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A model of activity-dependent anatomical inhibitory plasticity applied to the mammalian auditory system

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Abstract. We construct a model of activity-dependent, anatomical inhibitory plasticity. We apply the model to the mammalian auditory system. Specifically, we model the activity-dependent topographic refinement of inhibitory projections in the auditory brain stem, and we construct an anatomically abstract model of binaural band formation in the primary auditory cortex involving the segregation of different populations of inhibitory and excitatory afferents. Issues raised and predictions made include the nature of interactions between excitatory and inhibitory afferents innervating the same population of target cells, and the possibility that pharmacological manipulations of the developing primary auditory cortex might induce a shift in the periodicity of binaural bands. Any model of inhibitory plasticity must confront the issue of postulating mechanisms underlying such plasticity. In order to attempt to understand, at least theoretically, what the mechanisms underlying inhibitory plasticity might be, we propose the existence of a new class of neurotrophic factors that promote neurite outgrowth from and mediate competitive interactions between inhibitory afferents. We suppose that such factors are up-regulated by hyperpolarisation and down-regulated by depolarisation. Furthermore, we suppose that their activity-dependent release from target cells depends on Cl^- influx. Such factors are therefore assumed to be the physiological inverse of such factors as nerve growth factor and brain-derived neurotrophic factor, which are up-regulated by depolarisation and down-regulated by hyperpolarisation, with their activity-dependent release depending on Na^+, and not Ca^{2+}, influx.

Abbreviations: *BDNF* Brain-derived neurotrophic factor; *LSO* Lateral superior olive; *MGN* Medial geniculate nucleus; *MNTB* Medial nucleus of the trapezoid body; *NGF* Nerve growth factor; *SGC* Spiral ganglion cell

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1 Introduction

The mammalian auditory system is ideally suited, despite its complexity, as a model system for constructing and studying computational and mathematical models of activity-dependent anatomical inhibitory plasticity. For example, it has been established that glycinergic inhibitory projections from the medial nucleus of the trapezoid body (MNTB) to the ipsilateral lateral superior olive (LSO) undergo a period of activity-dependent topographic refinement associated with the onset of hearing in the gerbil, and that the MNTB projections are capable of sprouting (Sanes and Siverls 1991; Sanes and Takacs 1993). The inhibitory projections are associated mainly with the high-frequency region of the LSO, since during development an initially uniform distribution of glycine receptors becomes localised to the high-frequency region (Sanes et al. 1987; Sanes and Wooton 1987).

In addition, a feature of the primary auditory cortex in many species is the existence of alternating binaural bands, which run perpendicular to the isofrequency direction on the cortex (e.g. Imig and Adrian 1977; Kelly and Sally 1988; Kelly and Judge 1994). Binaural bands represent regions with either summation-type characteristics (excited by stimulation of either ear, denoted by 'EE') or suppression-type characteristics (excited by the contralateral ear but suppressed by the ipsilateral ear, denoted by 'EI'). During the development of binaural bands in the rabbit, evidence suggests that while thalamocortical afferents terminate in distinct patches in the auditory cortex prior to the onset of hearing, hearing onset is perhaps required to produce an adult-like terminal morphology (de Venecia and McMullen 1994). Auditory cortical cells inherit many of their response characteristics (summation, suppression, etc.) from cells earlier in the auditory pathway, such as those in the medial geniculate nucleus (MGN) (Middlebrooks and Zook 1983) and the inferior colliculus (Roth et al. 1978), rather than integrate them from separate and distinct

excitatory and inhibitory projections. However, any simplifying, anatomically abstract model of the overall projections from the two cochleas to the auditory cortex would need to consider anatomical plasticity associated with inhibitory afferents.

Activity-dependent, though not necessarily anatomical, plasticity of inhibitory synapses has also been observed in other systems, such as the cerebellar Purkinje cell (Llano et al. 1991; Kano et al. 1992), the teleost Mauthner cell (Korn et al. 1992) and the *Aplysia* siphon withdrawal reflex (Fischer and Carew 1993).

From a theoretical perspective, inhibitory plasticity presents some problems. The plasticity of excitatory afferents in many systems depends on post-synaptic activity. For example, the formation of ocular dominance columns in the striate cortex (Hubel and Wiesel 1962) and the elimination of polyneuronal innervation at the vertebrate neuromuscular junction (Redfern 1970) depend on post-synaptic activity (Srihari and Vrbova 1978; Reiter et al. 1986). It is standardly assumed that post-synaptic depolarisation results in Ca^{2+} influx, with Ca^{2+} acting as a second messenger, leading to pre- or post-synaptic changes, or both. However, inhibitory afferents act by hyperpolarising the post-synaptic cell and thus reducing Ca^{2+} influx. Potentiation of inhibitory transmission in cerebellar Purkinje cells does depend on a transient elevation of post-synaptic Ca^{2+}, but this appears to be mediated by activity in the excitatory climbing fibres (Konnerth and Eilers 1994). At the teleost Mauthner cell, evidence suggests that the potentiation of inhibitory transmission does depends on intracellular Ca^{2+} (Oda et al. 1995). It is also possible that inhibitory afferents activate pathways which lead to an elevation in post-synaptic Ca^{2+} via the release of Ca^{2+} from intracellular stores. In addition, it is logically possible that some forms of inhibitory plasticity do not depend on post-synaptic activity at all, but this would be hard to reconcile with, for example, activity-dependent topographic refinement of inhibitory afferents in the LSO, since this indicates that some mechanism must exist that can detect correlated pre-synaptic inhibitory activity (Sanes and Takacs 1993).

In the present paper we will construct a model of anatomical, inhibitory plasticity in order to attempt to address some of these problems. At first we will present the model in a rather abstract manner, and apply it to specific examples of inhibitory plasticity. In particular, we will use the model to simulate the activity-dependent topographic refinement of inhibitory projections from the MNTB to the LSO and the development of binaural bands in the primary auditory cortex. While the former model will be anatomically realistic, we will take a much simplified view of the auditory system in simulating binaural band formation.

