COMPUTATIONAL APPROACHES TO NEUROLOGICAL DISEASE

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Abstract

Computational models have contributed to current understanding of normal brain function, and can offer new insights into the pathophysiology of neurological disease. We define some of the outstanding clinical questions in stroke, CNS injury, Alzheimer's disease, Parkinson's disease, and epilepsy from a neurologist's perspective, and discuss the potential impact of computational neurology on computational neuroscience. We consider representative examples of models constructed at several different levels of biological detail--from detailed membrane-level simulations to connectionist networks. We focus on what has been learned from several generations of models concerned with the after-effects of neural injury. In particular, we discuss how model assumptions, sometimes of ancillary importance, have constrained the ability to predict subsequent experimental results.

1. Introduction

Computational modeling is not the first approach one might consider in seeking to understand neurological disease. First, there is the complexity of the problem: brain function, which is poorly understood under normal conditions, is further complicated in situations of dysfunction. And the major neurological conditions: stroke, Alzheimer's disease, Parkinsonism, epilepsy, and CNS injury are multifarious in their expression and protean in their manifestations. There is also the complexity of the solution: any framework proposed for explaining functional loss must take account of processes at multiple levels of organization--from the molecular to the behavioral. And it is difficult to see how a computational model can translate into rehabilitation or treatment strategies aimed at these various levels. Finally, in contrast to computational simulations, molecular biology offers both a reductionistic approach, and the potential for treatment and cure.

There are, however, several compelling reasons for attempting to develop models and simulations of disease--not as a replacement for other approaches, but as a means of new insight into pathogenesis and treatment. In some sense, the function of the brain is computation, thus the underlying computational processes must be uncovered to understand the basis of disease. Alzheimer's disease cannot be understood outside of the context of a model of memory consolidation and storage, and Parkinsonism requires an understanding of how the extrapyramidal system controls voluntary movement. The development of such models is made richer and more robust by consideration of clinical data, just as pathology has always enriched the understanding of physiology.

Secondly, the nervous system is sufficiently complex that understanding its function requires detailed simulation. How can one weigh the importance of calcium concentration, local recurrent excitation, loss of cell numbers, slowing of conduction velocities, and normal aging processes in assessing functional behavior in an Alzheimer's patient? Simulations provide a means of thinking about complex systems, particularly those with rich interactions between levels. Despite the fact that the principles of aerodynamics are well understood, no one would build a modern aircraft without extensive CAD-CAM simulations. How then can we hope to understand neural function, and perturbations to normal function, without detailed simulations. And how else can we hope to arrive at the neural equivalent of "aerodynamics", the underlying computational principles of brain function, without a process of building increasingly more complex approximations to real neural circuits.

Finally, disease may do more for computational neuroscience than modeling does for disease. Models have always considered how function breaks down as a result of various structural degradations, but it has only recently become possible to incorporate sufficient detail at the appropriate levels of organization to make use of the troves of clinical knowledge about the brain.

In this overview, we will consider some of these issues in the context of what would be useful to clinical neurology and what can be achieved by computational methods. We will define those clinical conditions which, from our perspective, appear most amenable to computational study. We will discuss some representative examples of promising approaches in this area, and try to draw lessons from some attempts in the past. And we will try to elucidate what strategies and techniques might be most successful in developing this new arena, particularly, how computational techniques may be combined with imaging and signal analysis.

The spectrum of neurological disease is wide and ravaging. From a public health perspective, it represents a multi-billion dollar a year problem, and from the patient's perspective it usually represents a diagnosis without much hope. Despite advances in anatomical imaging and molecular analysis, the major neurological diseases remain poorly understood. In what follows, we attempt to define how computational approaches may be of use in several of the major neurological conditions.

2. Alzheimer's Disease

Alzheimer's disease (AD) is a degenerative brain disorder that affects 3-4 million Americans, and accounts for over 70% of all cases of dementia (Katzman, 1986). After age 60, the prevalence of AD doubles every 5.5 years, and between 10-40% of Americans over the of age 80 suffer from AD (Evans et al, 1991). The disease is slowly progressive; rates of progression from initial symptoms to end stage dementia range from 2 to 25 years, with most patients in the 8 to 12 year range. AD may have a very long preclinical course of 20 or more years with biochemical and pathological changes preceding clinical symptoms.

