Addendum A

ADDITIONAL TEMPORAL CHARACTERISTICS

The model of the human Type I ANF developed in this study is verified against measured temporal characteristic data from literature. In Chapter 2 a review is presented on the temporal characteristics investigated in this study. For the sake of completeness, the temporal characteristics not covered are briefly reviewed in this addendum. These are:

1. discharge rate

2. adaptation

3. alternation

4. entrainment, also referred to as time-locking

5. phase-locking

6. synchronisation

A.1 DISCHARGE RATE

Discharge rate refers to the rate at which APs (also referred to as spikes) are elicited from a fibre given a specific input pulse train stimulus. In single-fibre studies of cat auditory neurons Moxon (1971) reported direct activation in response to pulsatile and sinusoidal electrical stimuli. Responses to pulsatile stimuli included *a*) an initial short latency (< 1.0 ms) and high firing rates (of up to 900 Hz); and *b*) an adaptation rate of tens of seconds to lower (up to 480 Hz) firing rates. Responses to sinusoidal stimuli included *a*) a very fast increase in firing rate for a small increase in stimulus intensity; *b*) a gradual threshold change with frequency; *c*) at high stimulus frequencies the appearance of a quasi-periodic firing which is not related to the stimulus period; and *d*) at high frequencies the occurrence of a substantial firing rate adaptation.

Interval histograms by Dynes and Delgutte (1992) indicated that at high stimulus frequencies (> 1.0 kHz) fibres show regular discharging in response to sinusoidal waves, similar to what has been seen in low-frequency studies. However, owing to the variation in interspike intervals that correspond to many stimulus cycles, high-frequency electrical stimulation causes fewer regular discharge responses than low-frequency stimulation. Javel (1990) also reported a decrease in discharge rate as the pulse rate of pulse train stimuli increased from 100 to 800 pps. The regularity of fibre discharge thus depends on both the stimulus frequency and stimulation mode, with discharge responses due to high-frequency stimulation falling between the irregular responses observed with high-frequency acoustic stimulation and regular responses observed with low-frequency electrical stimulation. These observations may be explained by the notion that repeated stimulation causes partial refractoriness in fibres, but other phenomena such as adaptation effects cannot be ruled out (Miller *et al.*, 2001a).

Discharge rate also increases for increasing stimulus intensities. Javel *et al.* (1987) observed this for biphasic pulse-trains and interpreted this as implying that *a*) the increase in discharge growth rate with increasing stimulus intensity does not differ much with pulse rate presentation; and *b*) the discharge rate depends on the stimulus intensity and not on pulse rate. They attributed this to the build-up of stimulus intensity and neural refractoriness.

A.2   ADAPTATION

Adaptation refers to the behaviour of fibres, after excitation with a long duration
pulse train, initially to start firing action potentials at a high discharge rate and, after
a certain time period, which can be as long as a few seconds in some cases, start to
reduce their discharge rate until a steady state is reached, i.e. reduced responsiveness
to stimuli. Smith and Brachman (1982) attributed adaptation partly to hair cell
synapses, but electrical stimulation can cause adaptation, even though it bypasses the
synapses. This suggests that a different mechanism may be causing the adaptation
effect seen in electrical stimulation.

Adaptation is observed in fibres stimulated with high-frequency pulse trains (Moxon,
1971). Responses to high-frequency pulsatile and sinusoidal stimuli initially show high
firing rates (of up to 900 Hz), after which a substantial firing rate adaptation of tens
of seconds to lower (up to 480 Hz) firing rates occur. Fibre discharge rates rise quickly
with increasing stimulus intensity up to as high as 900 pps for the first few seconds,
dropping thereafter to a more steady state rate of 500 pps. With shorter pulse trains
even higher discharge rates can be obtained. The same trend in discharge rate is also
observed by Van den Honert and Stypulkowski (1987b) for sinusoidal stimuli of up to
2.0 kHz stimulus frequency. Javel (1990) observed adaptation in fibres stimulated with
biphasic pulses of long phase duration at 200 Hz stimulation rate. The adaptation
effect is greatest for stimulation intensities falling in the dynamic ranges of the fibres,
while at high stimulation intensities, fibres prove to respond to every stimulus pulse
and the adaptation effect disappears. It is concluded that not all adaptation effects
originate from hair cell / fibre synapses, but that some adaptation effects in electrical
stimulation originate in the spiral ganglion cell.