There are a number of reasons for considering an anatomically abstract model of binaural band formation. First, the auditory cortex acquires many of its response characteristics from lower centres (Roth et al. 1978; Middlebrooks and Zook 1983). An anatomically realistic model would only need to consider two functionally distinct sets of excitatory inputs from the MGN to the auditory cortex, representing afferents with summation-type responses and suppression-type responses (Middlebrooks and Zook 1983). Such a model would shed no light on the mechanisms of inhibitory plasticity and would be based on principles similar to those used by models of ocular dominance column formation (Elliott et al. 1996a). Second, an anatomically realistic model which would shed light on inhibitory plasticity would essentially need to model the entire auditory pathway from the cochleas through the cochlear nuclei, superior olives, inferior colliculi and MGNs to the auditory cortex. Given the limited state of knowledge concerning the detailed anatomy of this pathway, such a model would be difficult to build. Finally, a posteriori we find that an anatomically simplified model of binaural band formation raises issues, questions and predictions not raised by the model of inhibitory topographic refinement.

Our interpretation of the model exploits recent findings concerning the release of neurotrophic factors. Specifically, the activity-dependent component of the release of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) from hippocampal neurons depends on Na^+ and not Ca^{2+} influx, although it does depend on intracellular Ca^{2+} (Blöchl and Thoenen 1995; Griesbeck et al. 1995; Blöchl and Thoenen 1996). Neurotrophic factors have recently been receiving much attention as possible mediators of activity-dependent neuronal plasticity and competition between afferents (reviewed in Thoenen 1995). Thus, if neurotrophic factors are a critical component underlying (excitatory) synaptic plasticity, then their unconventional activity-dependent release mechanism raises questions very similar in nature to those regarding the mechanisms of inhibitory plasticity: how can only $Na^+(Cl^-)$ influx be enough; what molecular mechanisms are involved; etc?

The plan for the remainder of the paper is as follows. First, we present our framework for modelling the anatomical plasticity of inhibitory afferents. Next, we present simulation results. Finally, we discuss our interpretation of our model, and the results and issues raised by our approach.

2 Materials and methods

In this section we describe the techniques used to simulate the sprouting and retraction of afferent axonal processes, and our use of statistical mechanics in this process. At this stage, we leave open the biological interpretation of the framework.

In simulating the activity-dependent, topographic refinement of the inhibitory projections from the MNTB to the LSO, we assume that the MNTB and the LSO can each be modelled as one-dimensional arrays containing s_{mntb} and s_{lso} cells, respectively. Each MNTB cell initially arborises over a line of a LSO cells, where the position of this line is determined by the requirement that the initial MNTB projections should roughly preserve topography.

In simulating an abstract model of the formation of binaural bands in the primary auditory cortex, we assume that the spiral ganglion cells (SGCs) of the cochlea can be modelled as a one-dimensional array of s_{sgc} cells, and that the primary auditory cortex can be modelled as a regular, two-dimensional $c \times c$ array of c^2 cells. The projections from the contralateral SGCs will be assumed

to be exclusively excitatory, while half those from the ipsilateral SGCs will be assumed to be inhibitory with the remaining half excitatory (for this abstract model of binaural band formation, we need not be concerned that one cell sends both excitatory and inhibitory projections; in a more anatomically realistic model, these pathways would arise not from the cochlea but from nuclei within the brain stem). Each SGC initially arborises over a line of a_x cells on the cortex in the cochleotopic direction (which we take to be the x-direction on the cortical array), where the position of this line is determined by the requirement of topography, while in the orthogonal, y-direction, each SGC initially arborises uniformly over every cell.

For computational convenience, all arrays are assumed to be periodic, so that one-dimensional arrays (MNTB, LSO, SGCs) have the topology of a circle and the two-dimensional cortex has the topology of a torus. The use of periodic boundary conditions is a convenient way of avoiding edge effects. Our model also operates without such boundary conditions, although results at the edges might suffer from disruptions.

Each afferent cell is taken to possess an axon from which emerge axonal processes. Each MNTB cell initially possesses $3a$ processes, so that an MNTB cell initially sends 3 projections to each LSO cell in its arbor region (this number is selected purely for reasons of convenience; our results are robust to changes in this number). To each cortical cell in its $a_x \times y$ arbor region, an SGC initially projects $2a_y$ processes, where a_y is defined later. For the contralateral SGCs, all are excitatory, while for the ipsilateral SGCs, a_y are excitatory and a_y are inhibitory. Letters such as i and j label all axonal processes, both excitatory and inhibitory, with $a_i \in [0, 1]$ denoting the state of activation of the cell from which process i emerges (though we shall restrict attention to binary-valued activity so that $a_i \in \{0, 1\}$) and $\epsilon_i \in \{-1, +1\}$ indicating whether the process is excitatory ($\epsilon_i = +1$) or inhibitory ($\epsilon_i = -1$).

The patterns of afferent activity in either the MNTB or the SGCs will be assumed to take the form of randomly located lines of length ρ of adjacent, active cells, with all other cells inactive. In modelling binaural bands we permit the possibility of correlated activity in the ipsilateral and contralateral arrays of SGCs. Given that one line of SGCs is active in one cochlea, we activate the corresponding cells in the other cochlea with probability q, and define a correlation index $C = 2q - 1$. Taking $C = -1$ means perfectly anti-correlated activity, $C = 0$ uncorrelated activity, and $C = 1$ perfectly correlated activity.

