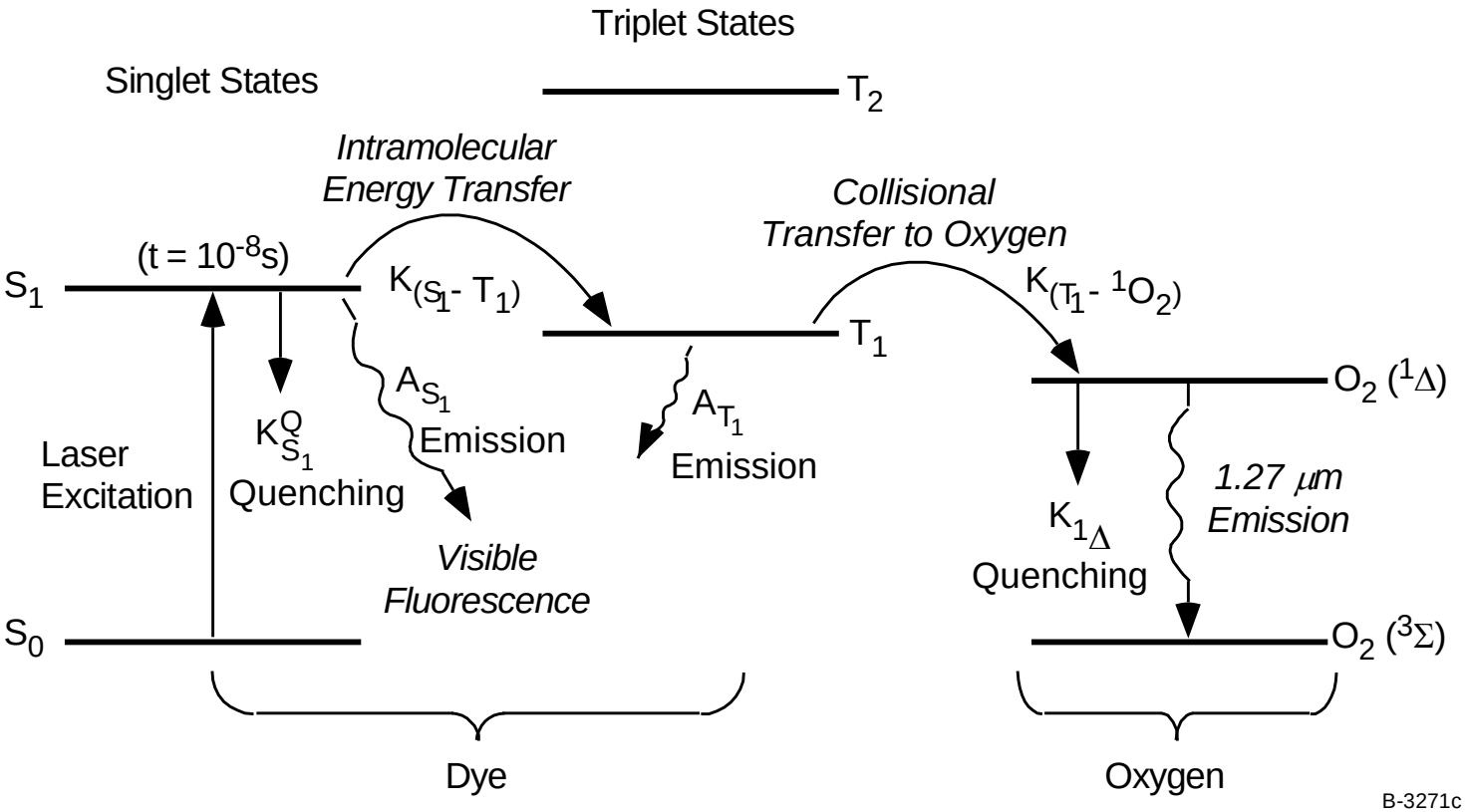
Type II PDT Mechanism



"Prompt" dye fluorescence
+
Energy Transfer

Singlet Oxygen luminescence

Time-resolved Detection for Singlet Oxygen

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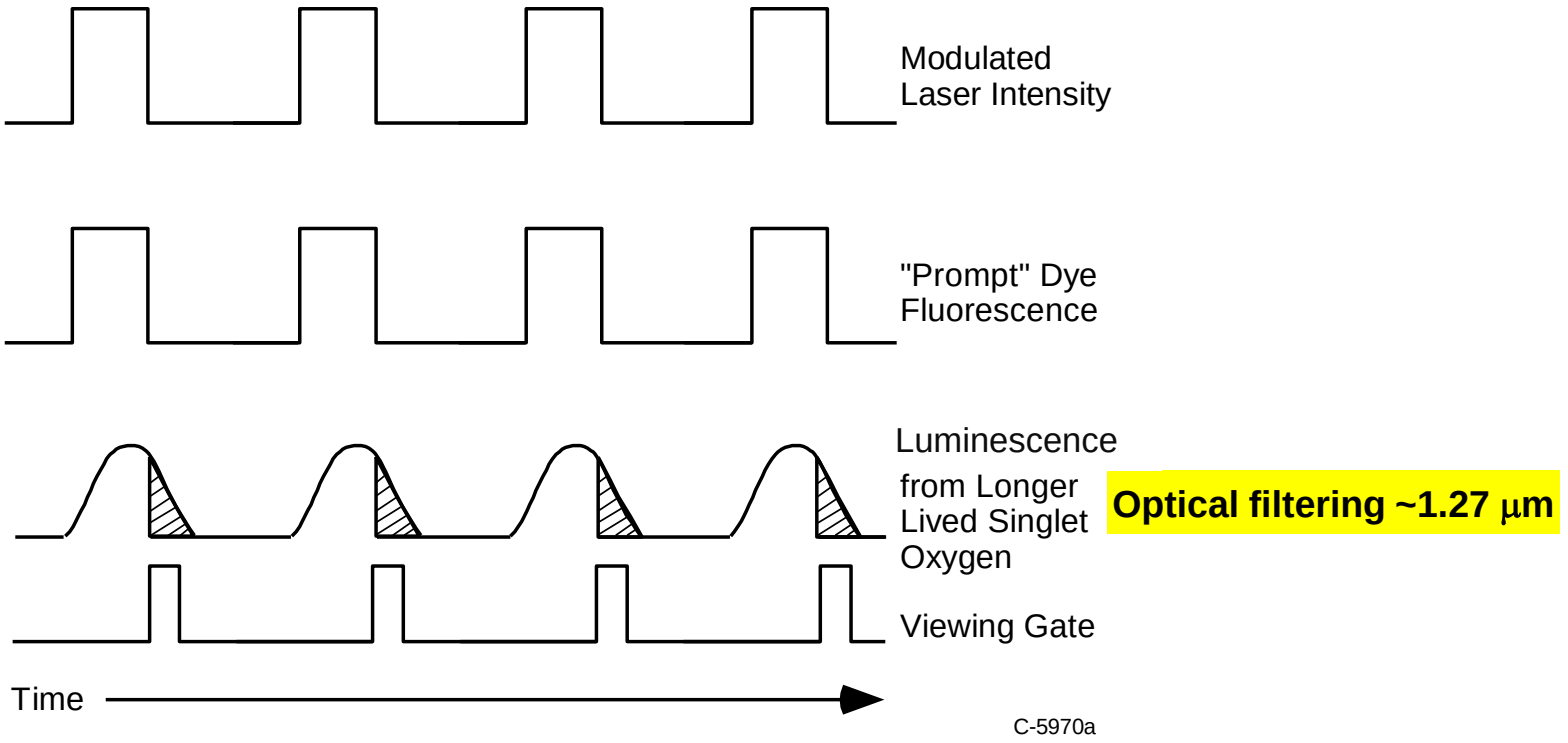
- **Pulsed Diode Laser → "Prompt" Dye fluorescence**