Pathologically, AD is characterized by degenerating neurites, abnormal accumulations of amyloid protein in so-called "senile plaques", and intracytoplasmic "neurofibrillary tangles". There is specificity to both the anatomical distribution of these lesions and the resulting clinical symptomatology. The first lesions of AD probably occur in entorhinal cortex and then "spread" to involve areas CA1, CA3, and the subiculum of the hippocampus. In later stages, the disease involves polymodal association cortex in the superior temporal and inferior parietal lobes and association cortex in the frontal lobe (Braak et al, 1991. However, even in severe disease, at most 40-60% of pyramidal cells are lost (Katzman, 1986). Immunological methods have demonstrated a substantial decrease in the concentration of specific synapse associated proteins in AD (Terry et al, 1991; Honer et al, 1992). In some studies, these measures were inversely correlated with global measures of cognitive function (Terry et al, 1991). Concomitant with these changes is severe "retraction of dendritic arbor" of the pyramidal cells (Scheibel et al, 1978). It is important to emphasize that some brain regions are spared even in end stage patients. Thus pyramidal cells within primary cortex such as Brodmann areas 1,2, 3, 4, 17, and 41 are rarely affected.

In the mid 1970s, two different observations led to the "cholinergic hypothesis" of AD. College students given the anti-muscarinic drug scopolamine showed memory impairment somewhat similar to that seen in AD (Drachman et al, 1974). Post mortem studies of AD brains showed that

although many neurotransmitter systems are impaired in AD, deficiencies in the cholinergic system are usually the most severe (Davies et al, 1976; Perry et al, 1978). These observations led to numerous studies to treat memory impairment in AD with drugs that modulate the cholinergic system. The acetylcholinesterase inhibitor, tacrine (or tetrahydroaminoacridine) is currently the only drug approved by the FDA specifically for treatment of AD (Summers et al; 1991; Davis et al, 1992); unfortunately, its efficacy is frequently marginal.

In the past 15 years, extensive studies of the biochemistry and genetics of AD have shown that the amyloid protein found in the cores of senile plaques results from abnormal processing of a larger protein, called amyloid precursor protein (APP). Mutations in the amyloid precursor gene are associated with some cases of autosomal dominant presenile AD. It has also been shown that late onset AD (starting after age 65) is associated with the apolipoprotein e4 genotype (Saunders et al, 1993). It is estimated that 40% of cases of late onset AD are due to this gene.

The challenge in understanding Alzheimer's disease is to be able to map what is known about biochemical and cellular pathology to the abnormal behaviors characteristic of the disease. To date, clinicopathological studies have taken a "black box" approach by correlating specific pathological markers with global measures of cognitive function. The choice of pathological marker is usually not made by an assessment of what structures are needed for specific cognitive functions, but rather with the underlying assumption that any widespread pathology probably interferes with cognitive function. Some of the most important studies of AD have taken this approach. Thus the seminal studies of Blessed, Tomlinson, and Roth (1968) that demonstrated that AD and not vascular disease was the most important cause of dementia in the elderly were based on demonstrating that cognitive impairment was correlated with quantitative measures of AD pathology. Two decades later, a similar approach was taken in the important studies of Terry and Masliah (1991) that showed significant correlations between global measures of cognitive function and immunological estimates of the concentration of synapse associated proteins.

Ruppin and colleagues (Horn and Ruppin, 1993; 1995; Ruppin and Reggia, 1995) have investigated the consequences of changes in synaptic connection densities in a series of network models. AD leads to decreases in the number of functioning synaptic connections, but several studies have shown that remaining synapses compensate by increasing in size. Ruppin and colleagues use attractor-type associative memory models to study the effect of synaptic depletion and compensation on the recall ability of such networks. They observe that local compensatory mechanisms can, under

some circumstances, maintain memory functions despite significant losses in other connections. Their models raise the possibility that the loss or saturation of local compensatory mechanisms plays a major role in the development of cognitive deficits.

A complete understanding of how the pathology of AD leads to its symptoms depends on answering fundamental questions related to the mechanisms of normal cognitive function. Human clinicopathological studies have demonstrated that many different brain regions must be intact for successful acquisition and consolidation of episodic memories. These regions include entorhinal cortex, hippocampus, amygdala, nucleus basalis, dorsal medial nucleus of the thalamus, mamillary bodies, mid-dorsolateral frontal cortex, and ventromedial frontal cortex (Petrides, 1989, 1994).

Alvarez and Squire (1994) proposed a connectionist-level model directed towards the role of some of these brain structures. They assume that learning between the neocortex and hippocampus (and then between hippocampus and neocortex) occurs quickly, but that forgetting occurs between these regions at a moderate rate. On the other hand, neocortical to neocortical learning occurs slowly, but forgetting is also very slow. In this model, the hippocampus slowly teaches the neocortex. An attractive feature of this model is that when lesioned it responds like patients with Alzheimer's disease. The model does well on associations it learned in early cycles, but less well on memories learned in later cycles.

