Temperature effect on the baseline noise in MEA measurements

T. Ryynänen[1] and J. Lekkala[1]

[1] BioMediTech Institute and Faculty of Biomedical Sciences and Engineering, Tampere University of Technology, Tampere, Finland

Abstract— **It is a well known fact that increasing temperature increases noise in all kind of electronics, which applies also to cell and tissue measurements by microelectrode arrays (MEAs). We show that ambient temperature may have a surprisingly big role in the noise level of MEA measurements. To study that we measured the baseline noise when the MEA amplifier was subject to temperature variations, either in a temperature chamber or by preventing amplifier unit's normal heat exchange. Around room temperature (+24°C) the RMS value of the baseline noise was found to increase approximately 0.14 µV/°C, which is a huge variation as the default RMS noise at that temperature with our setup was only around 5.5 µV. Additional cooling of the MEA amplifier could thus be a clever way to decrease the noise level at very sensitive measurements and on the other hand, one should not interfere the amplifier's normal heat exchange to the ambient air in order to avoid additional warming and thus increasing the noise level.**

Keywords— **noise, microelectrode array, MEA, temperature**

I. Introduction

As in whatever measurement, also in microelectrode array (MEA) measurements performed for the cells or tissues, one prefers to have as high signal-to-noise ratio as possible, as that enables detecting the finest and possibly the most interesting features from the measured signal. On the other hand one may want to keep the signal independent noise level constant in order to get comparable data. That would be the case, for example, if a MEA developer wants to evaluate the noise levels of different microelectrode materials. Throughout the history of the MEA development engineers have worked hard to decrease the noise level of the MEA signal by developing various porous low impedance and low noise electrode materials, like platinum black (Pt black) [1] or titanium nitride (TiN) [2].

However, there are also other significant noise sources in addition to the electrode/tissue or electrode/medium interface. One of those is the temperature, which may affect especially on the noise generated by the measurement electronics. As the cell culturing and measurements are naturally done usually at +37°C, one must either place the MEA amplifier inside an incubator, where not only the temperature is somewhat high for the electronics but also the humidity might be an issue. Or one must equip the amplifier unit with a MEA plate heater, which may heat up not only the MEA plate and the medium in the cell culturing chamber on top of it, but unavoidably also the amplifier electronics inside the same unit. The third option is to place the MEA plate and contact pins inside the incubator and let a connector cable to transfer the unamplified electrode signals to a separate amplifier unit placed outside the incubator. As in any electronics, long cables, however, add risk for other signal quality issues.

As two out of the three leading MEA amplifier manufacturers Multi Channel Systems MCS GmbH (Reutlingen, Germany) and Axion BioSystems (Atlanta, USA) prefer to have measurement electronics embedded in the MEA connector unit, in this work we have focused on the cable free options and to study, how the ambient temperature affects on the baseline noise level and could the inbuilt heater cause also temperature issues in the amplifier leading to the increased noise level, especially if the normal heat exchange to the ambient air is prevented.

II. Materials and methods

An older generation MEA-1060-Up amplifier (Figure 1A) from MCS was used as an MEA amplifier in this study. It contains all the measurement electronics, MEA plate connection pins and an integrated MEA plate heater in a single unit. Input voltage range was ±4 V with 16 bit ADC. The heater was controlled by TC02 temperature controller, also from MCS. Instead of using a real MEA plate in this experiment, Test-60MEA model probe (Figure 1B) from MCS was used. It is built on printed circuit board and to simulate a real MEA with medium, it includes 220 kΩ resistor and 1 nF capacitor between the ground and each of the 60 electrodes. MC_Rack software from MCS was used to record the noise data using 25 kHz sampling frequency. Typically a period of 65 seconds was recorded at each temperature or time point. Before each recording the system was let to stabilize for 3 minutes by measuring without saving the data. No software filtering was done for the measured data, but electrodes whose signals clearly deviated from the general noise level were excluded.

A. Ambient temperature experiment

In the first out of three experiments, the MEA amplifier was placed inside Vötsch VT4021 temperature chamber (Vötsch Industrietechnik GmbH, Balingen, Germany). The baseline noise was measured at four different temperatures, +4°C, +15°C, +24°C, and +37°C. Before measurements at each temperature the temperature was let to stabilize at least 30 minutes. At each temperature the measurement was repeated after about 12 min and an average of the RMS values calculated from the two measurements was given as a result.