- **Photon Counter with optical filtering → Singlet Oxygen Monitor**



Not applicable to PDT investigations using cw light

Spectral Discrimination of Singlet Oxygen from PS

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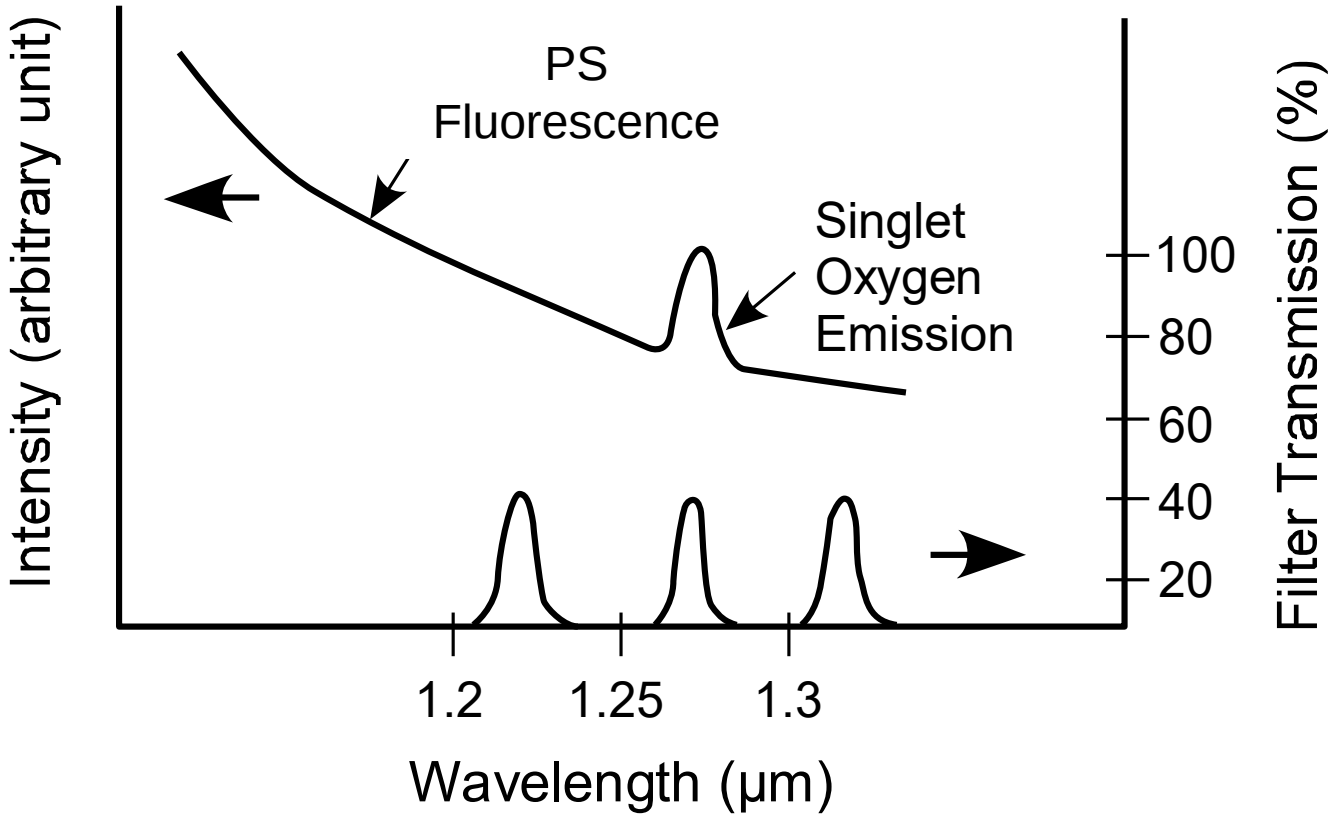
Use bandpass filters to extract the singlet oxygen signal from the PS