The adaptation effect only exists over a narrow intensity range. Dynes and Delgutte
(1992) observed adaptation of between 25% and 80% at high stimulus frequencies
($>$ 1.0 kHz) for sinusoidal electrical stimulation. Their results also indicate a con-
siderable inter-fibre variability in adaptation behaviour over time. Similar adaptation
effects are also observed by Shepherd and Javel (1997) for biphasic stimuli in normal,
short-term and long-term deafened cats.

Although not used in the true sense of the word, adaptation-like effects are observed
for monopolar, monophasic stimulation of cat fibres, showing a reduction in respon-

siveness to stimuli after some time of continuous stimulation has transpired (Miller *et al.*, 1999b). The reduction in responsiveness is more evident with anodic than with cathodic stimuli and resulted in an upward threshold shift of 0.85 dB for anodic and 0.28 dB for cathodic stimulation with time. ECAP simulation results with an empirically based model based on cat fibre data confirmed the more pronounced adaptation effects with anodic stimuli (Miller *et al.*, 1999a). The effect is thought to be due to refractoriness of the neural membrane as a result of prior stimulation rate. When the simulation rate is decreased, the responsiveness returns to levels prior to stimulation at the higher rate. Similar adaptation-like effects have been observed previously, but usually for shorter interpulse intervals (IPIs) (see for example Van den Honert and Stypulkowski, 1984; Van den Honert and Stypulkowski, 1987a).

A.3   ALTERNATION

In addition to the adaptation observed in electrically stimulated auditory nerve fibres, an alternation in response probability between successive stimulus pulses has been observed. Javel (1990) observed alternation with biphasic stimulus pulses in fibres when the stimulation rates exceed the maximum possible discharge rate of the fibre. The alternation appears to converge to an intermediate response probability steady state after a few tens of milliseconds. The effect is attributed to neural membrane refractoriness. Alternation in short-term deafened fibre responses due to biphasic stimuli is observed by Shepherd and Javel (1997) in fibres which show a reduction in entrainment for stimulus rates greater than 400 pps. Almost no alternation is observed in fibres having 100% entrainment for stimulus rates up to the tested 800 pps.

Matsuoka *et al.* (2000b) observed alternation in cat and guinea-pig ECAP responses for fibres stimulated with pseudomonophasic constant-amplitude pulse trains. Results indicate that amplitude alternation is stimulus intensity, polarity and IPI dependent. In cats, the maximum alternation amplitude increases with an increase in stimulus intensity. For cathodic stimuli maximum alternation amplitudes are observed at IPIs about 1.0 ms longer than with anodic stimulation, while more alternation is observed with cathodic than with anodic stimuli. This can be attributed to the combined effects of across-fibre synchronous responses and refractory properties of the stimulated fibres, with maximum alternation amplitude occurring when the pulse train's IPI falls

within the fibre's RRP. Furthermore, the persistence of the alternation pattern probably relates to the stochastic nature of the fibre, with reduced stochasticity resulting in a more persistent pattern. In guinea-pigs amplitude alternation is more pronounced than in cats, but polarity effects are not as clearly observable as in cats. These differences are attributed to the difference in cochlear structure between the two species which results in a difference in fibre excitation sites. The addition of Gaussian noise to the input constant-amplitude pulse train signal results in reversible across-fibre desynchonisation and hence reduced amplitude alternation (Matsuoka, Abbas, Rubinstein and Miller, 2000a). However, the added noise does not have an adaptive effect on the ECAP response amplitude, since its effect is only sub-threshold.

A.4 ENTRAINMENT, ALSO REFERRED TO AS TIME-LOCKING

An acoustic tone presented to an auditory nerve fibre will, if it is presented at a low enough frequency, cause the fibre's discharges to become partially entrained (time-locked) to the stimulus period. This means that intervals between successive discharges will synchronise around integer multiples of the stimulation period (see Javel *et al.*, 1987). Entrainment that is similar to acoustic entrainment is reported for fibres from normal cochleae (Javel *et al.*, 1987; Javel, 1990), except that for electrical stimulation, the degree of entrainment is much higher than for acoustic stimulation. Also, for high stimulus intensities at pulse rates exceeding 800 pps, the fibre's discharges are entrained to the period of the stimulus and the discharge rate will never exceed that of the stimulus. In short-termed deafened animals, Shepherd and Javel (1997) found 100% entrainment in some fibres for stimulus pulse rates of up to 800 pps, while in most others, 100% entrainment only occurred for stimulus pulse rates of up to 400 pps. At higher stimulus rates, activity will switch between 100% entrainment and periods of complete inactivity. Difficulty in following high stimulus rates at 100% entrainment is also observed in long-term deafened animals (Shepherd and Javel, 1997).