B. Heat exchange prevention experiment

In the second experiment the amplifier was covered all around with an aluminum foil (Figure 1C), which is not so uncommon way to create "cheap" Faraday cage replacement for the amplifier, and in this case also act as a way to prevent heat exchange to the ambient air. Otherwise the amplifier was kept at room temperature (+24°C) and the baseline noise was measured at several time points during one and half hours after turning on the MEA plate heater (set to +38°C).

C. Self heating experiment

In the last experiment the amplifier was let on, i.e. connected to a computer by USB-cord overnight, without turning on the MEA plate heater, without having any measurement running, and not being covered anyhow. Next morning, after 16.5 hours stabilization time, the temperature sensor of the MEA plate heater was turned on to measure the temperature of the MEA plate in order to see how much it had risen just because of the heat generated by the amplifier electronics.

III. Results

A. Ambient temperature experiment

RMS noise at normal room temperature, the MEA plate heater on, was around 5.5 µV. Typical baseline recording is presented in Figure 2. From +4°C to +37°C the RMS noise doubled from 4.1 µV to 8.0 µV (Figure 3A). Derivative of the 2^{nd} order polynomial fit gives 0.14 µV/°C as the approximate temperature dependency of the noise at room temperature. At higher temperatures the dependency slightly increases and at lower temperatures decreases. At the lowest ambient temperature of +4°C the MEA plate heater was unable to keep up the set +38°C temperature, but gradually decreased to around +35°C.

B. Heat exchange prevention experiment

Right after connecting the amplifier to computer and before turning on the MEA plate heater, the RMS noise was only 3.9 µV, but after covering the amplifier with aluminum foil and turning on the MEA plate heater, the RMS noise gradually reached 7.9 µV after 1.5 hours (Figure 3B).

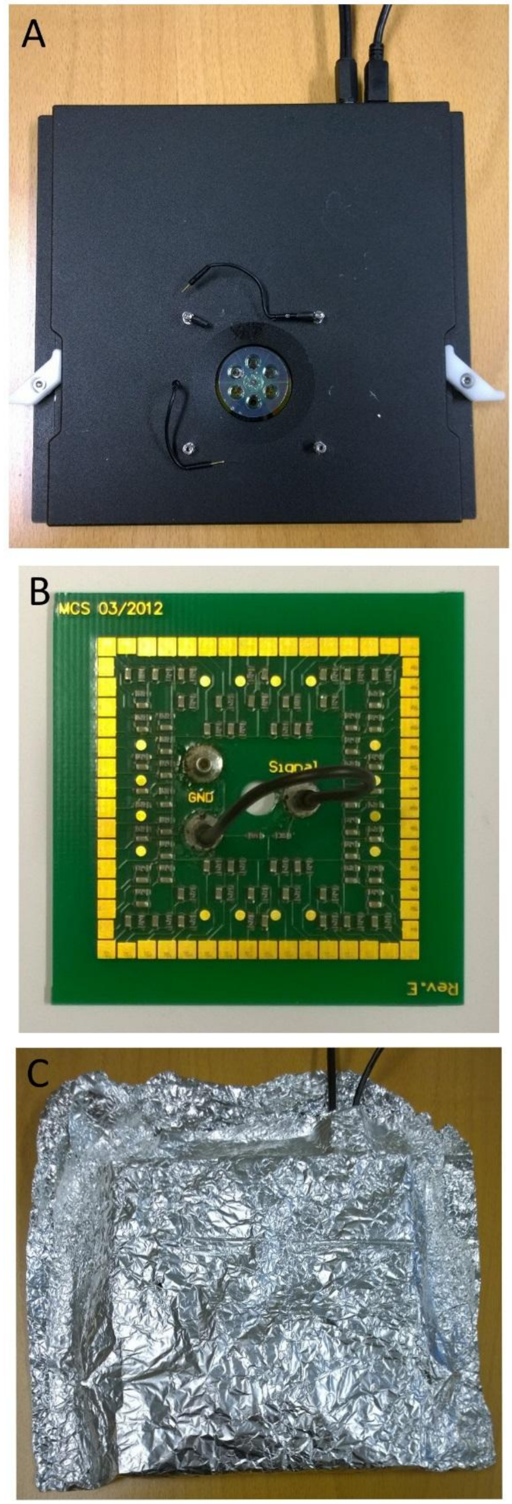

Fig. 1 A) Test-60MEA and B) MEA-1060-Up amplifier, both from Multi Channel Systems. C) The amplifier covered with aluminum foil.