Crucially important for cw PDT dosimeter

PS and Singlet Oxygen Spectrum from a Mouse 7 minutes after Injection of BPD (2mg/kg) Laser Power: 39 mW

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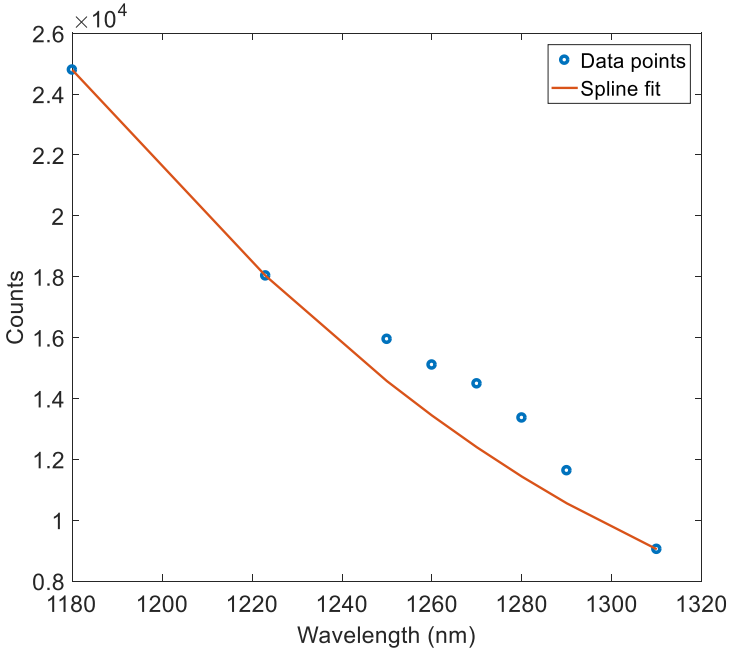

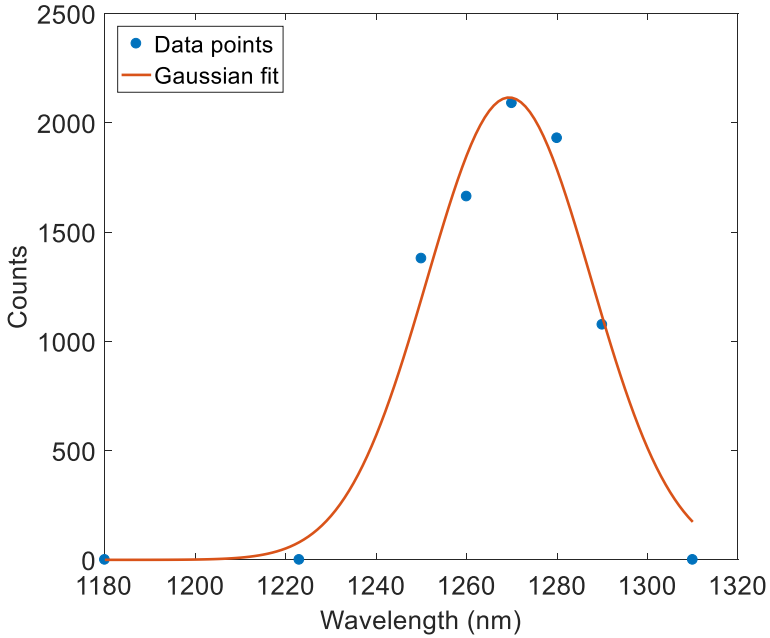

- **Large measurement variations associated with PS baseline fitting**
- **Collection of more spectral data points reduces fitting uncertainty**
- **Sequential spectroscopy approach (e.g. filter wheel) become inefficient for measurements of a large number (>10) of spectral data points**

Reduced SNR: $SNR = \sqrt{N/n}\ (n, number\ of\ spectral\ data\ points)$

Long measurement time: $T = t \bullet n$

A parallel recording spectrograph might be a better approach

Challenges and rational for designing a singlet oxygen spectrograph

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- **High photon collection efficiency (high collection NA and large collection area) is needed, which leads to the tradeoff between throughput and spectral resolution**

  Solution: high spectral resolution is unnecessary (traded for high throughput)