We assume the existence of an energy function which describes the underlying dynamics of sprouting and retraction. Furthermore, we assume that the dynamics of sprouting and retraction are such that the energy function is minimised during development, so that minima represent stable, mature patterns of connectivity. We take the total energy of the system to be given by (see the Appendix for a derivation)

$$E = -\sum_{i,j} \epsilon_i a_i \Delta_{ij} a_j \epsilon_j + \frac{1}{2} N \sum_{i,j} a_i \mathscr{D}_{ij} f_I(\epsilon_i, \epsilon_j) \tag{1}$$

The energy of any individual process i is given by

$$E_i = -2\epsilon_i a_i \sum_j \Delta_{ij} a_j \epsilon_j + a_i N \sum_j \mathscr{D}_{ij} f_I(\epsilon_i, \epsilon_j) \tag{2}$$

Here Δ_{ij} is a function characterising the diffusion of some factor through the target field and will, in general, be a function of the distance between the two afferent processes i and j in the target space. As a very crude model of the diffusion process, we take $\Delta_{ij} = 1$ if, and only if, the two processes are attached to neighbouring target cells (for a two-dimensional array of target cells this means the same or horizontally or vertically adjacent target cells, while for a one-dimensional array of target cells this means the same or directly adjacent target cells), and zero otherwise (we also take $\Delta_{ii} = 0\ \forall i$, so that there is no self-interaction). The symbol $\mathscr{D}_{ij} = 1$ if, and only if, the two processes are attached to the same target cell, and zero otherwise. The constant N is a diffusion normalisation constant, defined by $N = N_i = \sum_j (\Delta_{ij} / \sum_k \mathscr{D}_{jk})$, which is independent of i. Finally, f_I is a function characterising the interactions between excitatory and inhibitory terminals,

$$f_I(\epsilon_i, \epsilon_j) = \begin{cases} 1 & \text{competitive} \\ \frac{1}{2}|\epsilon_i + \epsilon_j| & \text{antagonistic} \end{cases} \tag{3}$$

where 'competitive' means that excitatory and inhibitory afferents explicitly compete with one another for control of target cells, while 'antagonistic' means that their influences are antagonistic but that they do not compete. We shall consider both possibilities.

To modify the pattern of connectivity between an afferent and its target, we consider performing small perturbations in the connectivity, representing sprouting, retraction or combinations thereof. For a particular state of afferent activity, we calculate the change in the total energy of the system, ΔE, which would be induced by performing the perturbation. The decision procedure used to decide whether to accept a candidate perturbation is based on the Gibbs distribution (Huang 1987). The probability, p, of performing the perturbation is given by

$$p = \frac{1}{1 + \exp[(\Delta E - \theta \Delta N)/T]} \tag{4}$$

where θ is the chemical potential and T is the temperature (both will be given a biological interpretation later), and ΔN represents the change in the total number of axonal processes in the system induced by the perturbation. This probability represents the probability of the old pattern of connectivity relative to the new pattern, and ensures that the distribution of states of connectivity approaches the Gibbs distribution. Subject to thermal fluctuations induced by non-zero T, the use of the Gibbs distribution allows us to find minima of the energy function which represent stable patterns of connectivity. Similar techniques borrowed from statistical mechanics were first introduced by Hopfield (1982), though while he used them to find new states of activation in an anatomically fixed network, we use them to find new patterns of connectivity in a network whose activity may also be varying.

By taking T initially very large and slowly reducing it to near zero, we may perform simulated annealing. This permits the system, provided that the annealing is performed sufficiently slowly, to find the global minimum of the energy function. If T is initially set to near zero (simulated quenching), the system will instead freeze into a nearby local minimum. The biological interpretation of the former, annealing, process is that the system is initially subject to high levels of noise which are slowly brought under control, while the biological interpretation of the latter, quenching, processing is that the system is never subject to significant levels of noise.

It is important to be clear that we do not assume that a system actually computes changes in the energy function, and on that basis decides whether to perturb its pattern of connectivity. This would require, for example, that the system determines its energy before the perturbation is applied, then performs the perturbation whether or not it will be retained, then determines its energy again, then calculates the difference, and then finally decides whether to retain the perturbation or whether to reverse it. It would be implausible to suggest that a neuronal system is capable of doing that. We suppose, rather, that we may think of the system in an identical fashion to a physical system, and this is why we employ statistical mechanics. In much the same way as the motion of individual atoms or molecules in a gas is characterised by an energy minimisation process, even though each atom or molecule presumably does not compute the direction in which to move in order to minimise its energy, we suppose that the process of anatomical rearrangement is such that each component of the system behaves in a manner which can be described by an energy minimisation process.

We may think of axonal processes as being attracted into regions of low energy and repelled from regions of high energy. Because the energy function is defined in terms of afferent activity, the regions of high and low energy fluctuate as rapidly as afferent activity changes, and perturbations in connectivity occur on the same

timescale. This could be regarded as biologically implausible. One way of overcoming this difficulty is to average the energy function over a time interval which is long compared to the rate at which afferent activity changes. Then anatomical rearrangement would occur on an acceptably long timescale. However, this averaging procedure has at least two difficulties. First, should we wish to examine the impact of reducing activity in particular subsets of afferent pathways (in order to model monaural deprivation, for example), we would be forced to make assumptions about how this would change the time-averaged energy function. Second, averaging prevents us from determining whether the model forms patterns of connectivity which are stable to rapid fluctuations in afferent activity. Such stability is an important feature of real nervous systems, and cannot be inferred from the long-term stability of a time-averaged system. Because we consider these two factors to be important, we therefore do not time-average the energy function, and thus must accept the implausibility of very rapid anatomical alterations. While we will consider, purely for reasons of computational convenience, large numbers of perturbations in response to each change in afferent activity, we could consider just one connectivity perturbation per afferent activation, which would go some way towards easing this problem. It is worth pointing out that most models are faced with this or related dilemmas.

In previous work we have studied three models based on this framework, the models being distinguished by the form of connectivity perturbations used (Elliott et al. 1996a,b). In the 'relocation' model, we suppose that an active axon retracts from one target cell and (eventually) sprouts onto another. Since, over time, this gives the impression that the axon has simply relocated a process, we considered the basic perturbations in network connectivity to be such relocations. In the 'interchange' model, we considered two coupled relocations, so that one axon sprouts onto one target cell while another axon (eventually) retracts from that target cell, and this occurs in reverse at another target cell. Again, over time, this gives the impression that the two axons have simply interchanged the locations of two processes, and the basic perturbations are taken to be such interchanges. We require that at least one process is active to perform the interchange. Then, in the 'sprouting-and-retraction' model, we uncouple sprouting and retraction and permit active axons either to sprout one new process or to retract one old process. These different models are summarised in Fig. 1. Finally, since each perturbation in the relocation and interchange models has $\Delta N = 0$, strictly speaking we employ the Boltzmann rather than the Gibbs distribution in deciding whether to accept a perturbation.

