# Design requirements for integrated biosensor arrays

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## ABSTRACT

Miniaturization and integration of biosensor platforms is appealing due to smaller reaction volumes, larger numbers of detection sites and integration of various functionalities. Proper design of integrated biosensors is crucial in such systems due to limitation in resources such as power, chip area and cost. The optimal design involves determining the required sensor metrics and achieving these metrics with minimum use of the available resources. The system-level requirements of various biosensor arrays are discussed in this paper. We will show here, that while in certain applications, the best sensor performance in terms of signal-to-noise ratio (SNR) or dynamic range (DR) is desirable, in others, these metrics can be traded off with power, area and ease of design and implementation. As a practical example, the design of a high DR sensor array for bioluminescence detection is considered. Various high DR schemes are qualitatively compared in order to determine the advantages and disadvantages of each scheme in terms of SNR and power consumption. Two schemes are shown to be most suitable for such applications: synchronous self-reset with residue readout and read-self reset. The SNR and suitable applications of these techniques are compared in greater detail through behavioral simulations.

**Keywords:** Biosensor Array, Dynamic Range, Bioluminescence, Signal-to-Noise Ratio, Minimum Detectable Level

## 1. INTRODUCTION

Biosensors have found widespread applications in all areas of life sciences research and diagnostics. The detection methodology as well as the exact transduction mechanism in these sensors are however quite varied, and range from optical (e.g., fluorescence detection) to electrochemical (e.g., amperometric methods). There is a recent trend to miniaturize the biological sensing systems. The parallelism made possible through such miniaturization is of great interest. Scaling enables integration of more components and detection sites on the same platform tremendously increasing the throughput of the analysis. Miniaturization also requires smaller amounts of reagents for the analysis, which leads to lower costs. Furthermore, advanced microfabrication techniques have facilitated integration of diverse sensor functionalities on the same chip making system automation more convenient.

In conventional biological analysis platforms, traditionally the highest performance equipment is utilized, ensuring that the measurements do not become limited by the detection system. For instance, the use of scientific-grade CCD cameras and photomultiplier tubes[1,2] is justified through the added value to the biological analysis system. Unlike these conventional systems, in miniaturized platforms high performance is generally limited by the integration requirements. Therefore, there is a need for development of custom-made sensors in chip-based integrated biosensor platforms. Furthermore, there is a great advantage to reduce the cost of the chips to make them suitable for portable and disposable detection systems. These criteria in fact question the implementation of the best possible sensor, and place more significance on the optimal design of the biosensor in view of the required metrics.

There are certain common specifications, which are generally desirable for biosensors, among which are high sensitivity, high DR, and high density in array formats. The precise specifications depend on the application and vary widely for various cases. In this paper, we first briefly go over various sensor specifications and their definitions in section 2. Since different types of applications pose different constraints on the design, we also briefly cover the most-widely-used detection systems such as fluorescence, luminescence, scattering/absorption, and electrochemical sensors in section 3. Finally in section 4, the design of an integrated image sensor array for bioluminescence detection is

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considered as an example. High signal-to-noise ratio (SNR) and high DR has been targeted to best suit luminescence detection purposes. Various high DR schemes have been devised for image sensors[3,4]. In this section, these schemes are qualitatively compared in order to determine the advantages and disadvantages of each scheme in terms of SNR and power consumption. Two schemes are shown to be best suitable for bioluminescence detection applications: synchronous self-reset with residue readout and read-self reset. Simulations are performed to compare the performance of these techniques in terms of SNR and hence their range of applicability for bioluminescence detection. The simulation results are presented in section 5.

## 2. BIOSENSOR METRICS

In most bioassays, it is imperative to implement the sensor in an array format. Instruments for reading microarray systems[5] and microplate readers are a few examples. The detectors for such systems need to measure the analyte quantity at different locations, which is typically carried out sequentially by a single detector across the array (scanning) or to dedicating an individual detector to each site[6]. Most bioassays require a single measurement (usually when the assay reaches its biochemical equilibrium) per detection site (pixel). Others require the capturing of the reaction kinetics, necessitating multiple measurements per pixel. For instance, fluorescence detection in microarray systems is usually performed through an end-point measurement, and an example of the other group is light absorption measurements in certain immunoassays[7]. In kinetic measurements, the speed of detection becomes of great importance compared to single-point measurement sensors. For the end-point data acquisition systems, the detection speed is immaterial unless the same sensor or read circuitry needs to be multiplexed among various pixels.

