Computer Music Meets Unconventional Computing: Towards Sound Synthesis with *In Vitro* Neuronal Networks

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We are interested in exploring ways in which unconventional modes of computation may provide new directions for future developments in Computer Music. Research into Unconventional Computing (Calude et al. 1998) is aimed at computational paradigms other than the standard von Neumann architecture, which have prevailed in computing since the 1940s. This paper presents an investigation into the feasibility of synthesizing sounds with hybrid wetware-silicon devices using *in vitro* neuronal networks.

The field of Computer Music has evolved in tandem with the field of Computer Science.

Computers have been programmed to play music as early as the beginning of the 1950's when the CSIR Mk1 computer was programmed in Australia to play popular musical melodies (Doornbusch 2005). The *Illiac Suite for String Quartet*, composed in the USA in late 1950's by Lejaren Hiller (composer) and Leonard Isaacson (mathematician), is often cited as the first piece of music involving materials generated by a computer; e.g., the fourth movement was generated using a Markov chain (Hiller and Isaacson 1959). Nowadays, the computer is ubiquitous in many aspects of music, ranging from software for musical composition and production, to systems for distribution of music on the Internet. Therefore, it is likely that future developments in Computer Science will continue to have an impact in music.

New computational paradigms based on and/or inspired by the principles of information processing in physical, chemical and biological systems are promising new venues for the development of new types of computers, which may eventually supersede classical paradigms. For instance, it has been reported that reaction-diffusion chemical computers have been capable of performing a number of complex computational tasks, including the design of logical circuits (Steinbock at al. 1996) and image processing (Kuhnert et al. 1989).

In short, unconventional computation takes the computation (or part of it) into the real world, thereby harnessing the immense parallelism and non-algorithmic openness of physical systems. There has been a growing interest in research into the development of hybrid wetware-silicon devices for non-linear computations using cultured brain cells (DeMarse et al. 2001, Potter et al. 2004, Bontorin et al. 2007, Bull and Uroukov 2007, Novellino et al. 2007). The ambition is to harness the intricate dynamics of *in vitro* neuronal networks to perform computations. Researchers have already mastered techniques to culture tens of thousands of brain cells in vitro (neurons and glia) on a scale of a few square millimeters in a mini Petri-like dish with embedded electrodes, referred to as multi-electrode array (MEA) devices (Figure 1). The electrodes can detect action potentials of aggregates of cells and stimulate them with electrical pulses (Figure 2). A MEA can record extra-cellular neural signals fast enough to detect the firing of thousands of nearby neurons as micro-voltage spikes. Thus the activity of multiple aggregates of neurons can be observed in parallel and neuronal network phenomena can be studied. Supplying electrical stimulation through the multiple electrodes typically induces widespread neural activity.

