Signal, noise, detectors

This discussion is centered on the luminometer application in collaboration with Jim Wells' lab using split luciferase to detect covid spike and N-protein using antibodies.

Luciferase signal expectations

- A single firefly luciferase enzyme generates about 0.6 photons/s (kcat = 1.6/s, QE = 0.4): https://bionumbers.hms.harvard.edu/bionumber.aspx?s=n&v=1&id=111084
- Although, this paper reports that the k_cat per enzyme is 38 / s, meaning that each enzyme can produce at most about 40 photons/s in optimal (flash) conditions.
- Nanoluc, the enzyme used by the Wells lab, is reported as being 150x brighter than firefly luciferase, and emits at 475 nm
- The relevant signal range, as provided by Susanna, is represented by 1 pM down to 1 fM enzyme concentration.

Detector Sensitivity and noise floor

As a first try, I'd like to go with the OPT101:

- Decent detector size
- Decent sensitivity
- Integrated amplifier
- Low-cost ($8)
- Incredibly low dark current (2.5 pA)

There are other detectors that are blue-enhanced and larger area. These will bring us more detection area (better collection) but at the cost of more dark noise. I've looked around and there are a few other options, but I have not found any that are anywhere near as cheap, and also there are hardly any that have these features and are pre-amplified. I would strongly prefer for the amplifier to be on-chip, as there is far less potential for noise corruption of the signal. That, and choosing the best amplifier is another challenge.

This was one of the most promising alternatives: http://www.osioptoelectronics.com/Libraries/Datasheets/Blue-Enhanced-Photodiodes.sflb.ashx

The blue-enhanced series has about 50% higher sensitivity as compared to OPT101, but 10x the noise effective power.

We characterize the detector sensitivity by its responsivity (0.23 A/W) at 475 nm, its quoted Noise Equivalent Power (NEP), as well as calculated dark shot noise and photon shot noise. Here are the sensor guidelines on usage in low light conditions:

8.3.3 Noise Performance

Noise performance of the OPT101 is determined by the op amp characteristics, feedback network, photodiode capacitance, and signal level. Figure 11 shows how the noise varies with R_F and measured bandwidth (0.1 Hz to the indicated frequency), when the output voltage minus the voltage on pin 3 (–V) is greater than approximately 50 mV. Below this level, the output stage is powered down, and the effective bandwidth is decreased. This decreased bandwidth reduces the noise to approximately 1/3 the nominal noise value of 300 μVrms, or 100 μVrms. This decreased bandwidth enables a low-level signal to be resolved.

To reduce noise and improve the signal-to-noise ratio, filter the output with a cutoff frequency equal to the signal bandwidth. In addition, output noise increases in proportion to the square root of the feedback resistance, while responsivity increases linearly with feedback resistance. To improve the signal-to-noise ratio performance, use large feedback resistance, if decreased bandwidth is acceptable to the application.

The noise performance of the photodetector is sometimes characterized by noise effective power (NEP), the radiant power that produces an output signal equal to the noise level. NEP has the units of radiant power (watts), or $W/\sqrt{Hz}$ to convey spectral information about the noise. Figure 12 illustrates the NEP for the OPT101.

Here is the noise floor of the OPT101 detector, without cooling and with standard gain levels:

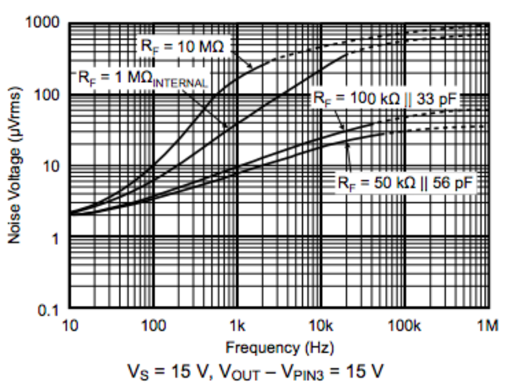


Figure 11. Output Noise Voltage vs Measurement Bandwidth

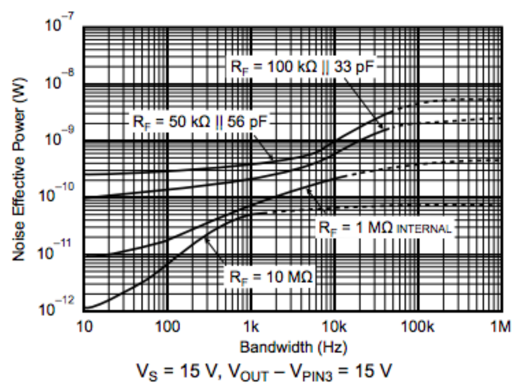
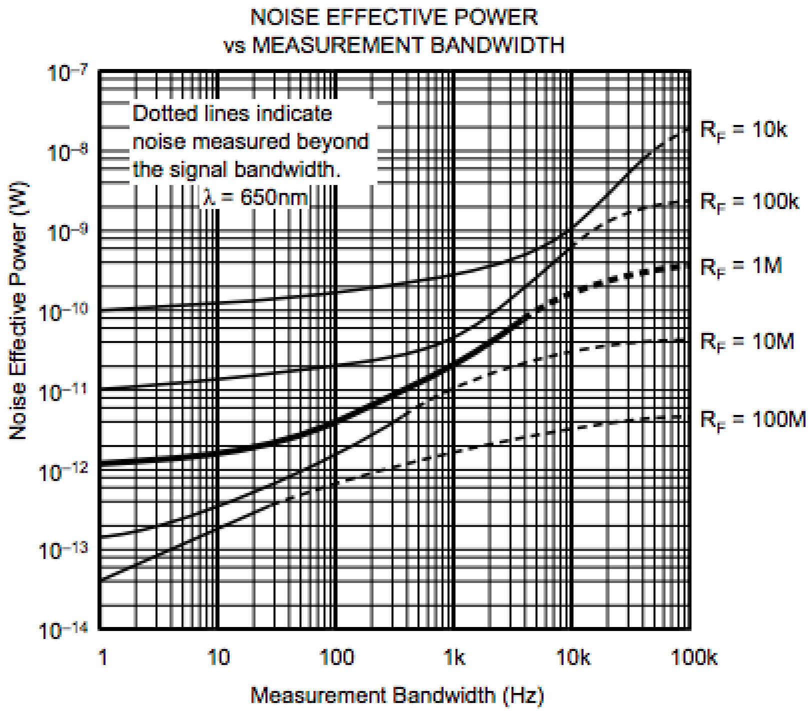