Independent of the application and sensor, signal-to-noise ratio (SNR) is always defined as the power of the detected signal to the power of the noise. SNR is a good measure of detection system sensitivity. The higher the SNR (for a certain input), the more sensitive the detection system. In a detection system, SNR generally decreases as signal power is reduced, assuming that the noise power remains rather constant. This is demonstrated in a sample SNR-input curve shown in Fig. 1. When the signal is decreased, at a certain limit, SNR goes below one (0 dB) indicating that the signal is practically indistinguishable from the background noise level. This gives rise to the definition of the minimum detectable level (MDL) for a sensor, which is the smallest input signal that can be differentiated from the background noise level by a tangible SNR (Fig. 1).

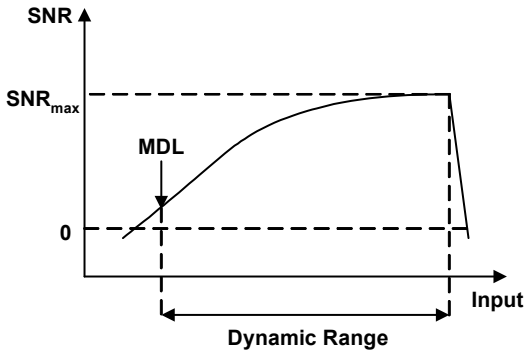



Figure 1: Typical SNR curve and demonstration of the sensor metrics.

The required SNR and MDL of the sensor depend directly on the application of interest. For very sensitive measurements (e.g., bioluminescence detection[1]), the goal is to detect the smallest possible signal, or in other words pushing the sensor MDL as low as possible. This might not be as important in other applications where the input signal range is comfortably above the sensor MDL. This case can happen if for instance the amount of target DNA or protein is not the limiting factor. At the high-input range, the sensor SNR can be designed to saturate by allowing the noise level to grow as the signal level increases. At the limit, the sensor operation is constrained by saturation mechanisms of the sensor or the readout circuitry. These phenomena will subsequently cause fast degradation of the SNR. The dynamic range (DR) of the sensor is defined as the ratio of the highest non-saturating input signal to the MDL.

The DR requirements of biosensors are quite varied. Some applications require a large DR to accommodate the large range of possible input signals. Bioluminescence signals can possibly span over 5-7 orders of magnitude[8,9] putting similar requirements on the detection system. Other applications might have a lower range of possible inputs, such as certain bioluminescence immunoassays with a linear DR of only two orders of magnitude[10]. Designing a sensor with a DR of 120dB (6 orders of magnitude) would be a waste of resources for such an application. The dynamic range requirement might be more than just the signal input range. Additional room might be required to accommodate a large (but constant) background signal. For instance assume the scenario where the input range of the sensor is 3 decades, i.e. from 1 to 1000, but a zero input signal read produces an output equal to 500. This means that half of the sensor range is already used for the background signal and only one half is practically available. Furthermore, accounting for signal variations due to assay variations and biochemical noise[11] is another important factor when choosing the DR of the sensor. These variations might cause the target signal to vary by a factor, which must be accounted for in the DR in order to make sure that we can cover the whole range of inputs for the entire range of variations.

To design an optimal sensor, the SNR requirement of the sensor should be considered for both low-input and high-input regimes. Although most biological applications require the lowest possible MDL, they might not require a high SNR at the high-input regime. This implies that SNR requirements for some applications might be different in the low-signal regime and the high-signal regime. In most applications, a higher SNR at the low-input regime is ideal since it defines the sensor MDL. For instance, in a bioluminescence detection assay where only presence (and not exact quantification) of the light signal is being detected[12], only a high SNR at the low-signal regime is of significance, and SNR at the high-signal range becomes immaterial. If a quantitative measure is necessary, the SNR at high end might be important as well. An optimal SNR curve might be a saturating one as described before. This design guarantees highest possible SNR at low-input regime and a high-enough SNR at the high-level regime.