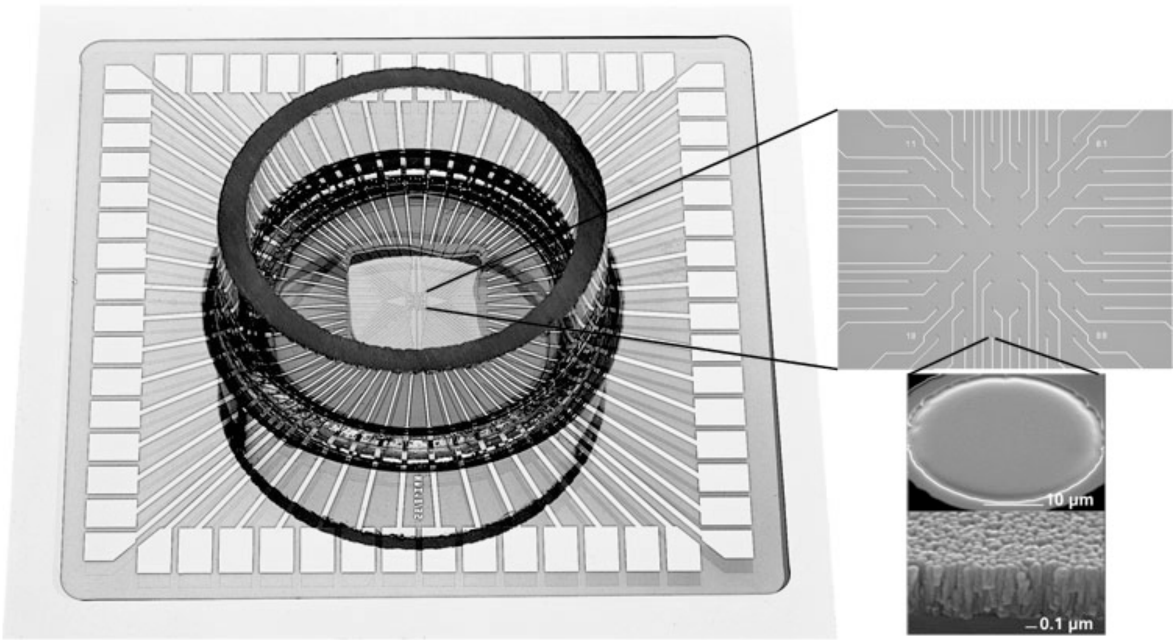


Figure 1. A typical MEA used to stimulate and record electrical activity of cultured brain cells on the surface of an array of electrodes. (Image printed with kind permission from Multichannel Systems http://www.multichannelsystems.com/)

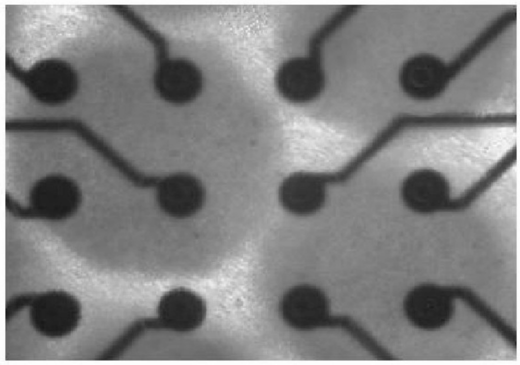


Figure 2. Phase contrast microscopy showing aggregates of cultured cells on a MEA device.

In vitro cultures of brain cells display a strong disposition to form synapses, even more so if subjected to electrical stimulation. It is well known that *in vitro* cells spontaneously branch out, even if left to themselves without external input other than nutrients in the dish. They establish connections with their neighbors and begin to communicate within days, demonstrating an inherent bias to form networks. Dissociated neurons begin to form connections within a few hours and an elaborate and spontaneously active living neuronal network is established within a few days. After one month in culture, the development of these networks becomes relatively stable and is characterized by spontaneous bursts of activity (Kamioka et al. 1996). Potter and DeMarse (2001) have developed methods to maintain cultures of brain cells for a number of months, allowing for long-term continuous observations of their behavior.

Research into hybrid wetware-silicon devices with *in vitro* neuronal networks has been making continual progress in recent years. DeMarse et al. (2001) reported the development of a neurally-controlled artificial animal - or Animat - using dissociated cortical neurons from rats cultured on a MEA device. Distributed patterns of neural activity (also referred to as spike trains) controlled the behavior of the Animat in a computer-simulated virtual environment. The Animat provided electrical feedback about its movement within its virtual environment to the cells on the MEA device. Changes in the Animat's behavior were studied together with the neural processes that produced those changes in an attempt to understand how information was encoded and processed by the cultured neurons. Potter et al. (2004) described a similar study, but they have used physical robots instead of simulated Animats. In this case, different patterns of spike trains triggered specific robotic movements; e.g., step forward, turn right, etc. The robot was fitted with light sensors and returned brightness information to the MEA as it got closer to the light source. The researchers monitored the activity of the neurons for new signals and emerging neuronal connections. Potter at al. (2004) also described an art installation created with artists at SymbioticA in Australia. They connected a MEA device with cultured neurons in their lab in Atlanta to a robotic drawing arm in Perth. A video camera relayed the drawing process to Atlanta comparing the image in progress with a photograph of a person. The comparison generated a feedback signal for the cells on the MEA device.

The dynamics of *in vitro* neuronal networks represent a source of very rich temporal behavior and we are interested in exploiting this behavior to make music with.