- **High sensitivity and large area array detector**

  Solution: high QE and deep-cooled InGaAs cameras are commercially available

- **Potential motion artifacts in in-vivo measurement**

  Solution: a non-imaging device may be clinically viable

2-D camera based spectrometer

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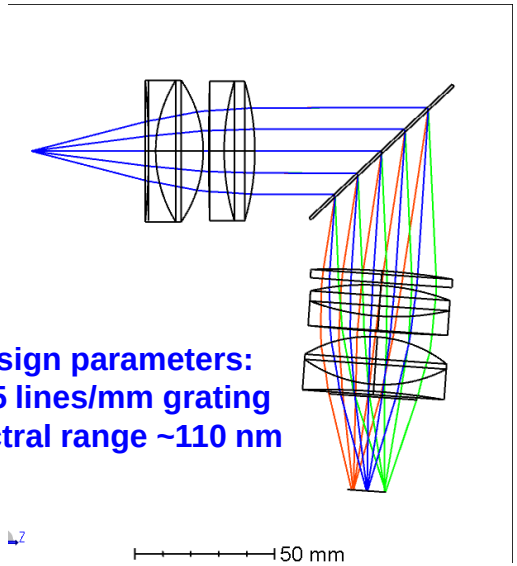
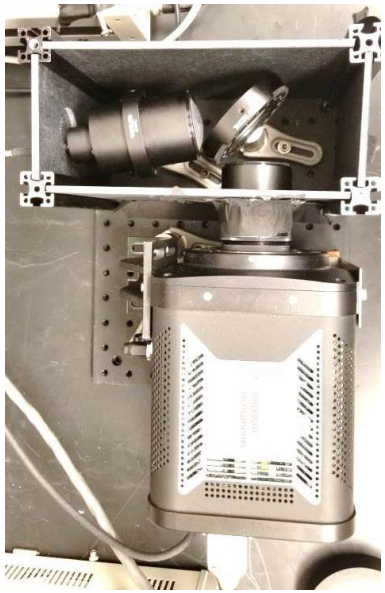
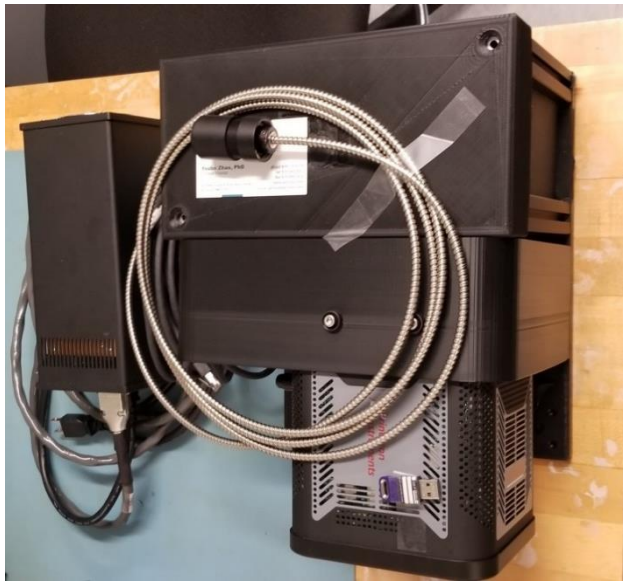


Design parameters:
1145 lines/mm grating
Spectral range ~110 nm





- **Large collection NA (f#1.6) and a 3 mm collection fiber**
- **2-D camera with a 12.8 x 10.2 mm sensor (512x640 pixels)**
- **Simultaneous measurement of multiple wavelengths**
- **Simple, compact, and easy to operate**

System aberration and numerical correction (observing an Ar lamp)

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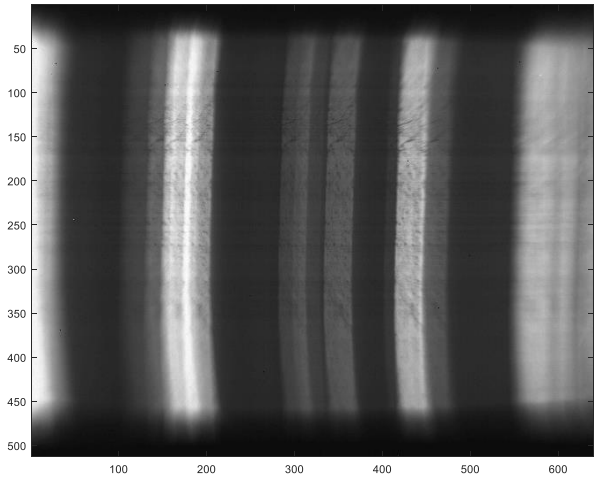
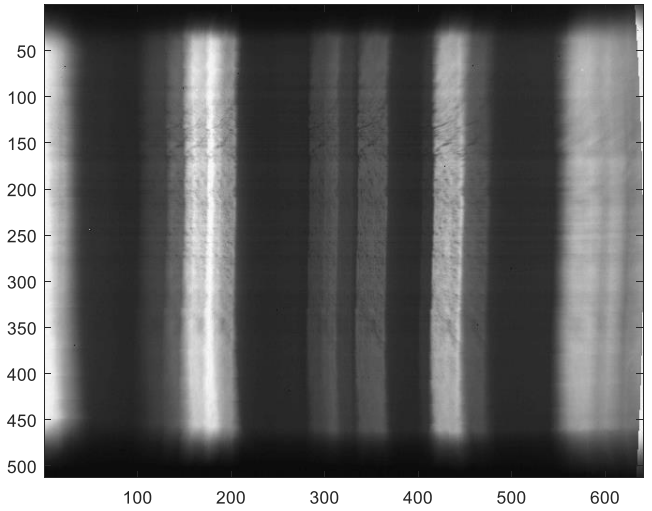
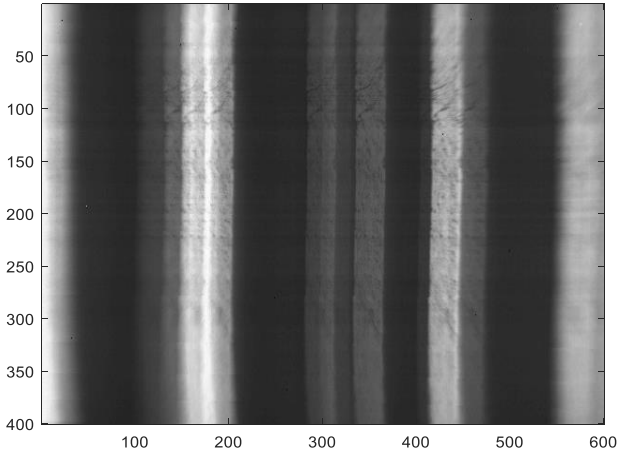
Raw image