## 3. TYPICAL DETECTION METHODS

In this section, we present the conventional detection systems used in biological assays. After giving a brief introduction into each type of sensor, we will examine the importance of the sensor metrics for each specific type.

### 3.1. Fluorescence detection

Fluorescence imaging is extensively used in the laboratories and research centers for a variety of applications. These include but are not limited to nucleic acid/protein detection and quantification, DNA sequencing, blotting, and real-time PCR analysis. The components of a typical fluorescence detection system are shown in Fig. 2. The source is filtered to produce a single-frequency excitation. This excitation induces photon emission (at a different frequency) from the fluorescent label in the sample material. Filtration of the emission spectrum and detection follow to form the fluorescence image of the sample.

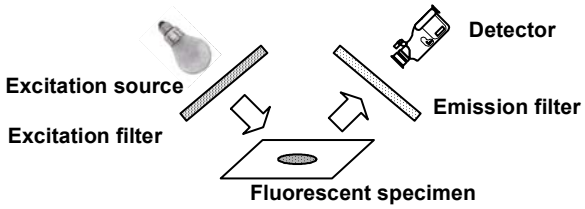



Figure 2: Basics of a fluorescence detection system.

There are two types of fluorescence detection systems for array-based platforms. In one system, the excitation source is scanned across the array and a single-pixel very high-performance detector such as a photomultiplier tube is used for detection. The other approach is to use a homogeneous excitation light source for the entire assay at once and measure fluorescence emission at different pixels through a 2D array of detectors e.g. a CCD camera[2]. In these implementations, the resolution of the CCD camera and the number of photosensitive pixels determine the possible array size.

In most classical analytical experiments, the aim is to resolve a small signal from the background noise. The principal source of sensor noise is the dark current from the photodetector and the associated electronics in the detection circuitry. In certain experiments, on the other hand, the goal is to look for a small change in the level of a large fluorescence signal. This is the case, for example, in the measurement of fluorescence polarization, quenching assays, and in ratio fluorescence[13]. In these applications, the fluorescence detection system must have excellent stability and low noise to detect very small changes in the intensity of the signals. In these applications, excitation source stability, drift of the detector, and the signal shot noise determine the system sensitivity. The low level, random, dark noise from the detector and electronics is usually of less concern, since their contribution is low in comparison to the noise contributed by the other sources. Time-resolved fluorescence is another type of fluorescence assay[13]. After excitation with a short pulse laser, the excited molecules emit an either short or long-term fluorescence signal, both following an exponential decay. If light integration starts a short period of time after excitation is removed, the short-lived fluorescence signal is effectively eliminated and the long-term one can be detected.

Integrated platforms for fluorescence detection have been reported[14]. One major challenge in integration of the fluorescence detection system is the emission filter. In typical fluorescence detection applications, the signal DR is not as high as DR of the bioluminescence signals[6], and the integration times are relatively smaller. However, to accommodate the large background, and signal variations, we might require a larger than expected DR for the sensor. Nevertheless, most applications do not require implementation of a specific high DR scheme. The DR in array-based fluorescence detection systems is limited by the noise and the background variations on the low end, and by the surface immobilization capacity at the high end.

On the other hand, the MDL of the fluorescence detection assays needs to be as-low-as-possible. Generally, a high SNR is the main requirement of a fluorescence detector. Some applications such as fluorescence quenching immunoassays, fluorescence polarization immunoassays and ratio fluorescence measurements, a high SNR at the high-signal range might be needed as well. Of course, if the background signal variation is higher than the detection system noise, having a high SNR detection system is not justified.

### 3.2. Chemi and bioluminescence detection

Traditionally for luminescence detection, photomultiplier tubes and CCD cameras have been utilized. CMOS image sensors have not been used until recently because of poor performance and lower SNR, although the application of CMOS image sensors is growing rapidly[15]. Recent advances in fabrication, and low-noise read techniques have enabled decreasing both dark-signal and read-noise of CMOS detectors. Furthermore, CMOS sensors provide tremendous flexibility of design, which can be exploited to design customized chips for the application of interest.