The paper is organized as follows: it begins by introducing the basics of culturing brain cells. Then, it briefly presents the procedures that we have established to stimulate the *in vitro* neuronal networks and record their behavior, followed by an introduction to a technique that we have developed to sonify their behavior. Next, we report on the initial results from our research into the development of techniques to steer the behavior of the networks. The aim is to exert some form of controllability and repeatability in the system, which is the next step towards effective renderings of *in vitro* neuronal networks technology into controllable sound synthesizers.

Culturing Brain Cells

The majority of research into *in vitro* neuronal networks exploit monolayer (two-dimensional) cultures of rat cortical cells; the cells grow across the surface of a MEA device (Shahaf and Marom 2001). However, it is now possible to differentiate neuronal and neuroglial cells obtained from hen embryos at day seven *in ovo* and maintain them for relatively long periods of time, typically several months. We have recently described how the maturation of spontaneous spiking behavior in cultures of such cells is typically very similar to that reported in rat cortical cells (Uroukov et al. 2006a). Hence, we have opted for using three-dimensional neuronal cell cultures from hen embryos, rather than monolayer cultures of rat cortical cells. The behavior of 3-D cultures is potentially more akin to in vivo networks than 2-D monolayer cultures and therefore exponentially richer in behavior (Seeds 1971).

Figure 3 shows a typical hen embryo aggregate neuronal culture, also referred to as a *spheroid*. In our experiments, spheroids are grown in culture in an incubator for 21 days. Then, they are placed into a MEA device in such a way that at least two electrodes make connections into the neuronal network inside the spheroid. The achievement of an appropriate connection is ascertained through the recording of the constant spontaneous spiking activity within the spheroid on a given electrode. Next, one electrode is arbitrarily designated as the input by which to apply electrical stimulation and the other as the output from which to record the effects of the stimulation on the spheroid's spiking behavior. The reader is referred to (Uroukov et al. 2006b) for more information on the protocols for culturing cells and placement into a MEA device.

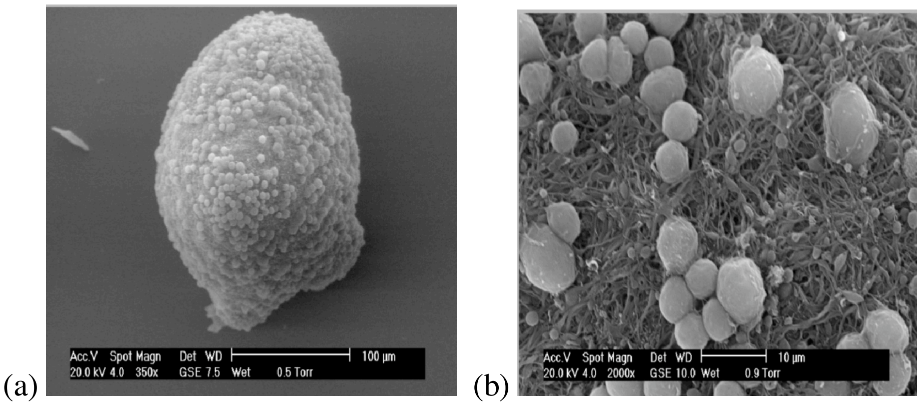


Figure 3. Images of a typical hen embryo aggregate neuronal culture on a scanning electron microscope. (a) Magnified 350 times and (b) magnified 2000 times.

Stimulation and Recording

We used 3-D MEA devices supplied by Multi Channel Systems MCS GmbH, Germany. The MEA dish surface was modified with 10µg/ml aqueous solution of Polymer Ethylene Imine (PEI) under sterile conditions. The molecular weight of PEI varied between 0.610 and 1.010 according to product specifications. After the modification, two washing steps with demineralized (DEMI) water were undertaken before the plating of a spheroid.

Stimulation at the input electrode consisted of a train of biphasic pulses of 300mv each, coming once every 300ms. This induced change in the stream of spikes at the output electrode, which was recorded and saved into a file. The sampling frequency of the output electrode was set to 25kHz and the spikes were detected by threshold depending upon the standard deviation and the offset of noise (Uroukov and Bull, 2008). Each simulation session lasted for 60secs, with a 600-second rest between them. We observed an increase in the spiking behavior after each session, which is an indication that such stimulations seem to foster self-organisation within the spheroid.

The neuronal networks form in such a way that external stimulation causes significant excitation within the structure.