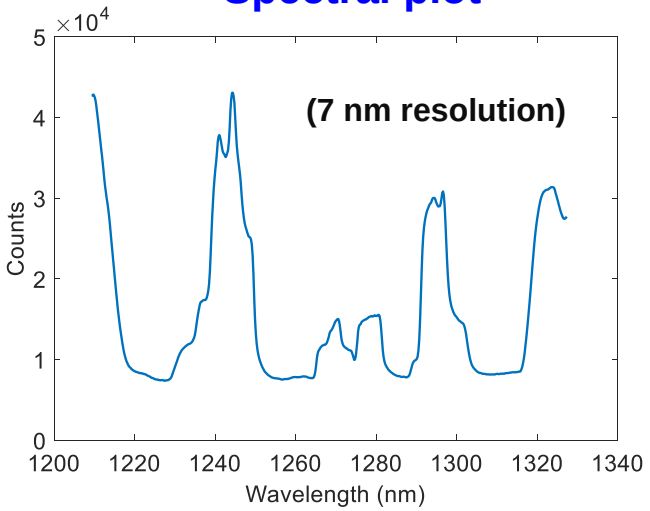
De-warping processed image



Cropped image



Spectral plot



10 µM BPD in methanol, 30 s integration

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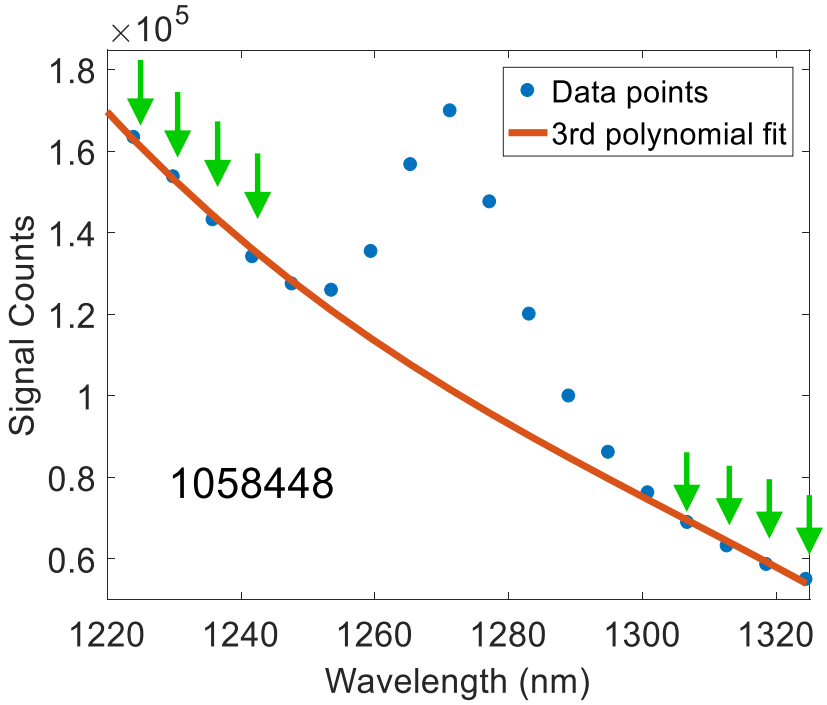
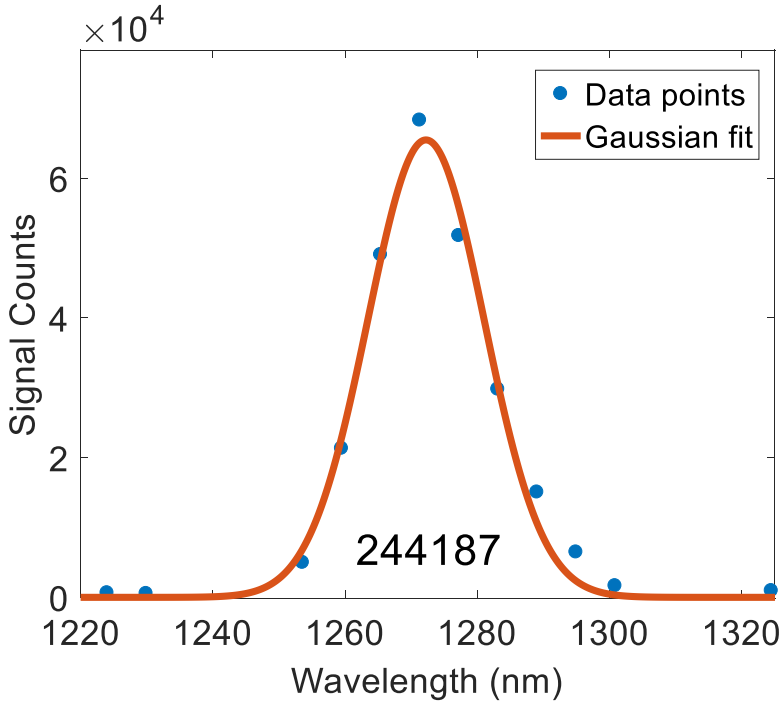
Wavelength pixel binning is used to the smooth the spectra