Both kinetic and end-point data might be needed in luminescence detection systems. In most detection/quantification assays, endpoint measurements are sufficient, but if for instance analysis of enzyme activity is of interest, kinetic measurements need to be performed. Bioluminescence systems typically have long-lasting signals, which suggest use of integrating sensors with long integration times to take full advantage of the entire available signal. Long integration time can lead to a large accumulated signal when the signal is present and to a very small background signal in absence of the positive signal, necessitating a high DR sensor. The DR requirements for detecting bioluminescence signals are the highest among all the detection techniques. Signals spanning over 5-7 decades are not uncommon in bioluminescence detection[8,9]. In order to detect such signals, high DR schemes need to be implemented in the sensor to boost the DR.

Furthermore, the sensitivity of detection is of great importance in most bioluminescence applications. The sensitivity of these systems is often limited by the read noise or quantization noise. The background signal is lower than in fluorescence detection platforms. In order to reach shot-noise-limited performance, the noise in the read circuits needs to be controlled and reduced. Furthermore, the resolution of the ADC needs to be chosen high enough to reduce the quantization noise level to below the appropriate levels. Low-noise operation in the low-light regime leads to low MDL of the luminescence sensor and is of great importance in most of the applications. SNR requirement at the high-light regime is dependent on the application of interest. In some applications, a saturating SNR curve as shown in Fig. 1 is suitable. In applications regarding nucleic acid (DNA/RNA) or protein detection[6,16], a saturating SNR in the high-light

regime is a suitable approach. For these detection systems, a high SNR at the low signal regime guarantees a low MDL, while in the high signal regime, where SNR is much less important, it is traded with power, simplicity of implementation, and therefore cost.

Some other bioluminescence applications require a level of quantification rather than mere detection. For these systems an SNR limit can be specified beyond which extending SNR is useless. Therefore, the sensor system can be designed to saturate at this SNR limit. This can be illustrated by an example; Assume a bioluminescence signal of 10 relative light units (RLU). In order to reach an SNR of 60dB (or 1000), the sensor noise variance must be less than 0.1 $RLU^2$. In the same system, a 100 RLU signal can be detected with an SNR of 100dB with a similar noise power. Such a high SNR might not actually be required for the analysis of interest. The other option is keep the SNR constant by increasing the noise level proportionally. In our example, this can be accomplished by increasing the noise power to 10, which is equivalent to increasing the standard deviation of the detected signal from $\sqrt{0.1}$ to $\sqrt{10}$ .

A third type of application includes cases where exact quantification of the signal is required. A good example of these applications is a DNA sequencing technique using bioluminescence detection called Pyrosequencing[17]. For Pyrosequencing, the level of light signal is proportional to the number of incorporated nucleotides in the DNA sequence as well as the amount of the DNA strands. For these applications it becomes important to quantify the signal with highest possible SNR since a very small difference in the signal level might demonstrate the difference between *n* and *n+1* base incorporations.

These various types of requirements for bioluminescence detectors might lead to different biosensor designs based on the biological application of interest. In section 4, various high DR schemes are described and compared in terms of SNR and power for bioluminescence detection. As discussed in this section, the application might require a high DR and low SNR in the high range while others might require both a high DR and a high SNR in the entire range. The proper choice of architecture guarantees effectiveness of the design and prevents unnecessary power consumption and design effort and minimizes the cost of the overall system.

### 3.3. Light Scattering and Absorption detection

The basics of these techniques are shown in Fig. 3. One measures the amount of the scattered light at an angle to the excitation direction, whereas the other measures the change in the intensity of the excitation source passing through the solution due to reflection, scattering and absorption.

As an example, some antibody-antigen reactions form a precipitate in the solution. Focusing a light source on the sample and measuring the amount of scattered light can determine the amount of precipitation. The measure of precipitation can be used to give an indication of how the antibody-antigen reaction is proceeding[7].