The resulting neural activity for each session was saved on separate files. Figure 4 plots an excerpt lasting for 1sec of typical neuronal activity from one of the sessions. Note that the network is constantly firing spontaneously. The noticeable spikes of higher amplitude indicate concerted increases of firing activity by groups of neurones, which are most probable due to response to input stimuli.

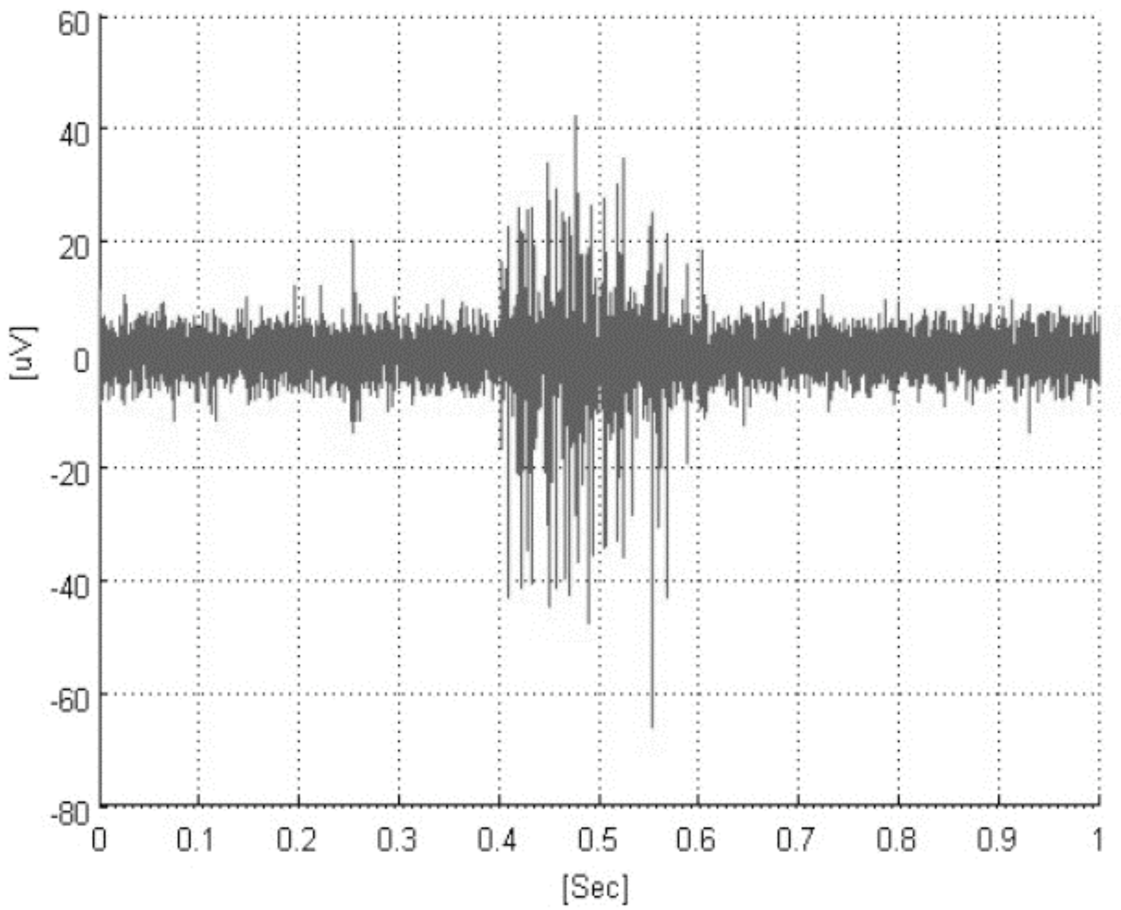


Figure 4. Plot of the first 1sec of a data file showing the activity of the spheroid in terms of µV against time. Induced spikes of higher amplitudes took place between 400ms and 600ms.

Sonification

We developed and tested a number of sonification methods using different synthesis techniques, including FM, AM, subtractive synthesis, additive synthesis and granular synthesis (Miranda 2002). Here we introduce the method that was chosen as the most successful, which combines aspects of granular synthesis and additive synthesis. This choice was informed by three criteria: a) ability to hear the behavior of the data, b) simplicity of the synthesizer architecture and c) interestingness of the results for use in musical compositions.