In-vivo data from a mouse measured during PDT treatment

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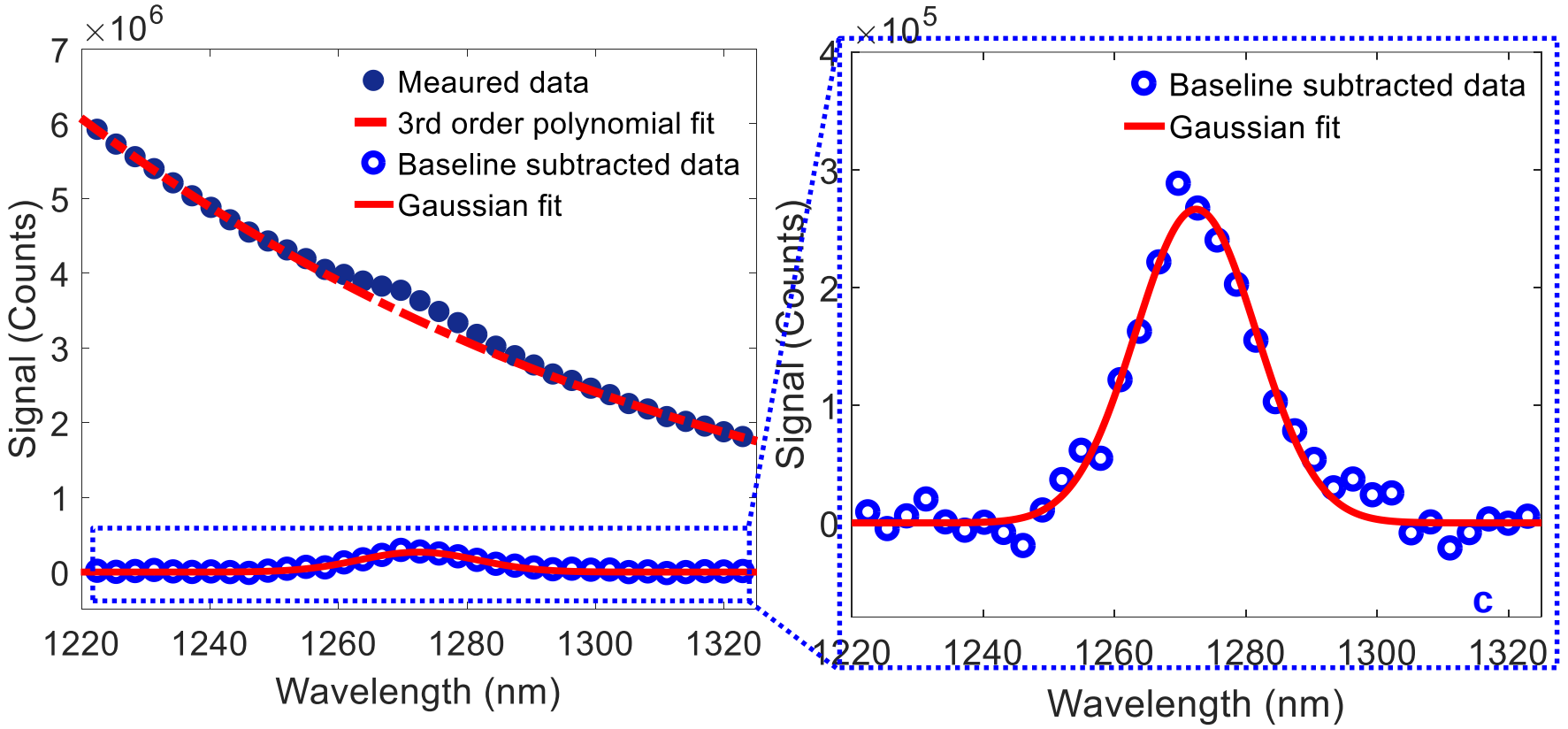