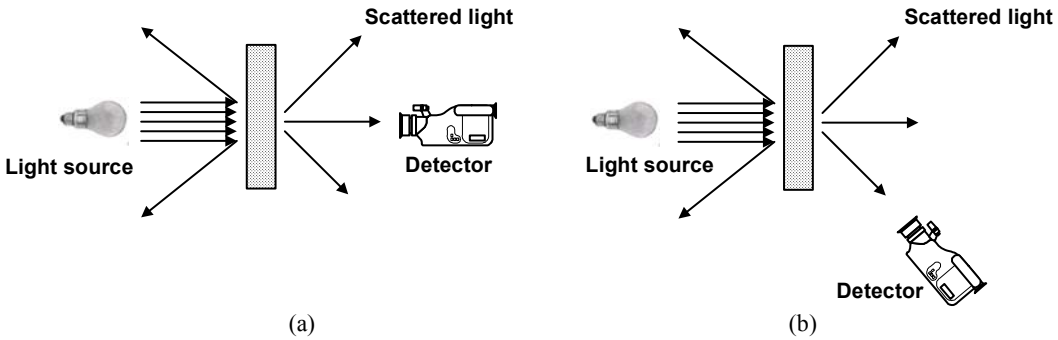



Figure 3: Basic (a) Absorption (turpidimetric) and (b) Scattering (nephelometric) optical analysis systems.

Both end-point and kinetic detection methods have been developed for these types of measurements. Kinetic measurements (i.e. measurement of the rate of change of the scattered signal) provide better sensitivity than end-point measurements[7].

The sensor requirement for the scattered light measurement is very much like fluorescence measurement. Kinetic data acquisition requires taking samples more frequently necessitating faster integration times. The MDL of the sensor needs to be as small as possible, and the DR requirement is not very high since out-of-range data indicating an excess of antibody or antigen does not need to be quantified. For transmission or absorption sensors, the zero-signal corresponds to the full un-scattered light source. Any signal is measured as a drop of the detected signal compared to the un-scattered case. This poses a high SNR requirement on the sensor particularly at the high-input range. For these sensors, the highest possible signal is known beforehand. This sets the DR requirement for the sensor at the high end. The SNR at the lower end of DR is not as important.

### 3.4. Electrochemical detection

In recent years, there have been great advances in the electronic detection of the biological entities[18-22]. Detection is based on a change in an electrical quantity such as voltage, current impedance or charge by a biochemical reaction. These sensors are very suitable for integration and microfabrication because the electrical nature of the signal simplifies the system integration. The DR requirement of electrochemical detections platforms is usually less compared to optical sensors, but the sensitivity (MDL) requirement is high although the sensor MDL might be relaxed to the level of the background signal variations

In summary, the design requirements for integrated platforms for the mentioned four types of sensors are summarized in table 1.

Table. 1: Summary of design requirements for common biological sensors. A (+) indicates significance of the factor for the corresponding sensor and a (-) indicates its irrelevance.

| Sensor Type | Target | Measurement type | DR | MDL | SNR at the high range |
|---|---|---|---|---|---|
| Fluorescence | Detection | Endpoint | - | + | - |
| | Quantification | Endpoint | +/- | + | + |
| Bioluminescence | Detection | Endpoint | - | ++ | - |
| | Quantification | Endpoint/kinetic | ++ | ++ | + |
| Absorption | | Endpoint/Kinetic | + | - | ++ |
| Scattering | | Endpoint/Kinetic | - | ++ | - |
| Electrochemical | | Endpoint/Kinetic | +/- | + | +/- |

## 4. HIGH DYNAMIC RANGE SCHEMES FOR BIOIOLUMINESCENCE SENSOR ARRAYS

As mentioned in section 3.2, the main common features of most bioluminescence detection platforms are long integration times, high DR, and low MDL. There are various high DR schemes introduced for image sensors. These schemes can be applied to increase the DR of bioluminescence detection systems. In this section, we qualitatively discuss the various high DR schemes and introduce two schemes, which we find most suitable for these applications.

High DR schemes are classified into two general categories: (i) varying integration time schemes, and (ii) well recycling schemes[3]. In the first category, the basic idea is vary the effective integration time depending on the signal level. A few high DR schemes in this category are: well-capacity adjustment, time-to-saturation and multiple capture. The basic idea behind the well recycling schemes is to subtract a known amount of charge from the integration capacitor during the fixed integration period. The charge-subtraction can be done by simply resetting the integration capacitor as well. A few of the high DR schemes in the category are: synchronous or asynchronous self-reset, sigma-delta-based architectures, and folded multiple capture[23].

### 4.1. Varying integration time

In these schemes, the read mechanism is such that the effective integration time varies for various pixels. The brighter pixels get less effective integration time while the lower-intensity pixels receive a longer effective integration period.

