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A novel non-invasive biosensor based on electric field detection for cardio-electrophysiology in zebrafish embryos.

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Abstract

In this paper we report a novel biosensor based on electric field detection for recording cardiac electrical activity in zebrafish embryos. Using Sussex patented Electric Potential Sensing technology, a portable, non-invasive and cost-effective platform is developed to monitor *in vivo* electrocardiogram activity from the zebrafish heart. Cardiac activity signals were successfully detected from living zebrafish embryos starting at 3 days-post-fertilization. The recorded waveforms contain typical traces such present in electrocardiogram, such as the QRS complex, P and T waves. This research opens new pathways for investigating cardiac related pathologies present at embryonic stages using a novel non-invasive biosensor.

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Keywords: Bioelectronics; Biological sensing; Biosensors; Cardiovascular systems; Electrode Potentials; Electrophysiology;

1. Introduction

Zebrafish (*Danio rerio*) has become a useful model organism for cardiac research especially for the assessment of drug toxicity. Its heart development occurs very rapidly having an already beating heart after just 24-28 hours post-fertilization (hpf). Moreover, the zebrafish cardiac myocytes action potential characteristics, coronary vasculature system hear-rate (120-180 bpm) and electrocardiogram waveform, have a remarkable resemblance to those of humans [1]. In spite of the current advances in sensing technology, today, there is no effective technology available to monitor the electrocardiogram (ECG) activity of the living zebrafish heart at embryonic level. Most of the methods are based on visually inspecting the heart using a microscope, being limited to quantifying the heart rate. Invasive methodologies requires either the insertion of electrodes or open heart surgical procedures mostly performed with adult samples.

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In this paper we report the continuous detection of the cardiac electrical activity in embryonic zebrafish using a non-invasive approach. We develop a portable and cost-effective platform based on the Electric Potential Sensing (EPS) technology, to monitor *in vivo* electrocardiogram activity from the living zebrafish heart.

2. Experimental platform and results

The EPS sensor is a feedback enhanced and stabilized electrometer-based amplifier that operates based on displacement current measurements. This means that no real charge current is applied, eliminating the need to make direct electrical contact with the sample surface. It includes associated feedback loops providing the functions of bootstrapping and neutralization [2]. The design incorporates a mini fish tank which includes an integrated electro active EPS sensor with internal input bias current circuitry and guarding. Fig 1(a) shows the representation of the central EPS sensor using a 2 mm diameter sensing electrode. The electrode interface was built using a metallic titanium (Ti) based central electrode coated with a titanium dioxide (TiO_2) substrate acting as a dielectric. This combination allows the detection of electric field measurements generated by the *in vivo* zebrafish heart immersed in E3 saline buffer (Sigma Aldrich). We visualized embryos using a custom made bright field microscope, based on an Olympus 4X NA 0.1 objective equipped with a monochrome camera placed on top of the experimental set-up. Fig. 1 (a) also shows the top view representation of the Ti based central EPS electrode together with an image acquired using our custom built microscope. Also note that the heart has been outlined to simplify its identification.

Fig 1 (b) shows an example of the recorded cardiac activity using a 3 dpf zebrafish embryo. The recorded waveforms were averaged aiming to show detailed features contained in typical ECG traces such as QRS complex, P and T waves. Fig 1(c) shows the raw data collected using the prototype. The mean heart rate was 169 bpm having an R-R interval of 0.37 ± 0.09s. The recorded mean peak amplitude was 28.5 ± 3 µV [3].

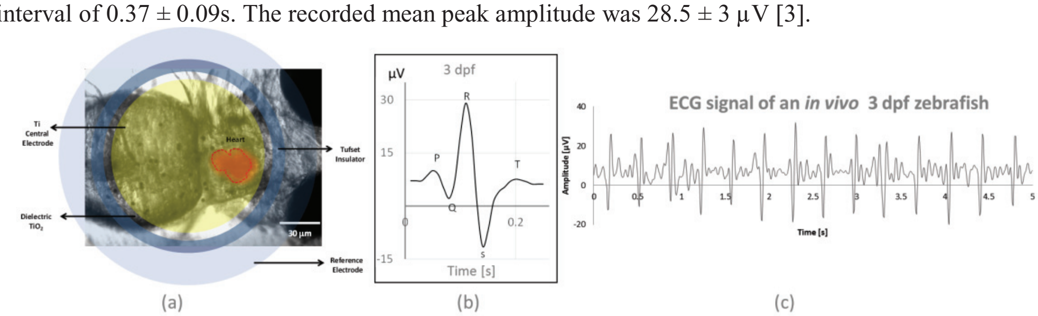

Fig. 1. (a) EPS electrode interface; (b) Example of an averaged ECG trace; (c) ECG signal raw data.

In summary, using the developed biosensor based on electric field detection, it was possible to monitor cardiac electrical activity from the zebrafish heart non-invasively. This was carried out at early embryonic stages (i.e. 3 dpf), just 8 hrs. after the heart was formed. This research has the potential to be used for drug screening applications where cardiac toxicity needs to be assessed.

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