SNR of singlet oxygen "area" > 30:1

Tumor growth inhibition results for a treated and an untreated control mouse

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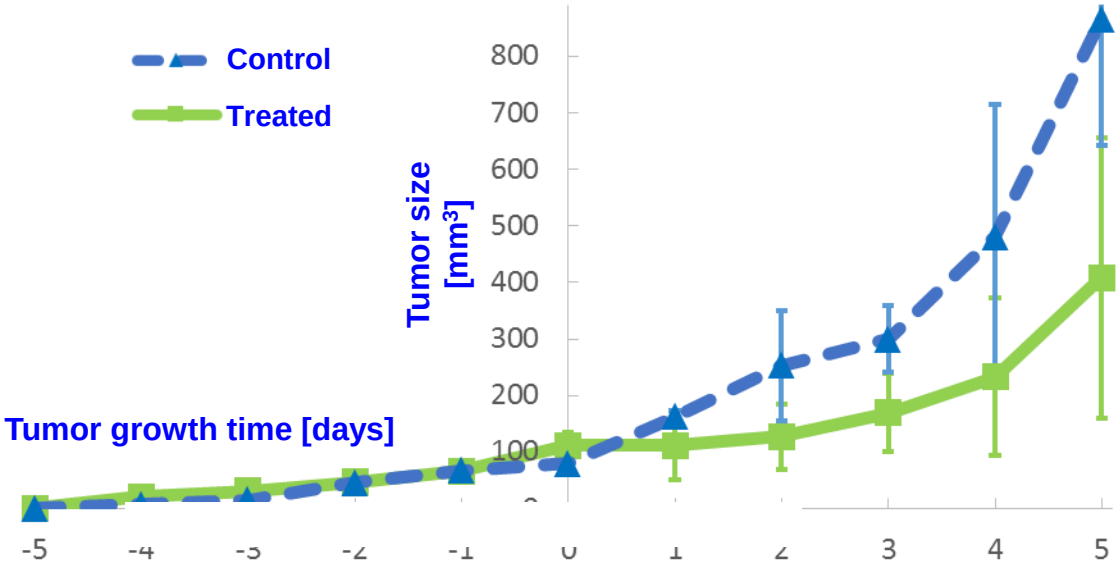
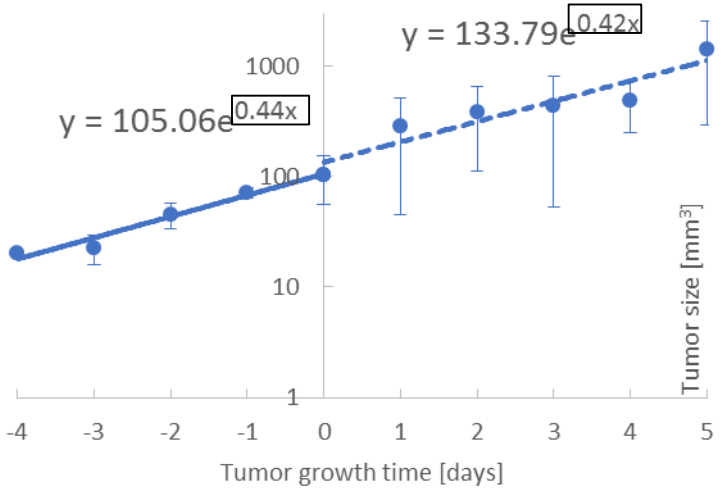
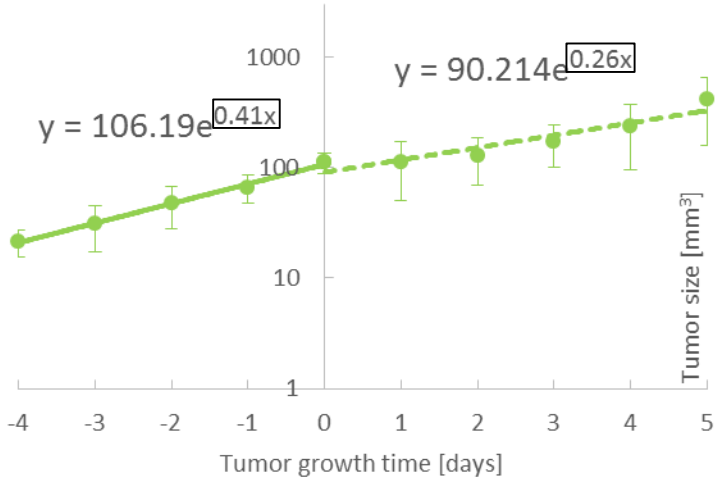




Control avg



Treatment avg

Correlations of tumor growth inhibition (BPD) with PS and $^1O_2$

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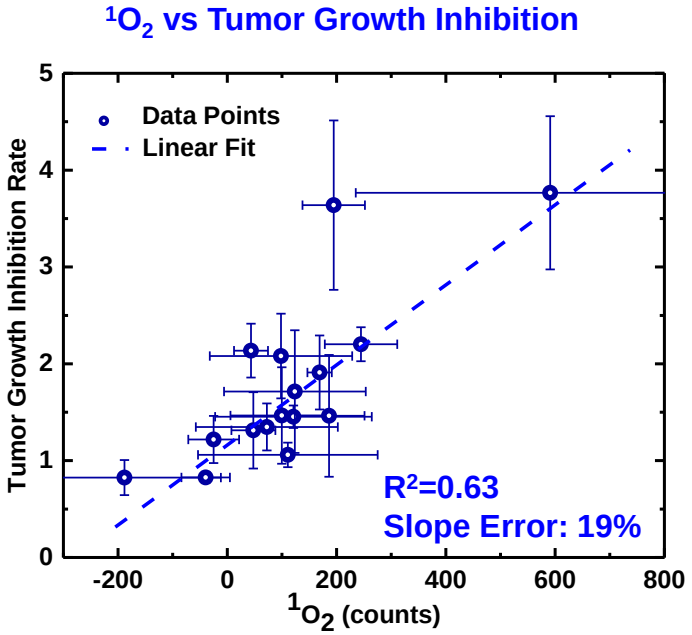