In modelling the activity-dependent refinement of the inhibitory projections from the MNTB to the LSO, we use the relocation model. Relocations are only permitted provided that a process remains within the afferent's arbor region. In modelling the formation of binaural bands, we use the interchange model. Interchanges are only permitted provided that the two processes are within each others' arbor regions. In the binaural band system, the arbor region of an axonal process is defined to be a rectangular box of size $a_x \times a_y$ centred on the initial position of that process. While an SGC may arborise over the full extent of the y-direction, individual processes are therefore confined to a smaller region. This restriction constitutes some attempt to account for the fact that, in a more anatomically realistic model of binaural band formation, afferents from higher centres in the auditory system, particularly the MGN, would be expected to arborise more selectively.

The interchange model rather than the relocation model is used to simulate the formation of binaural bands because it provides a convenient way in which to enforce a lower bound on connectivity while retaining the capacity for plasticity. This is necessary because there is a tendency in our models for excitatory and inhibitory afferents to segregate completely, whether their interactions are 'competitive' or 'antagonistic'. Were a target cell to experience a loss of excitatory drive, we would expect it, or associated glial cells, to exhibit a hypertrophic response in an attempt to encourage reinnervation by excitatory afferents (cf. Gomez-Pinilla et al. 1992; Rassendren et al. 1992; Caroni and Schneider 1994; Conner et al. 1994; Gwag et al. 1994; Guthrie et al. 1995). We thus impose a lower limit on the number of excitatory terminals supported by a target cell as a very crude representation of a hypertrophic response from target cells when their excitatory inputs are eliminated, and this is adequate to prevent a complete segregation of excitatory and inhibitory afferents.

3 Results

In this section we discuss the results of the simulation of the topographic refinement of inhibitory projections from the MNTB to the LSO and the anatomically abstract model of binaural band formation.

3.1 Inhibitory topographic refinement

We consider only the quenched relocation model, that is, we set $T = 0$ always. Because we do not consider any excitatory projections to the LSO, there is no distinction, in the present context, between the 'antagonistic' and the 'competitive' cases defined in Eq. 3. We set $s_{\mathrm{mntb}} = s_{\mathrm{lso}} = 39$ and $a = 9$, so that each MNTB cell initially arborises over nearly one quarter of the extent of the (high-frequency region of the) LSO. We impose an upper limit, u, on the number of synapses supported by each LSO cell, which we take to be $u = 30$. We randomly activate three adjacent MNTB cells at any one time (so that $\rho = 3$), and, for each activation, we consider 10 000 candidate process relocations. Such large numbers of relocations are permitted for reasons of computational convenience only, in order to reduce simulation time. Significantly reducing the number of

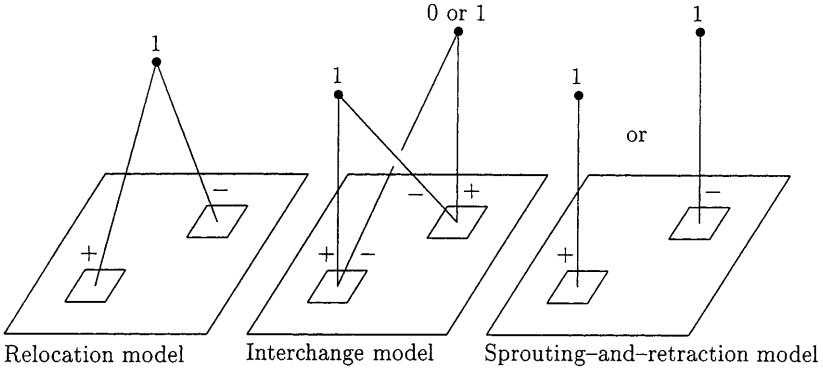

Fig. 1. A graphical summary of the three different models discussed in the text. The *bottom sheets* represent arrays of target cells, while the *blobs* represent afferent cells. Each number represents the state of activation of the associated afferent cell, and a '+' ('−') sign denotes sprouting (retraction)

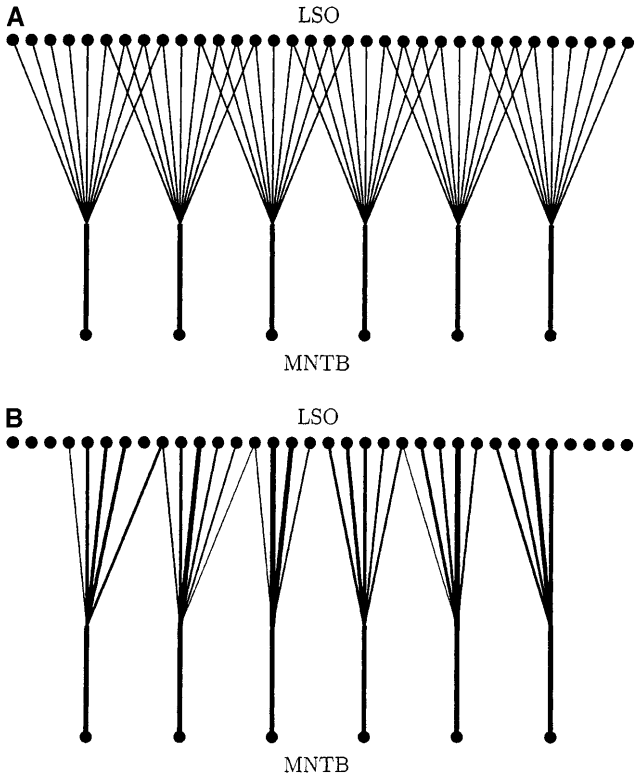

Fig. 2a,b. An example of the topographic refinement of inhibitory projections from the medial nucleus of the trapezoid body (MNTB) to the lateral superior olive (LSO) produced by the relocation model. The width of each line projecting to an LSO cell indicates the number of connections. In **A**, the initial projections are shown, while **B** shows the final pattern of connectivity following a period of activity-dependent plasticity. For clarity, only six MNTB cells are shown in each case. The parameters are: $s_{\text{mntb}} = s_{\text{lso}} = 39$, $a = 9$, $\rho = 3$, $u = 30$

relocations per activation pattern does not affect our results, although the number of activations used per simulation would, of course, have to be increased. For 10 000 relocations per activation pattern, we perform a total of 500 random MNTB activations.