The concept is in general based on the assumption that the photocurrent is unchanged during the entire integration time. This assumption is then used to interpolate the charge that could have potentially been accumulated on the integration capacitor for the entire integration time if no saturation had occurred. This basic concept is shown for the multiple-capture scheme in Fig. 4. For this scheme, in the low photocurrent regime, the last sample is used for the estimation. For high photocurrent values, the last non-saturating sample (of the integrated photocurrent) and its time stamp are used to give a measure of the slope. In order to measure the entire accumulated charge, linear interpolation is used to estimate the potential accumulated charge for the entire integration time $t_{\text{int}}$:

$$Q_{multiple\_capture} = \begin{cases} CV_{\text{int}} & \text{if } t_{sat} \geq t_{\text{int}} \\ CV_{read}\dfrac{t_{\text{int}}}{t_{sat}} & \text{if } t_{sat} < t_{\text{int}} \end{cases}$$

where $C$ is the photocharge integration capacitor.

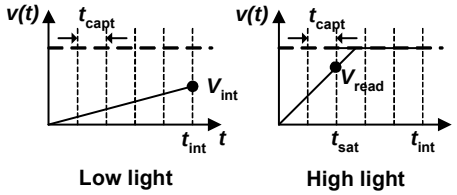



Figure 4: Multiple capture timing scheme.

The constant-current assumption is the main drawback of such schemes for bioluminescence detection especially for flash bioluminescence signals leading to a large charge overestimation.

### 4.2. Well Recycling

These schemes are based on subtraction of charge out of the integration capacitor. Among these schemes are sigma-delta-based techniques, and self-reset schemes.

In ΣΔ-based schemes, instead of resetting the well, a constant charge is subtracted from the integration capacitor each time the capacitor well gets close to saturation. Saturation is detected by a comparator. There are two possible types of readout for sigma-delta schemes. In one approach estimation of the photocurrent is done based on the comparator output. In another scheme called extended counting (EC), the comparator output bit series is combined with one extra read at the end of the integration time to provide a better SNR[24]. The sigma-delta approaches can potentially give the profile of the photocurrent in time. Although this is advantageous for kinetic measurements, for endpoint measurements where only the total accumulated charge is of importance, it produces too much unnecessary information, at the cost of extra power consumption and silicon area. As mentioned before, this becomes prohibitive when designing for large sensor arrays.

One basic way to do well recycling is to monitor the integration charge, and once it reaches a certain level right before the saturation happens, to reset the well and restart the integration cycle. This makes sure that no charge is missed in the integration period. This procedure can be done in either a synchronous or an asynchronous manner. Before recycling, some measure of the previous charge needs to be stored. This can be done through counting the number of resets in the integration time. In order to provide a high SNR at the low photocurrent regime, one read can be included at the end of the integration cycle, $t_{\text{int}}$. This provides a better estimate of the accumulated charge at the low signal regime, and is called self-reset with residue readout. The timing scheme is shown in Fig. 5. This can be further improved by an extra read at the beginning of the integration time. Subtraction of the voltages at the end and the beginning of the integration cycle can get rid of the fixed pattern offset and potentially the reset noise and is known as correlated double sampling (CDS). A CDS operation is most effective for the low-light regime where no reset happens between the two reads and reset noise can get cancelled effectively. For these schemes, the photo-charge can be estimated as:

$$Q_{selfreset\_residue\_readout} = \begin{cases} CV_{\text{int}} + n_{reset}.CV_{\max} & \text{without CDS} \\ C(V_{\text{int}} - V_0) + n_{reset}.CV_{\max} & \text{with CDS} \end{cases}$$

The synchronous vs. asynchronous schemes differ in the comparator timing. For array implementations with a large number of pixels, the synchronous scheme burns less power and provides similar performance given a fast enough comparator clock[3]. This technique also maintains an acceptable SNR at the high light regime. The SNR at the high end becomes limited by reset noise, fixed pattern noise, comparator offset, and comparator noise. This is verified in the simulations as well.