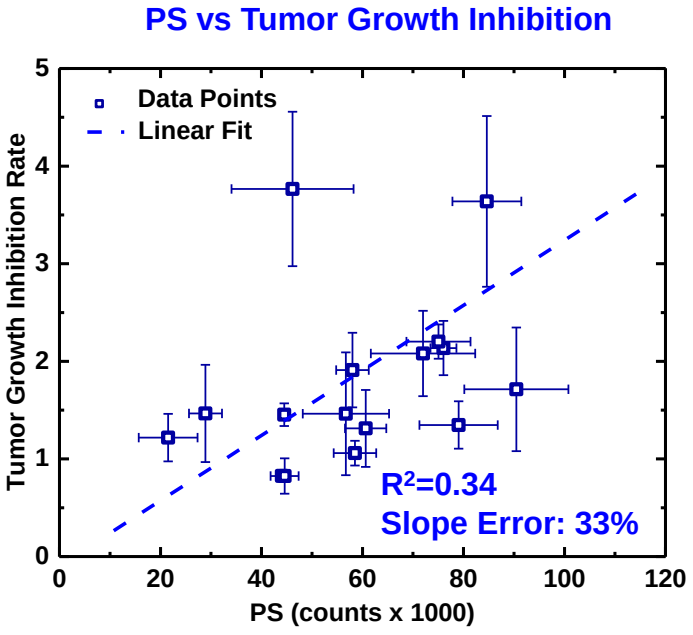

Inter-sample variations

	PS (Control)	PS (Treatment)	$^1O_2$ (Control)	$^1O_2$ (Treatment)	Tumor Growth Inhibition (Control)	Tumor Growth Inhibition (Treatment)
Mean	38662.42	65511.28	-33.00	165.11	1.08	2.01
STD	11436.39	17416.00	126.43	147.62	0.31	0.87
Variation	0.30	0.27	3.83	0.89	0.29	0.43

Better correlation of $^1O_2$ with tumor regression

Correlations of tumor growth inhibition (VisuDyne) with PS and $^1O_2$

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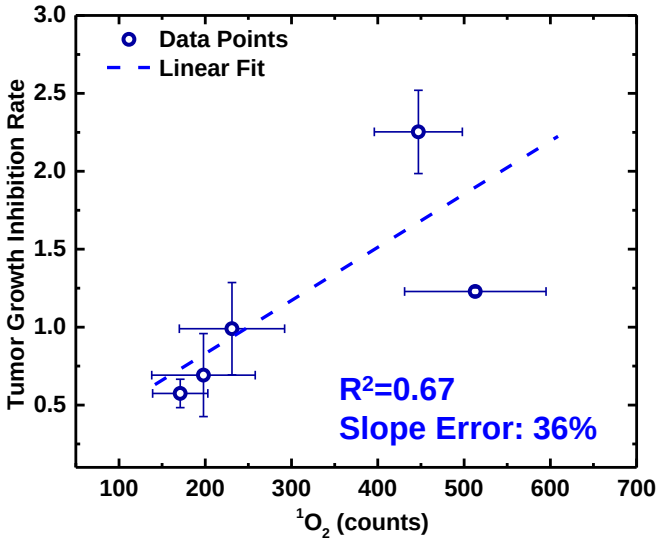
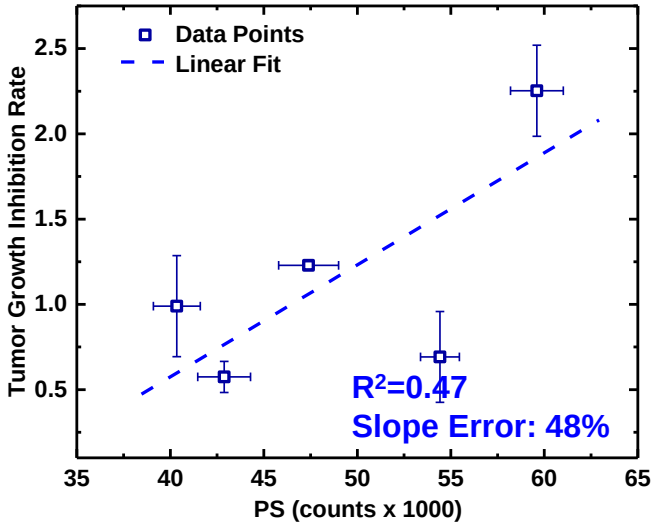
$^1O_2$ vs Tumor Growth Inhibition



PS vs Tumor Growth Inhibition



- **Tumor growth inhibition correlates better with $^1O_2$, which further supports the conclusion that the variations in $^1O_2$ is real biology phenomenon. This demonstrates the $^1O_2$ dosimetry is more definitive than PS only dosimeter.**

In-vivo Measurements of PS and Singlet Oxygen

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- **Simultaneous measurements of multiple spectral bands with high light collection efficiency and improved SNR**
- **Simultaneous measurements of both PS fluorescence and singlet oxygen luminescence**
- **Large variations in singlet oxygen correlate with inter-animal treatment variations**
- **Single shot measurement with adequate SNR is attainable within ~30s**

Summary

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- **Successful development of a singlet oxygen spectrometer applicable for PDT treatment using a cw laser**
- **Preliminary demonstration during in vivo animal experiments**
- **Continued animal study is ongoing.**
- **Next step will be to reduce the system cost and potentially include time-gated measurement capability.**

Acknowledgement

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