Figure 2 shows an example of the simulated activity-dependent, topographic refinement of the inhibitory projections from the MNTB to the LSO. We see that an initial, diffuse set of projections becomes refined so that each MNTB cell finally arborises over a more restricted set of target cells. This topographic refinement is a function of ρ. As ρ approaches and exceeds a, topographic refinement becomes increasingly disrupted, and eventually breaks down.

3.2 Binaural bands

We consider both the quenched and the annealed interchange model. We set $s_{\text{sgc}} = c = 19$ with $a_x = 3$ and $a_y = 9$, so that each afferent process is confined to interchanges within a rectangle whose longer side is perpendicular to the cochleotopic x-direction (cf. McMullen and de Venecia 1993). We impose a lower limit, l, on the number of excitatory processes which a cortical cell may support, which we take to be $l = 2a_x a_y$. We set $\rho = 3$. As before, 10 000 candidate network perturbations (interchanges) are considered for each particular pattern of SGC activation. We set the correlation index, C, to be $C = 0$, so that ipsilateral and contralateral SGC activity is uncorrelated. Each simulation, for $T = 0$, consists of 50 separate SGC activations. For annealed systems, we start with $T = 400$ and reduce it to $T = 0$ in 41 step of $\Delta T = 10$. At each temperature step, 50 different SGC activations are presented, each with 10 000 candidate interchanges.

In Fig. 3 are two examples, one quenched and one annealed, of the final pattern of binaural bands produced by the 'competitive' version of the energy function, defined in Eq. 3. Also shown are the associated cochleotopic positions of each target cell, which position we take to be the position of the contralateral SGC that projects the greatest number of processes to a given target cell. There is no qualitative difference in our results for different values of ρ, nor for $C = \pm 0.5$ (correlated/anti-correlated SGC activity). Figure 4, for 'antagonistic' interactions, demonstrates that there is no qualitative difference in our results for this case. Were we to set $a_x = a_y$ instead of taking an elongated arborisation regions in the y-direction ($a_y > a_x$), we would find that some simulations would result in binaural bands running in a direction perpendicular to the experimentally found direction. Of particular note, in the present results, is the fact that the periodicity of binaural bands for quenched simulations is smaller than that for annealed simulations.

4 Discussion

We have shown that our proposed model of activity-dependent, anatomical inhibitory plasticity can account for the topographic refinement of inhibitory afferents in the LSO, and the formation of binaural bands in the primary auditory cortex. So far, we have left the mathematical formalism relatively uninterpreted. Since one of our purposes in developing the model was to attempt to shed some light, at least theoretically, on the mechanisms of (anatomical) inhibitory plasticity, we now discuss the biological interpretation and motivation of the model.

In previous work (Elliott et al. 1996a,b), when considering the plasticity of only excitatory afferents, we have interpreted the energy function as related to the levels of neurotrophic factors for which afferents compete during development. Experimentally, much evidence implicates retrograde neurotrophic interactions in the activity-dependent plasticity of and competition between excitatory afferents in the visual system (e.g. Carmignoto et al. 1993; Cabelli et al. 1995; Riddle et al. 1995), the somatosensory system (e.g. Henderson et al. 1994) and at the neuromuscular junction (e.g. Rassendren et al. 1992; Caroni and Schneider 1994; English and Schwartz 1995; Kwon and Gurney 1996). Furthermore, neurotrophic factors are intimately involved in the regulation of the complexity of afferent axonal arbors (e.g. Campenot 1982a,b; Cohen-