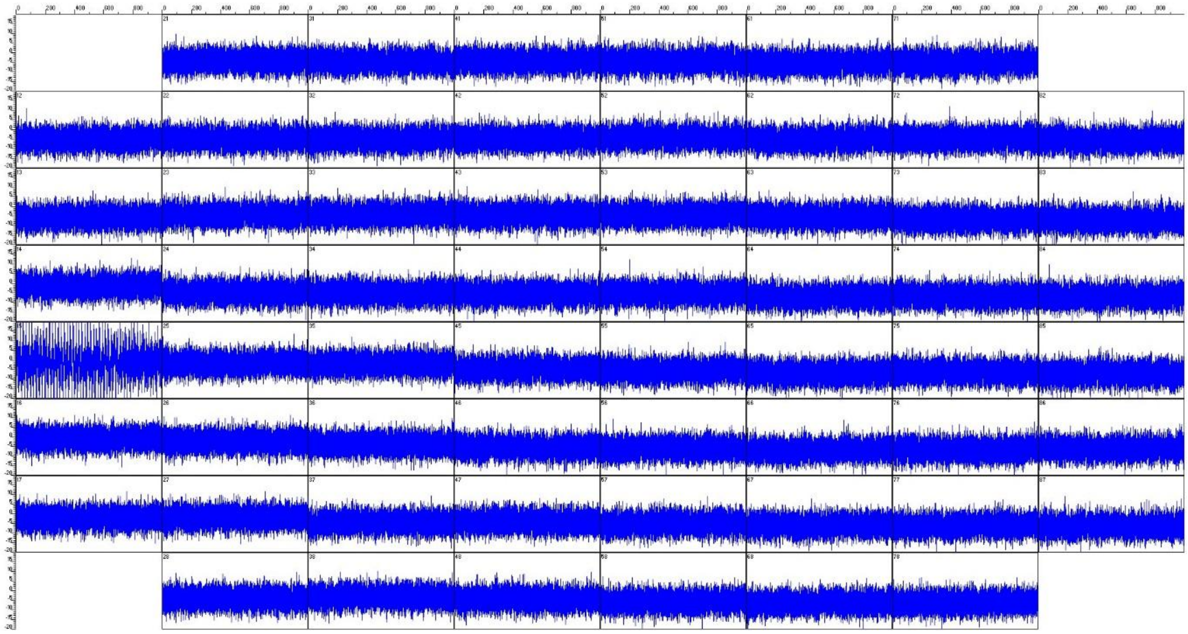

Fig. 2 Typical baseline noise recording as seen in MC_Rack software.

C. Self heating experiment

After 16.5 hours stabilization time, the temperature of the MEA plate was measured to be +30.5°C.

IV. Discussion

The effect of temperature on noise level is a well-known fact for everybody working with electronics, but it was still surprising how big the effect is already at relatively small temperature range in MEA measurements. What is the importance in real cell or tissue measurements naturally varies case by case, and one should note that the results given in this paper are just unfiltered baseline measurements, not any real cell data, which is often manipulated by signal processing means for better signal-to-noise ratio. However, if the MEA electrode material comparison is considered, based on our earlier studies [3], the RMS noise level of different electrode materials may well be only tenths of µV and to enable reliable comparison one must be able to ignore the differences of the same scale caused by the temperature variations.

Although the general trends of the results of this study apply whatever MEA amplifier, one should note that this experiment was performed with an older generation device, having a rather thick and closed metallic body, which is undoubtedly good for mechanic stability and blocking some external electric noise, but it also tends to store heat easily, no matter is it generated by external sources or internally. It would be interesting to repeat the experiment with another amplifier of more recent generation to see, if its electronics and packaging design are less temperature sensitive.