Another way to perform the self-reset is to actually read the output value before doing the reset, and then do one extra read at the end of the integration cycle and add all the values together. Correlated double sampling (CDS) can also be implemented by reading the pixel value both at the beginning of each ramp (right after the reset) and at the end of the ramp right before the reset. This technique is illustrated in Fig. 6. The estimate is calculated as

$$Q_{read\_selfreset} = C\sum_{i=1}^{m}(V_{rsti} - V_{0i}) + C(V_{\text{int}} - V_{0m+1})$$

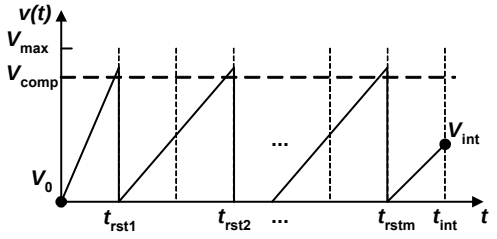



Figure 5: Synchronous self-reset with residue readout (and CDS).

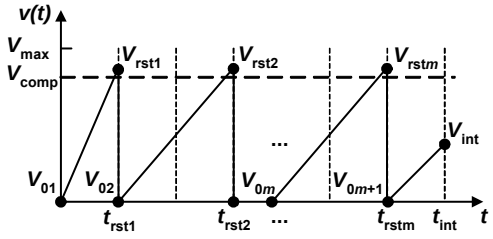



Figure 6: Read-self reset.

Due to the CDS operation, the reset noise and fixed pattern noise get cancelled out. Also the operation is independent of comparator offset and noise. The great advantage of this scheme is that it provides a large SNR for the entire range of the input signals. This is therefore ideal for applications where both high DR and high SNR are required. This technique of course consumes more power since it requires more ADC read operations compared to just counting the number of resets. Power consumption is however dependant on the signal level, since no ADC read is done unless commanded by the comparator output. Therefore, for small photocurrents, only two reads are performed similar to the conventional case, and the number of reads increases as the photocurrent increases and multiple resets are necessary, raising the level of power consumption.

One other feature of this read scheme is that it can support kinetic measurements without any extra hardware. This is done by reading and resetting the well at constant time intervals rather than at the comparator signal.

Table. 2: Summary of comparison of high DR schemes for bioluminescence detection.

| Scheme | Constant current assumption | SNR at the low signal regime | SNR at high signal regime | Power |
|---|---|---|---|---|
| Well capacity adjustment | × | ✓ | × | ✓ |
| Multiple capture | × | ✓ | × | ✓ |
| Time-to-saturation | × | ✓ | ×× | ✓ |
| Incremental ΣΔ | ✓ | × | ✓ | ×× |
| Extended counting ΣΔ | ✓ | ✓ | ✓ | ×× |
| Folded multiple capture | × | ✓ | × | ✓ |
| Self-reset with residue readout | ✓ | × | × | ✓ |
| Self-reset with residue readout and CDS | ✓ | ✓ | × | ✓ |
| Read-self reset | ✓ | ✓ | ✓ | × |

Table 2 summarizes advantages and disadvantages of the high DR schemes for bioluminescence detection. As seen, from the high DR schemes, the self-reset with residue readout and read-self reset are the most appropriate schemes for this application. The choice of which scheme to use is based on the SNR requirement at the high signal regime and power. Performance of these schemes will be further studied through simulations in the next section.

## 5. SIMULATIONS

We have performed simulations to derive the SNR-input signal curve for the two schemes introduced in the previous section: synchronous self-reset with residue readout and read-self reset. With these simulations, we can compare the two schemes in terms of SNR and sensitivity to circuit parameters. The results can help decide which scheme to use for a certain bioluminescence detection application.

### 5.1. General parameters

The sensor component parameters used in the simulation are summarized in table 3. We have tried to pick typical practical values where available. Gain fixed pattern noise has not been modeled in the simulations. The dominant component of gain fixed pattern noise is the variation in photodiode area, and it has been assumed that the pixels used for bioluminescence applications are large therefore the variation due to mismatch is negligible.