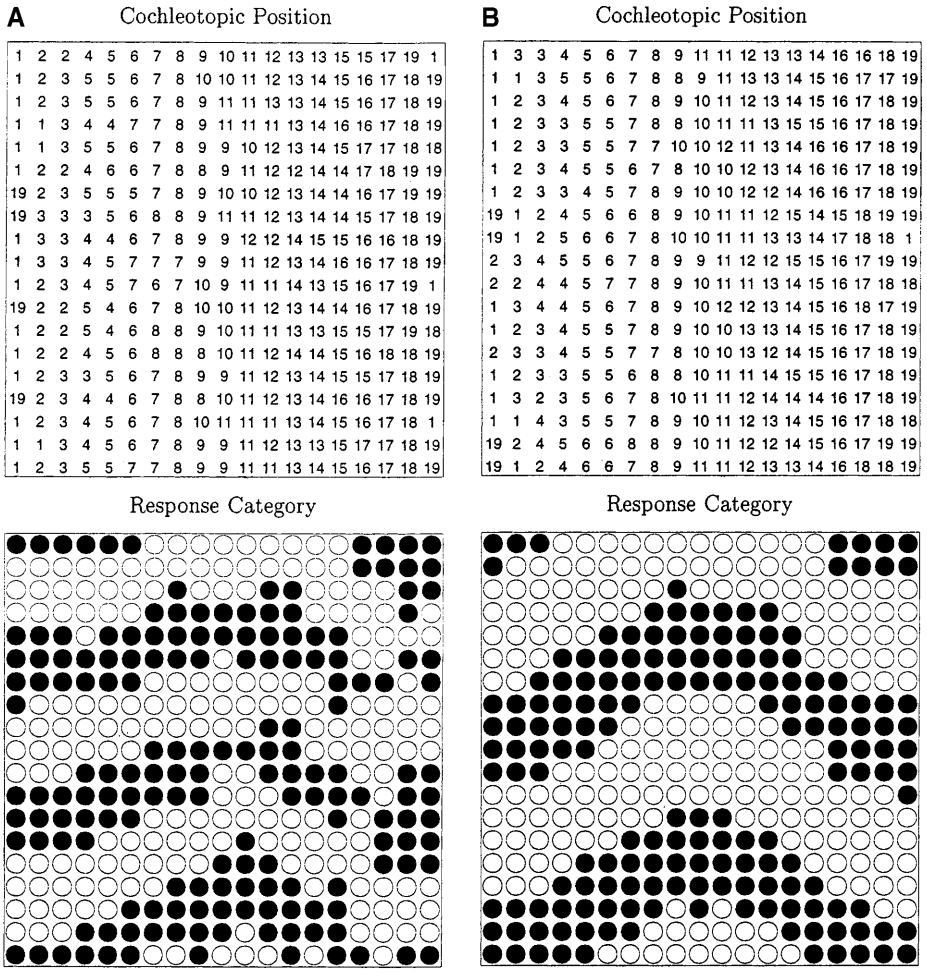

Fig. 3a,b. Two examples of the final pattern of binaural bands produced by the interchange model, for the 'competitive' case. Each entry in the maps denotes a cell, with the *top map* giving the cochleotopic position of the cell and the *bottom map* giving the response category. A *filled circle* represents a cell which is excited by both the contralateral and the inhibitory cochleas (EE), whereas an *open circle* represents a cell which is excited by the contralateral cochlea but inhibited by the ipsilateral cochlea (EI). In **A** the system has been quenched at $T = 0$, while in **B** the system has been annealed according to the strategy discussed in the text. The parameters are: $s_{\mathrm{sgc}} = c = 19$, $a_x = 3$, $a_y = 9$, $\rho = 3$, $l = 2a_x a_y$, $C = 0$

Cory and Fraser 1995). Thus, a neurotrophic interpretation of a model of (excitatory) anatomical plasticity appears to be especially appropriate.

The energy E_i of any particular excitatory afferent process i is therefore taken to reflect the level of some neurotrophic factor, that is, a factor which we take to be involved in maintaining and promoting neurite outgrowth from excitatory afferents, taken up by process i in an activity-dependent manner. Afferents are expected to sprout into regions of high support (low energy) and retract from regions of low support (high energy). Because changing the density of innervation by sprouting and retracting axonal processes changes the relative control of target cells by afferents, competition between afferents occurs directly, without having to impose the unsatisfactory mathematical device of synaptic normalisation (von der Malsburg 1973), for which there is very little evidence.

The process of energy minimisation, for excitatory afferents, is therefore a model of the process of afferents searching out, by sprouting and retracting axonal processes, regions of greatest neurotrophic support on the target space. Stable patterns of connectivity represent those in which afferents have maximised, at least locally, their neurotrophic support. Thus, we regard the minimisation process not as merely a computational procedure for finding such solutions, but as an hypothesis regarding how afferents might search out regions in target space best suited to the afferents' neurotrophic requirements.

Because we regard the minimisation process as characterising the real, biological dynamics of anatomical rearrangements for excitatory afferents, the parameters θ and T in Eq. 4 must possess biologically meaningful interpretations. Increasing θ increases the probability of sprouting ($\Delta N > 0$) and decreases the probability of retraction ($\Delta N < 0$), while decreasing θ has the opposite effect. Thus, we take θ to be a measure of the level of either exogenously applied neurotrophic factor ($\theta > 0$) or exogenously applied substances which inhibit the generation and release of a target cell's neurotrophic factors ($\theta < 0$). In previous work (Elliott et al. 1996b) we have used θ to model the infusion of either BDNF (Cabelli et al. 1995) or the γ-aminobutyric acid receptor agonist muscimol (Hata and Stryker 1994) in the kitten primary visual cortex. Increasing T, on the other hand, increases the level of 'noise' in the decision whether to accept a candidate perturbation. For $T = 0$ there is no noise, while for sufficiently large T, all candidate perturbations are accepted with a probability very close to 0.5. This latter means that sprouting and retraction occur randomly. Since biological systems are intrinsically noisy and 'decisions' are subject to such noise, the parameter T thus finds a natural interpretation.