Another issue to consider is the role of the Test-60MEA model probe used in study instead of a real MEA plate. Undoubtedly the resistors and capacitors in the Test-60MEA have somewhat different temperature behavior than the microelectrode-medium interface in real MEAs. However the motivation for this study originates from the similar observations we made with real MEAs in the conditions close to the ones in the heat exchange prevention experiment of this study, so we believe that the Test-60MEA results can be well generalized to apply also real MEAs.

What can be learned from this experiment is that if aluminum foil or similar has to be used to replace a proper Faraday cage, one should evaluate whether covering the amplifier all around is necessary or could the similar effect of blocking some external noise be achieved with a smaller foil cap covering e.g only the MEA plate opening in the amplifier unit.

Despite the above mentioned heat related problems, one may also take a benefit from the temperature dependence of the noise. If one needs to measure signals that are hard to separate from the noise, one could try to decrease the noise level by arranging additional cooling for the amplifier. In such case one should, however, take care that the MEA plate heater has sufficient capacity to maintain the wanted temperature for the MEA plate and cells or tissues on it, and that the

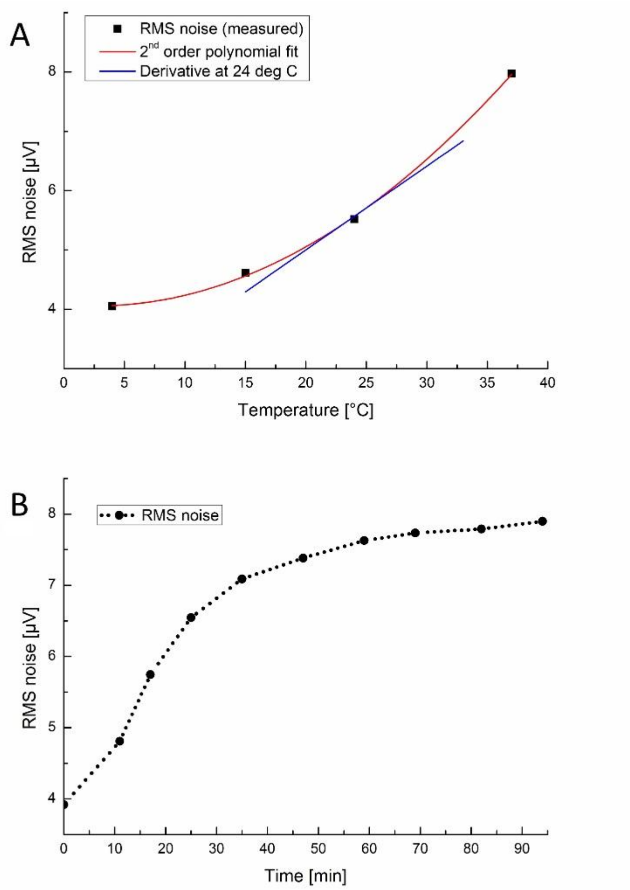

Fig. 3 A) RMS noise as a function of ambient temperature in temperature chamber and B) as a function of time when the amplifier was covered with aluminum foil.

cooling system doesn't generate more noise by itself, for example via vibration.

Our results also proof the old thumb rule that if one wants to get repeatable and comparable measurement results, one should not start the measurements immediately with a cold device, but wait maybe even for hours the system to find its temperature balance before starting the measurements.

V. CONCLUSIONS

Based on our results we highly recommend paying special attention on the temperature sensitivity of one's MEA amplifier, and on design of foil structures used as simple Faraday cage replacements. Even a small change in the room temperature or arrangements blocking the normal heat exchange from the amplifier to its surroundings, or just neglecting the temperature stabilization time the amplifier needs after being turned on might cause such a large difference in the noise level (in this experiment 0.14 µV/°C) that it may have a crucial effect on whether one can separate some interesting signal feature from the noise or not, or whether one can consider the data comparable from the noise point of view.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Author: Tomi Ryynänen
Institute: BioMediTech Institute and Faculty of Biomedical Sciences and Engineering, Tampere University of Technology
Street: Korkeakoulunkatu 3
City: Tampere
Country: Finland
Email: tomi.ryynanen@tut.fi