The synthesizer is an additive synthesizer with nine sinusoidal oscillators, which required three input values to generate a tone: frequency (*freq*), amplitude (*amp*) and duration (*dur*). The data produced *freq* and *amp* values for the first oscillator only. The values for the other oscillators are relative to the values of the first oscillator; e.g., $freq_{osc2} = freq_{osc1} \times 0.7$, $freq_{osc3} = freq_{osc1} \times 0.6$, and so on. The synthesizer was implemented in Csound (Boulanger 2000) and we wrote an application in C++ (Stroustrup 1997) to generate the respective Csound score files from the data files.

Initially, we synthesized a tone for every datum. However, this produced excessively long sounds. In order to address this problem a data compression technique was developed, which preserved the behavior that we were interested to sonify in the data, namely patterns of neural activity and induced spikes. For clarity, we firstly describe the method whereby we produced a tone for every datum. Then we present the method using data compression.

In the case of synthesis of one tone per datum, each datum yielded three values for the synthesiser: frequency (*freq*), amplitude (*amp*) and duration (*dur*). The frequency value is calculated in Hz as follows: $freq = (datum \times \varphi) + \alpha$. We set $\alpha = 440$ as an arbitrary reference to 440Hz; changes to this value produce sonifications at different registers. The variable φ is a scaling factor, which accounts for the range of values in the data file. This scaling factor needs to be variable because the range of μV values produced by the spheroids may vary with different experimental conditions. For the sonifications described in this paper $\varphi = 20$.

The synthesizer's amplitude parameter is a number between 0 and 10. The amplitude is calculated as follows: $amp = 2 \times \log_{10}(abs(datum) + 0.01) + 4.5$. This produces a value between 0.5 and 9.5. In order to avoid negative amplitudes we take the absolute value of the datum. Then, 0.01 is added in order to avoid the case of logarithm of 0, which cannot be computed. We later decided to multiply the result of the logarithm by 2, in order to increase the interval between the amplitudes. Since $\log_{10}(0.01) = -2$, if we multiply this result by 2 then the minimum possible outcome would be equal to -4. We add 4.5 to the result because our aim is to assign a positive amplitude value to every datum, even if it values 0μV.

The duration of the sound is calculated in secs; it is proportional to the absolute value of the datum, which is divided by a constant *c*: $dur = \frac{abs(datum)}{c} + t$. In the case of the present example $c = 100$. The higher the value of *c*, the more "granular-like" (Miranda 1995, Roads 1988) the results. We add *t* to the result in order to account for excessively short or possibly null durations (e.g., $t = 0.05$).

In the case of sonification of compressed data, the compression algorithm was implemented as follows: it begins by creating a set with the value of a datum. To start with, this will be the first sample of the data. Then it feeds in the second sample, the third, and so on. The value of each incoming sample is compared with the value of the first sample in order to check if they are close to each other according to a given distance threshold *Δ*. If the difference between them is lower than *Δ*, then the incoming datum is stored in the set. Otherwise, the values of all data stored in the set are averaged and used to generate a tone. Then, a new set is created, whose first value is the value of the datum that prompted the creation of the last tone, and so forth. In this case, the frequency of a tone is calculated as follows: $freq = \left(\frac{(set\_average - n) \times 900}{x - n} \right) + 100$, where n is the minimum value found in the data file that is being sonified and x is the maximum value. (The values of n and x do not necessarily need to be the minimum and maximum values in the data file; they can be set arbitrarily, with the condition that $n < x$.) The result is scaled in order to fall in the range between 100Hz and 1kHz. The amplitude is calculated as for the case of one tone per datum, as described above, with the only difference that the *datum* is replaced by the *set average*. The duration is also calculated as described above with the difference that we introduce a bandwidth defined by minimum and maximum duration thresholds. If the calculated duration of a tone falls outside the bandwidth, then the system assigns a predetermined duration value; e.g., the tone is assigned a duration of 0.1sec if its calculated duration is below the minimum threshold.

Figure 5 shows the cochleogram of an excerpt of a sonification, where one can clearly observe sonic activity corresponding to induced spiking activity. Figure 6 zooms into the details of the fist 5ms of a sonification, where one can observe variations in amplitude and the granular characteristic of the sound.