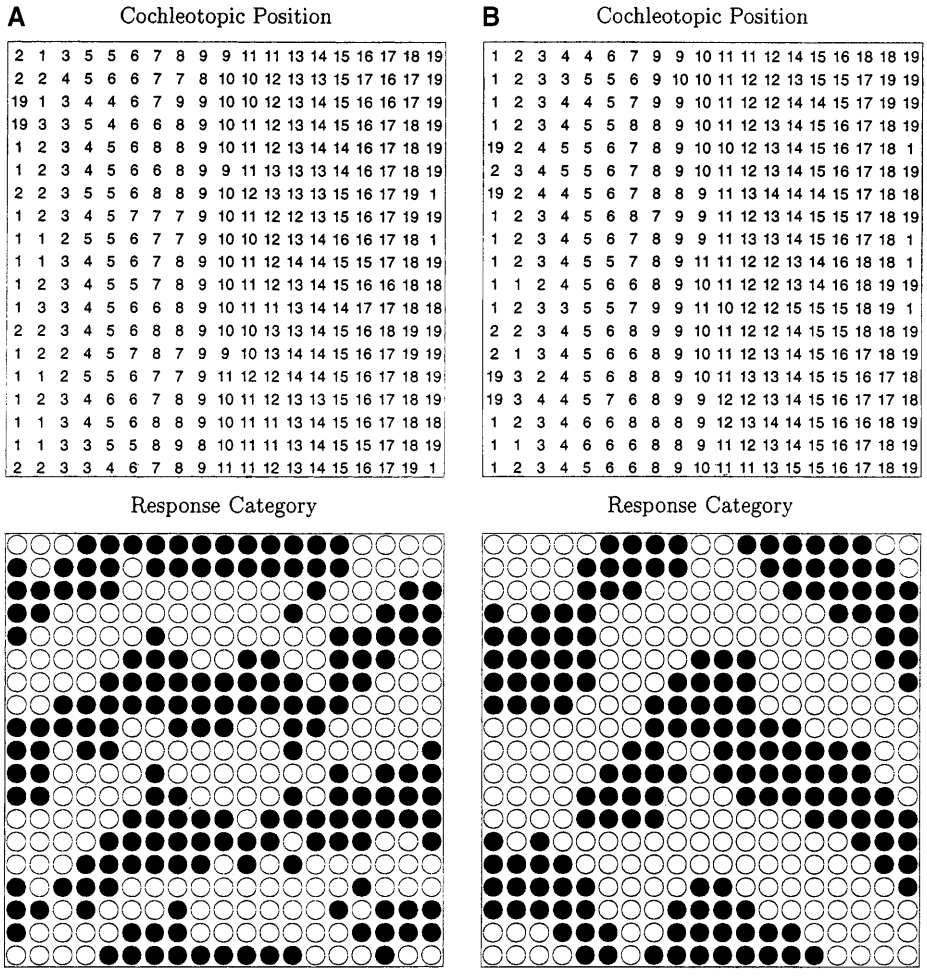

Fig. 4a,b. Two examples of the final pattern of binaural bands produced by the interchange model, for the 'antagonistic' case. Parameters are as in Fig. 3

Is it possible to carry over the neurotrophic interpretation of the energy function for excitatory afferents to inhibitory afferents? Inhibitory neurons do appear to be responsive to the same class of neurotrophic factors to which excitatory neurons are responsive (e.g. Widmer and Hefti 1994). However, inhibitory afferents down-regulate the target cell production of BDNF and NGF mRNAs in the hippocampus (Zafra et al. 1991; Gwag and Springer 1993; reviewed by Lindholm et al. 1994; Thoenen 1995). Furthermore, the activity-dependent component in the release of NGF and BDNF from hippocampal neurons depends on Na^+ (and not Ca^{2+}) influx (Blöchl and Thoenen 1995; Griesbeck et al. 1995; Blöchl and Thoenen 1996). Therefore, if activity-dependent anatomical inhibitory plasticity is dependent on the same class of neurotrophic factors as activity-dependent anatomical excitatory plasticity, then it appears that inhibitory afferent activity would induce a reduction in the production and release of those neurotrophic factors which are involved in maintaining and promoting neurite outgrowth from inhibitory afferents. That is, inhibitory afferent activity would lead to a reduction in their own neurotrophic support, and presumably the retraction of their synapses.

If we wish to extend the neurotrophic interpretation to inhibitory afferents, then we are forced to postulate the existence of a new class of neurotrophic factors. Such factors must be assumed to be up-regulated by hyperpolarisation and down-regulated by depolarisation. It must be assumed, in addition, that the level of these new neurotrophic factors determines the complexity of inhibitory afferent axonal arbors. Furthermore, we must assume that the activity-dependent release of such factors depends on Cl^- and not on Ca^{2+} influx. While this last assumption might appear to be particularly problematic, it should be borne in mind that the activity-dependent release of BDNF and NGF from hippocampal neurons depends on Na^+ and not on Ca^{2+} influx. Thus, our proposal for the existence of a new class of neurotrophic factors, to which inhibitory neurons primarily respond, together with the required dynamics for their production and release, puts inhibitory plasticity on an equal but mirror-image footing with excitatory plasticity. Indeed, this symmetry could be construed as providing a natural account of why the activity-dependent release of BDNF and NGF does not depend on Ca^{2+}: because, in the absence of parallel excitation of the post-synaptic cell (e.g. Konnerth and Eilers 1994), the activity-dependent release of neurotrophic factors for inhibitory neurons could not depend on Ca^{2+} influx.

If we assume that inhibitory afferents are influenced by a new class of neurotrophic factors, then new questions are raised, particularly when modelling

simultaneous excitatory and inhibitory plasticity, as in the abstract model of binaural band formation discussed above. While it is likely that inhibitory afferents will compete with each other for their neurotrophic resources, it is not clear how inhibitory and excitatory afferents synapsing on the same population of target cells will interact. Their effects will be at least antagonistic, in the sense that one class of afferent (excitatory or inhibitory) will induce a decrease in the production and release of the neurotrophic factor required by the other class. This should be enough, as shown in Fig. 4, to induce excitatory and inhibitory afferents to segregate, subject to a possible hypertrophic response from target cells, or associated glial cells, experiencing a loss of excitatory drive (Gomez-Pinilla et al. 1992; Rassendren et al. 1992; Caroni and Schneider 1994; Conner et al. 1994; Gwag et al. 1994; Guthrie et al. 1995). However, while we propose that excitatory and inhibitory afferents require different neurotrophic resources, it is possible that either afferents compete indirectly for neurotrophic resources by competing directly for the sites of activity-dependent neurotrophic factor release or that afferents take up all neurotrophic factors indiscriminately. It this case, inhibitory and excitatory afferents would explicitly compete. Our simulations, however, show that there is no qualitative difference between the 'antagonistic' and the 'competitive' scenarios, at least in the binaural band system.

This does not mean, however, that the two scenarios could not be distinguished experimentally. Selective partial denervation or activity blockade of one class of inputs, to the LSO for example, might induce sprouting not only by the remaining or active inputs in that class but also by inputs from the other class. If only the former occurs, then this might be interpreted as indicating merely antagonistic interactions between excitatory and inhibitory afferents, while the latter might be interpreted as indicating competition between them. This latter case would not establish competition for different resources, though it would be a necessary first step before attempting to identify a new class of neurotrophic factors for the support of inhibitory neurons.