A.5   PHASE-LOCKING

Phase-locking to the formant frequencies in a speech signal have proved to be an important cue for speech discrimination. Several studies show that the auditory fibres phase-lock to sinusoidal and pulse train stimuli for frequencies below 1.0 kHz (Kiang and Moxon, 1972; Javel *et al.*, 1987; Van den Honert and Stypulkowski, 1987b; Javel, 1990).

At high stimulus frequencies (> 1.0 kHz), discharges tend to be only moderately phase-locked to the stimulus, unlike the phase-locked response to low-frequency stimuli, not displaying the sharp peak in the period histograms but rather a roughly sinusoidal shape (Dynes and Delgutte, 1992).

For low-frequency, large amplitude, bipolar sinusoidal stimulation, Van den Honert and Stypulkowski (1987b) reported discharges during both the opposite phases of the signal, with sometimes even multiple discharges during one half cycle. At threshold, however, discharges occur for only one of the phases. They attributed this to a difference in excitation sites along the fibre for the opposite phases. Stimulation with triangular and square pulses shows the same behaviour, although the threshold current needed is always highest for triangular pulses and lowest for square pulses for a given frequency. At frequencies below 200 Hz double-peak responses are often seen within the same phase, but sometimes even in both phases. The points within the phases where the responses occur only show very small variations with stimulus intensity, with those for sinusoidal and triangular pulses similar in timing and stimulus intensity dependence. Responses to square pulses differ from those to sinusoidal and triangular pulses. The dominant response peak has a higher synchrony, appears in a different phase and shifts between phases with increasing stimulus intensity. Jitter and discharge rate also vary non-monotonically with increasing stimulus intensity. Dynes and Delgutte (1992) also reported less frequent responses to opposite stimulus phases at high-frequency stimulation and concluded that the origin of this effect is not clear.

A.6   SYNCHRONISATION

Synchronisation refers to the tendency of an ensemble of fibres to fire in synchrony. Kiang and Moxon (1972) and Hartmann *et al.* (1984) reported spike fire synchronisation to electrically delivered sinusoidal stimuli with an increase in synchronisation as the stimulus intensity increases. This tendency is confirmed by Van den Honert and Stypulkowski (1984) and Javel *et al.* (1987) who reported an increase in synchronisation, together with an increase in FE, with an increase in pulsatile electrical stimulus intensity in normal hearing and acutely deafened cats respectively. In cats that had undergone a laminectomy, synchronous firing occurs even at low stimulus intensities, with no spontaneous activity present. Observations by Miller *et al.* (1999b) on latency, jitter and FE with monopolar, monophasic stimuli of acutely deafened cats also suggest an increase in synchronisation and FE.

Synchronisation also decreases as the stimulus frequency is increased. Results reported by Van den Honert and Stypulkowski (1987b) indicate that at high frequencies (> 500 Hz), fibres do not fire at each stimulus cycle of the sinusoidal stimulus signal.

Since synchronisation decreases the dynamic range of the implantee, a decrease in synchronisation may lead to an increase in dynamic range. Rubinstein *et al.* (1999) introduced pseudospontaneous activity, and hence less synchrony, in fibres through electrical stimulation with a sufficiently high rate. Runge-Samuelson, Abbas, Rubinstein, Miller and Robinson (2004) confirmed the possibility of simulating increased spontaneous nerve fibre activity in cats and guinea-pigs with electrical stimulation by adding a high rate conditioner to sinusoidal stimuli. The results from a study by Runge-Samuelson *et al.* (2004) confirm the results of a similar study by Hong, Rubinstein, Wehner and Horn (2003) performed on humans that decreased synchrony leads to a dynamic range increase in implantees by lowering thresholds.