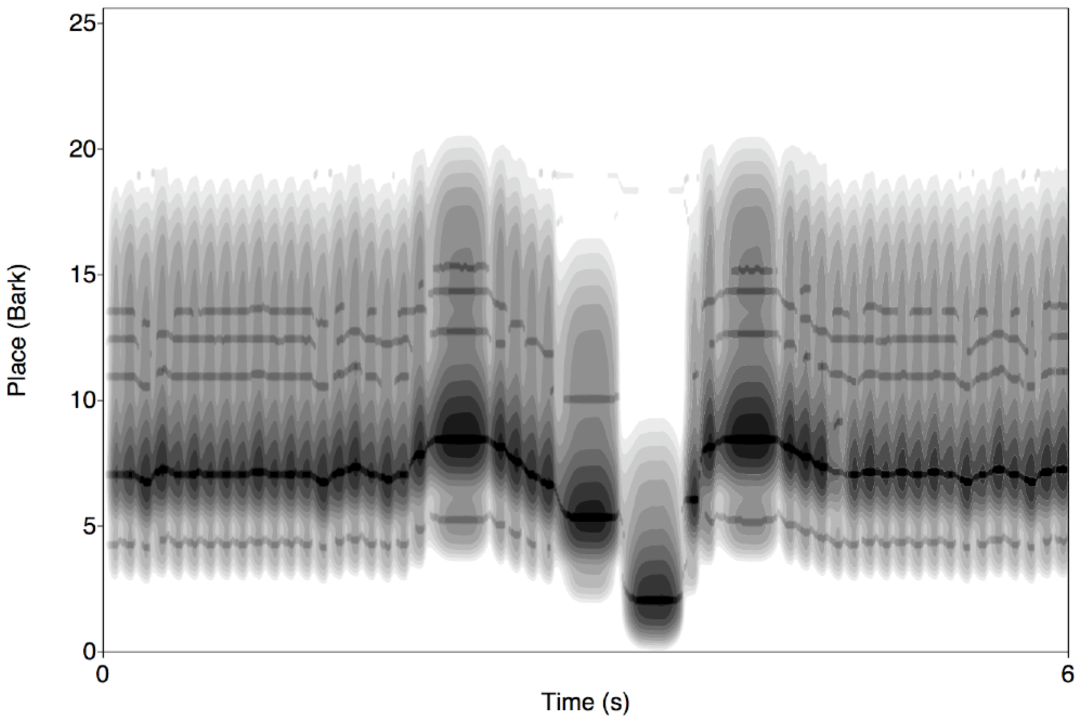


Figure 5. Cochleogram of an excerpt of a sonification where spikes of higher amplitude can be heard between 1sec and 4.2secs.

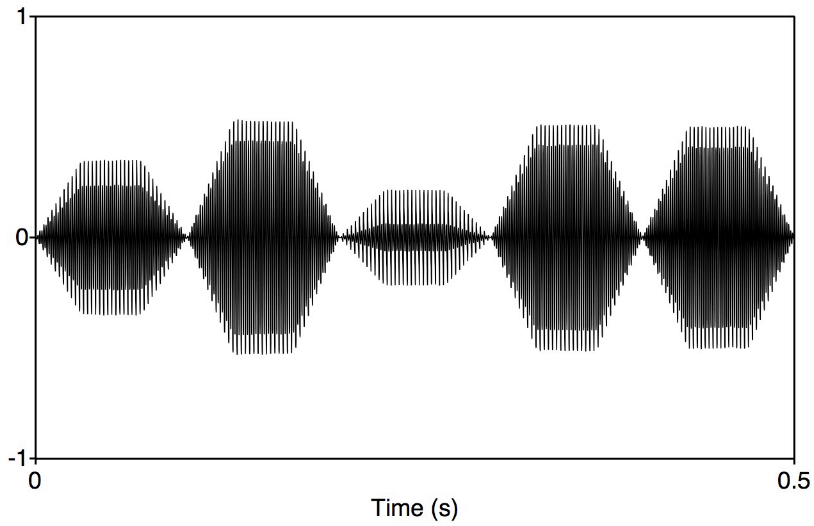


Figure 6. The first 500ms of a sonification where one can observe a sequence of five very short tones at different amplitudes. In this case, their durations have been assigned a pre-established value of is 100ms each.