Evidence from the rabbit indicates that single thalamocortical afferents innervate multiple patches in the auditory cortex prior to the onset of acoustically driven hearing (de Venecia and McMullen 1994), and that these patches match the electrophysiologically identified pattern of binaural bands (McMullen and de Venecia 1993). It is therefore likely, at least in some species, that the development of binaural bands is either independent of electrical activity or dependent on spontaneous activity in the auditory pathway. Spontaneous activity in the visual pathway is known to be important for the pre-natal development of the visual system (e.g. Rakic 1977; Shatz and Stryker 1988) and might be provided by waves of correlated, spontaneous activity sweeping across retinal ganglion cells (Maffei and Galli-Resta 1990; Meister et al. 1991). The situation in the somatosensory system is less clear. The normal post-natal development of whisker barrels (Woolsey and Van der Loos 1970) in rodents does not depend on electrical activity (Chiaia et al. 1992; Henderson et al. 1992). However, the rearrangement of afferents within the pattern of barrels does depend on electrical activity (Fox et al. 1996). Furthermore, a response to post–natal perturbations, such as the destruction of a row of vibrissae follicles, requires activity (Schlaggar et al. 1993), as does the pre-natal development of whisker-related structures in the trigeminal brain stem, since gene knock-out mice lacking functional *N*-methyl-D-aspartate receptors fail to develop such structures (Li et al. 1994; cf. Henderson et al. 1994 in relation to Gwag and Springer 1993).

In presenting an activity-dependent model of the formation of binaural bands, we have thus tacitly assumed that spontaneous activity drives their pre-natal development, at least in some species such as the rabbit (de Venecia and McMullen 1994). Since nothing is known about the correlations in possible spontaneous activity in this system, we have selected a simple model for such activity and shown that our results do not exhibit any qualitative changes in response to changes in the parameters characterising our model of spontaneous activity. The same model of activity has also been used, for convenience, in simulating the activity-dependent topographic refinement of inhibitory projections from the MNTB to the LSO, this process occurring, in species such as the gerbil (Sanes and Siverls 1991), after the onset of hearing.

Our results in Figs. 3 and 4 suggest that the periodicity of binaural bands in the primary auditory cortex is capable of change. Binaural bands generated by simulated annealing exhibit a larger periodicity than those generated by simulated quenching. Previously we have found striking qualitative differences in the overall pattern of ocular dominance columns (Hubel and Wiesel 1962) in the primary visual cortex, depending on whether they are generated by annealing or quenching (Elliott et al. 1996a). We suggested that it might be experimentally possible to 'anneal' the primary visual cortex of a kitten by infusing substances into the cortex which increase the level of noise influencing sprouting and retraction of axon terminals, and then gradually reducing their levels to near zero significantly before the end of the critical period. We are thus again led to suggest that similar experiments could also be tried in the primary auditory cortex, looking instead for a shift in binaural band periodicity.

In conclusion, we have presented a model of anatomical inhibitory plasticity. We have applied the model to the development of the mammalian auditory system. We have provided a neurotrophic interpretation of the model which proposes the existence of a new class of neurotrophic factors for which inhibitory afferents compete. Several interesting issues and predictions are raised, including the need to address the nature of the interactions between excitatory and inhibitory afferents innervating the same population of target cells and the possibility that the periodicity of binaural bands in the primary auditory cortex could be changed by pharmacological manipulations.

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Appendix

Here we derive the energy function used above. The total afferent input, both excitatory and inhibitory, to the target cell on which afferent process i synapses is taken to be $\sum_j \mathscr{D}_{ij} a_j \epsilon_j$, and the level of some diffusible substance released by that cell is assumed to be

$$R_i = f_R\left(\sum_j \mathscr{D}_{ij} a_j \epsilon_j\right) \tag{5}$$

where f_R constitutes some model of the production and release process. The substance released by target cells is taken to undergo diffusion through the target field (the temporal dynamics of which we do not consider), and we assume that the total amount at each target cell following diffusion is given by

$$A_i = \frac{1}{N}\sum_j \tilde{\Delta}_{ij} R_j \tag{6}$$

where $\tilde{\Delta}_{ij} = \Delta_{ij}/s_j$ with $s_j = \sum_k \mathscr{D}_{jk}$ being the total number of afferent processes synapsing on the target cell on which process j synapses. The amount of the substance available at each synapse on the target cell on which process i synapses is then taken to be

$$\tilde{A}_i = \frac{A_i}{\sum_j \mathscr{D}_{ij} f_I(\epsilon_i, \epsilon_j)} \tag{7}$$

where f_I is defined in Eq. 3. For the 'antagonistic' case in Eq. 3, we assume the existence of two distinct substances, one which is taken up by inhibitory afferents and one which is taken up by excitatory afferents. We assume that excitatory afferents do not take up the substance taken up by inhibitory afferents, and vice versa. The 'competitive' case, in contrast, is assumed to result from the indiscriminate uptake by terminals of even the inappropriate substance, in addition to the substance appropriate for that terminal.

We assume that uptake is activity–dependent, and that the action of the (appropriate) substance on afferent processes also depends on activity. The action of the substance is taken to promote anatomical change, either by inducing sprouting or by inducing retraction, depending on how much is taken up, and the resting level required to maintain existing terminals. This is quantified by defining

$$\tilde{E}_i = -a_i(\epsilon_i \tilde{A}_i - \tau^{-1}) \tag{8}$$

where τ is interpreted as either an activity–dependent requirement or a baseline, resting requirement by each afferent process. Writing

$$\tilde{E}_i = \frac{E_i}{\tau N \sum_j \mathscr{D}_{ij} f_I(\epsilon_i, \epsilon_j)} \tag{9}$$

we obtain

$$E_i = -\tau \epsilon_i a_i \sum_j \tilde{\Delta}_{ij} f_R\left(\sum_k \mathscr{D}_{jk} a_k \epsilon_k\right) + a_i N \sum_j \mathscr{D}_{ij} f_I(\epsilon_i, \epsilon_j) \tag{10}$$

and setting $\tau = 2$ and $f_R(x) = x$, the latter being a simple, linear model of the production and release of the substance(s) by target cells, and summing over all afferent processes, we have

$$E = \frac{1}{2}\sum_i E_i = -\sum_{i,j} \epsilon_i a_i \Delta_{ij} a_j \epsilon_j + \frac{1}{2} N \sum_{i,j} a_i \mathscr{D}_{ij} f_I(\epsilon_i, \epsilon_j) \tag{11}$$

which is the energy function used above.

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