Table 3: Simulation sensor parameters.

| Parameter | Value |
|---|---|
| Pixel area | 100μm×100μm |
| Integration time | 30sec |
| Well Capacity | 22,500,000e- |
| Pixel Offset FPN (σ) | 125,000e- |
| Comparator Offset (σ) | 500,000e- |
| ADC resolution | 13bit |
| Dark Current | 50fA |
| Comparator frequency | 1KHz |

### 5.2. Synchronous self reset with residue readout

The SNR curve for this approach has been given in Fig. 7(a) for the two cases of with and without CDS. Also the SNR curves have been shown for the self-reset scheme without the residue readout. The factors limiting the SNR curve at the high end are: 1) comparator offset 2) fixed-pattern noise 3) reset noise, and 4) comparator noise. In order to improve the SNR, the offset components need to be cancelled. At the low-light regime, CDS improves the SNR considerably since it gets rid of the pixel offset and also the reset noise. In this regime no comparator offset is present since no reset takes place. The jump in the CDS curve is when the first reset happens and comparator offset starts to show up as the major error component.

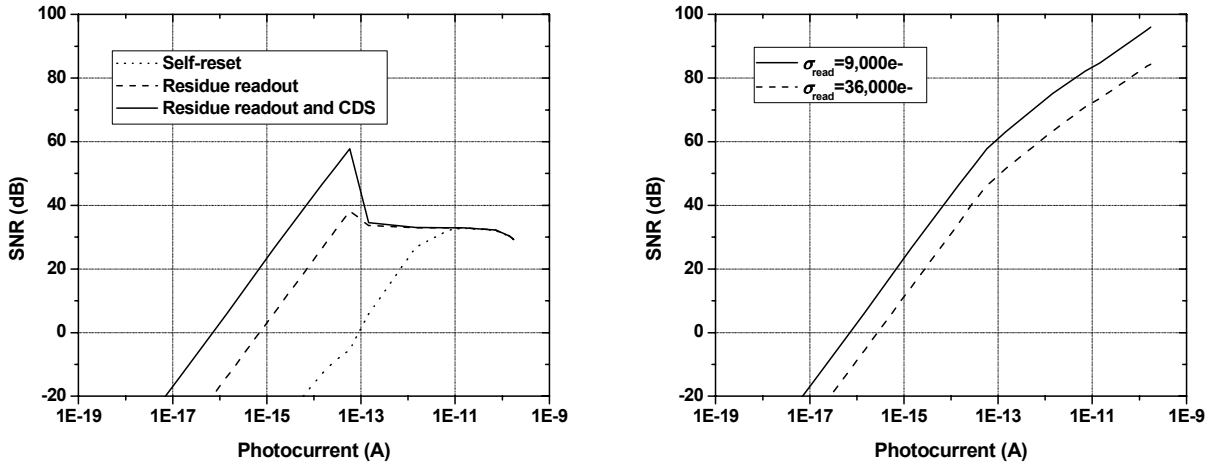
### 5.3. Read-self reset

The SNR vs. input signal curve is depicted in Fig. 7(b) for the read-self reset scheme for two different values of read noise. As expected, this technique is much more insensitive to circuit parameters and provides much higher SNR at the high-light regime. SNR is mainly limited by 1) read noise, and 2) ADC quantization noise. In this scheme, DR is limited by comparator frequency and the hardware limitation for implementing the charge additions before the resets.

## 6. CONCLUSION

In this work, we have looked into a wide variation of biological sensing systems. The goal is to design a customized integrated platform for biological detection. Typical detection techniques are briefly reviewed and the required design metrics for each have been briefly discussed. Array implementation and low minimum detectable level (MDL) are

generally needed for most assays, while high DR and high SNR at high-signal regime may or may not be required. The unnecessary detection features can be traded-off with power/area resources leading to the most efficient design of the integrated detection system. As an example, design of high DR sensors for bioluminescence detection has been studied more specifically. Two high DR schemes of self-rest with residue readout and read-self reset are found to be suitable in terms of SNR and power. The former scheme gives a reasonable SNR with reasonable power consumption, while the later provides a larger SNR and potentially consumes more power.




(a) (b)

Figure 7: (a) SNR curve for synchronous self-reset, synchronous self-reset with residue readout and synchronous self-reset with residue readout and CDS assuming $\sigma_{read}$=9,000e-. (b) SNR curve for read-self reset scheme for two cases of $\sigma_{read}$=9,000e- and $\sigma_{read}$=36,000e-.

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