Towards Control through Machine Learning

Sonification of data is an interesting practice on its own right, with applications in science (Baier et al. 2007) and sonic arts (Kabisch et al. 2005). However, this project does not stop here. The natural progression is to move on to sound synthesis, were control and repeatability of some sort are often desired. It is at this stage of the project that the potential of performing non-linear computations with hybrid wetware-silicon devices begins to be explored.

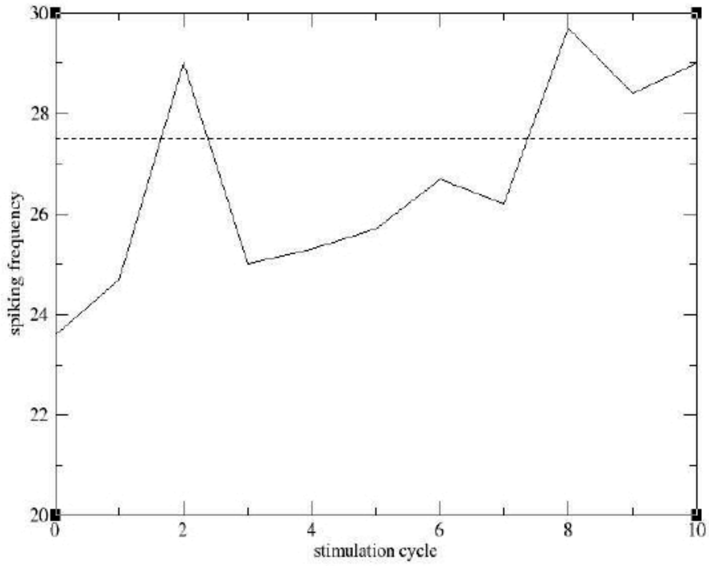
In this section we report the first results of our research into the development of protocols to control spiking behavior (*in vitro* wetware computing) through machine learning (*in silicon* computing). Currently, we are looking into the possibility of producing spike trains with controllable temporal structure.

Shahaf and Marom (2001) have demonstrated stimulus-response learning behavior in cultured rat neurons: a required response for a given input was obtained from a pre-determined electrode. We have made good progress in obtaining similar behavior with cultured neurons from hen embryos. We adopted an evolutionary computing reinforcement learning approach, which employs a form of Holland's Learning Classifier System, known as XCS, to create generalizations over a state-action space (Holland 1986, Wilson 1995). Such systems learn production rules of the general form IF <state(s)> AND <action> THEN Reward = *x*.

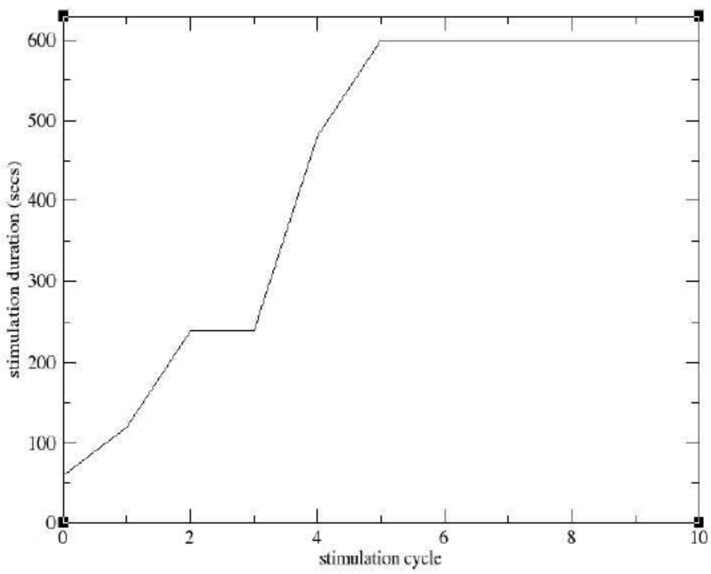
The average spontaneous spiking frequency of an output electrode of the MEA device is ascertained over a window lasting for 300secs. The standard deviation of the spikes is detected over the window. The task of the XCS controller is to cause the chosen electrode to reply to the simple stimulus described above with a spiking frequency of the spontaneous mean plus two standard deviations; a significant increase in typical spiking frequency is required.