Figure 12. Noise Effective Power vs Measurement Bandwidth

- We will be using tons of gain when the light is low. The plot on the right is more relevant, with the noise effective power (NEP) being equivalent to optical power hitting the sensor.
- Our target gain is ~1GOhm, so we're expecting even lower NEP than these charts show

Actually I found this plot from OPT301, which seems to be same sensor in a different package. So indeed the NEP keeps dropping with higher gain. Our target measurement bandwidth is 1 Hz:

Correction 16 Jul 2020 : OPT301 has lower dark current than OPT101 (0.5 pA vs. 2.5 pA) and therefore superior NEP:



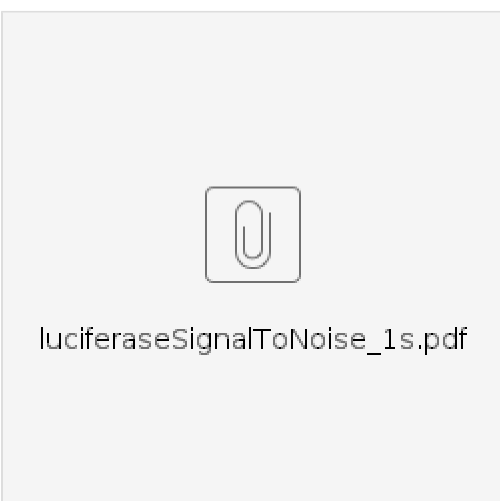
This suggests that we should be able to reduce our NEP below (4E-14) W without cooling.

Calculation of SNR based on assay parameters

@ Diane Wiener, I wrote up our SNR discussion and made some plots. SNR looks promising with this detector, even at the lower end of the concentration range. Of course, we did not add any other spurious noise sources beyond what the datasheet reports or photon shot noise.

Updated 16 Jul 2020 to correct for having used the OPT301 NEP curve, which actually has lower dark current than OPT101. I also included the ability to use longer integration times and the corresponding effect on signal averaging.

1s integration:



100 s integration:

Comparison of different detector options:

Note that the higher sensitivity of the APD with TIA is complicated by the fact that it needs an additional 100-240V low current power supply to bias the APD module, with the TIA running off a ~5V supply.

Manufacturer	Part Number	Price	Sensitivity (A/W)	Dark Current	Vsupply	Angle of Half-Max	Collection Area	Operating Temp	Onchip Amp?	Notes
Texas Instruments	OPT101	$8	0.45A/W (650nm), 0.23 A/W (475 nm)	2.5 pA	2.7 - 36	65	2.29 x 2.29mm	0 - 70C	1 MOhm	http://www.ti.com/lit/ds/symlink/opt101.pdf
Texas Instruments	OPT301M	$73	0.47 A/W	0.5 pA	2.25-18	40	2.29 x 2.29mm	-55 - 125 C	1 MOhm	https://www.mouser.com/ProductDetail/Texas-Instruments/OPT301M?qs=sGAEpiMZZMu97qiQi8P%252BuoXUuN8GQaTN1h3d%252BNU3N1Q%3D
Roithner LaserTechnik	IQ800L	$83	0.6A/W (850nm)	30 pA	18V	50	2.2 x 2.2 mm	-25 - 85C	1 / 10 / 100 MOhm	http://www.roithner-laser.com/datasheets/pd/IQ80xL-series.pdf
Osioptoelectronics	UDT-455	$106	0.6A/W (970nm)	250 pA	15V	50	2.2 x 2.2 mm	0 - 70C	1MOhm	http://www.osioptoelectronics.com/Libraries/Datasheets/Photops.sflb.ashx
Texas Instruments	OPT301	$90	0.57 A/W (650nm)	0.5 pA	2.25-18V	40	2.29 x 2.29mm	-55 - 125 C	1MOhm	http://www.ti.com/lit/ds/symlink/opt301.pdf
AMU	TSL257	$2.60	0.19 A/W (565 nm)	47 pA	2.7 - 5.5	40	2.5mm^2	0 - 70C	320 MOhm	https://www.mouser.com/ProductDetail/ams/TSL257LF?qs=sGAEpiMZZMu97qiQi8P%252Buu0TPzLWvl5iBsLtTUHfKSZBLiCePG2Djw%3D%3D
First Sensor	3001225 (not amplified)		0.32 A/W (475 nm)							https://www.first-sensor.com/en/products/optical-sensors/detectors/pin-photodiodes/series-6b-blue-green-sensitive-photodiodes/
APD with TIA										
First Sensor	5000041 - Integrated APD	$200	60 A/W (905 nm)	0.1nA	100-240 V		0.196 mm^2	0 - 60 C	20kOhm	https://www.mouser.com/ProductDetail/First-Sensor/5000041?qs=qSfuJ%252Bfl%2Fd7w11F97Kdj%2FQ%3D%3D