The input to the XCS is the spiking frequency averaged over the last three seconds and the time length of the stimulus. The first number is presented as a fraction of the maximum spiking frequency observed under the 300secs of spontaneous behavior. The second number is presented as a fraction of the maximum allowed stimulation time of 600secs. The XCS returns one of three actions: to double, halve or maintain the current stimulation time. A reward of 500 is given if the spiking frequency increases over the last stimulation period compared to that immediately prior and a reward of 1000 is given if the target spiking frequency, or one greater, is achieved. We allow a 300 second rest period between applications of the stimulus and truncate the maximum duration of stimulation to 600secs. Thus 300secs after the last stimulation period, the XCS controller is given the last recorded spiking frequency of the neuronal network under stimulation, as a three-point running average, and the amount of time for which the stimulus was applied that caused the response. It then adjusts or maintains the stimulus duration for the coming cycle. A stimulation period of 60secs is used for the initial cycle. Hence, the XCS is presented with an input consisting of two real numbers scaled between 0.0 and 1.0. The condition part of the classifiers is encoded as un-ordered pairs of real numbers in the range [0, 1], one pair for each input. A pair is considered to match the corresponding input value if one element of the pair is smaller or equal to the target, and the other is larger or equal. The action of the classifier results in an integer value.

The control problem that we face here is not trivial. Nevertheless, we have succeeded in steering the behavior of the *in vitro* neuronal networks with the XCS controller in at least a third of our experiments so far. Figure 7 shows an example where the XCS controller was able to cause the required spiking response to the stimulus. As can be seen, and as was typical here, the XCS controller achieves this by increasing the duration for which the stimulation is applied. However, there were cases where no significant change in spiking appeared to have occurred regardless of how the XCS adjusted the stimulation. And in other cases the average spiking response decreased during the experiment regardless of stimulation.



(a)



(b)

Figure 7. Example learning behavior under XCS control, showing the spiking frequency response becoming repeatedly higher than the target indicated by the dashed line (a) and how XCS altered the stimulus application time to achieve this (b).

Concluding Discussion

Sound synthesis with *in vitro* neural networks still is in its infancy, but so is the field of Unconventional Computing with *in vitro* neural networks. This paper reported an initial investigation into the feasibility of such an approach. To the best of our knowledge, this is the first time that this modality of Unconventional Computation has been investigated in the context of Computer Music.

We introduced a technique to sonify the behavior *in vitro* neuronal networks, which proved the concept: it works (in the sense that we can hear the behavior of the data) and it is simple. We acknowledge that one of the given evaluation criteria (see Sonification section) is rather subjective and biased by the aesthetic judgment of the authors, one of whom is a composer. Nevertheless, we have decided to take this subjective criterion into account because this technology is being developed primarily for making music and we are of the opinion that composers should ultimately decide upon the nature of the technology and sounds they wish to make music with.

An important property of a sound synthesis technique is its ability to produce different types of sounds with a certain degree of predictable control. Controlling behavior and understanding how information is coded and processed by the cultured neurons are two Holy Grails of research into *in vitro* neuronal networks. We introduced an evolutionary computing reinforcement learning approach to tackle the problem of control and demonstrated how stimulus-response learning behavior in cultured neurons from hen embryos can be achieved.

Our ability to steer the behavior *in vitro* neuronal networks in a third of cases is very encouraging because it demonstrates that the problem is tractable. From a control engineering perspective, it would be highly desirable to be able to fully control the *in vitro* neural networks, especially if one intends to exploit this technology to build new digital musical instruments (Miranda and Wanderley 2006). However, our currently inability to exert full control or predict the behavior of these networks should not be taken as a limitation of this technology for music. On the contrary, this may open a number of attractive possibilities, especially for musicians interested in the musical thoughts initiated by John Cage (1961) and possibly others, where indeterminism is welcomed in the creative process. Moreover, a less conservative approach to music technology is definitely needed here in order to take advantage of one of the major strengths of Unconventional Computing, namely non-linear computation.

This work was partially supported by EPSRC Grant No. GR/T11029.

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