The model of Alvarez and Squire makes assumptions and predictions that can be tested to some degree in physiologic or functional MRI studies. And it begins to address fundamental questions such as 1) how does hippocampal data get back to specific neocortical regions? and 2) how much data reduction is there between neocortex and hippocampus? In order to correctly answer these questions it is necessary to construct models at a more detailed level. One can postulate a variety of mechanisms, and construct "black-box" analogies, but the details of how the system actually works may be incompatible with many such schemes. For example, much of the current experimental evidence on hippocampus suggests that patterns of neuronal activations, representing events, are generated and ultimately stored in cortex, but are associated in a context-dependent fashion in the hippocampus. The "fusion" of cortical and hippocampal representations may occur through temporal synchronization of activity patterns. Buzsaki and colleagues have shown that this synchronization is probably mediated by super-networks of inhibitory GABA-ergic cells, many of which establish widespread, long-distance connections (Buzsaki and Chrobak, 1995). There are multiple classes of inhibitory cells, each with layer-specific patterns of connections, so that inputs to various regions of pyramidal cell dendrites (e.g., from perforant

path, commissural path, etc.) can be specifically inhibited. Inhibition of a dendritic region may prevent calcium entry during back-propagating action potentials, preventing selected sets of synapses from becoming potentiated through LTP (Buzsaki and Chrobak, 1995). The point is that the details are critical, and can lead to models that are counter-intuitive. Synchronization by a network of inhibitory cells has very different properties as that achieved by excitatory-excitatory couplings. To appreciate the dynamics of such networks, a much more detailed understanding of cell properties is required. Once such detailed models have been studied, it may be possible to abstract the essence of the model in a computationally efficient manner. Thus, the scheme proposed by Buzsaki and Chrobak (1995) for how inhibitory supernetworks can synchronize pyramidal cells--based on extensive experimental investigation--actually turns out to be quite similar to the simple computational model proposed by Hopfield (1995) as a mechanism of representing spatial patterns in a temporal neural code (G. Buzsaki, personal communication). Without detailed modeling, however, there can be no assurance that the more abstract model represents the correct choice of mechanisms.

The studies of Hasselmo et al. (1992, 1993, 1994; Barkai et al, 1994a,b,c) represent an attempt to incorporate more detail into the modeling process. Both excitatory and inhibitory neurons are modeled with interconnection densities corresponding to those in vivo. In recent models, biologically realistic neurons are studied which contain 6 intrinsic ion currents and 3 synaptic currents. Hasselmo proposes that the cholinergic system might function to toggle networks between learning and recall states. Acetylcholine is proposed to suppress synaptic transmission at intrinsic connections and also to decrease adaptation of afferent input. Hasselmo and his colleagues showed that these two combined effects could enhance efficiency of learning more than either effect alone.

One prediction of Hasselmo's model is that studies of the effects of cholinesterase inhibitors should match neuropsychological task to periods of high or low cholinergic state. Their model would suggest that learning would occur best with high cholinergic state, but that recall would occur best with low cholinergic state. A subject with AD could be taught a task while receiving intravenous cholinesterase inhibitors, and then tested on recall after the drug is no longer active.

One goal for future models is to integrate additional cellular and network mechanisms with behavioral properties such as memory consolidation and recall. These models may help unravel the principles of higher cognitive function and the relationship between hippocampus and neocortex.

3. Parkinson's Disease

Parkinson's disease is a degenerative neurological disease characterized by resting tremor, rigidity, bradykinesia (slowing of movements), akinesia (difficulty initiating movements), and poor balance (Adams and Victor, 1993). Cognitive impairment and/or depression occur in a substantial percentage of patients (Mayeux et al, 1988).

The pathological hallmark of Parkinson's disease (PD) is loss of the dopaminergic neurons in the substantia nigra that project to the putamen. (Most surviving neurons will have a characteristic cytoplasmic inclusion called a Lewy body.) Other brain regions are often affected, but pathology in the substantia nigra is the sine qua non of the disease.

About 500,000 Americans have PD; the vast majority have idiopathic PD, although some cases are drug-induced. A specific form of PD developed among many survivors of the encephalitis epidemic of 1918-1921. However, few of these patients are still alive. Idiopathic PD is primarily a disease of middle age and late life.

A significant breakthrough occurred in the early 1980s when it was discovered that young people abusing the "designer drug" MPTP (a derivative of the narcotic meperidine) soon thereafter developed severe Parkinson's disease (Langston et al, 1983; Ballard et al, 1985). This neurotoxin became invaluable as a tool for developing animal models of PD. MPTP itself is not toxic, within the brain it is oxidized to itself toxic form, MPP+. Several investigators suggested that a similar process might occur in patients with idiopathic PD, and started studies asking whether drugs that blocked this oxidative step might slow the rate of progression of PD. Although several studies have suggested that PD patients treated with oxidase inhibitors do progress more slowly (Parkinson study group, 1989, 1993; Tetrud et al, 1989), interpretation of these data remain controversial (Schulzer et al, 1992)

The discovery that dopamine was deficient in the substantia nigra led to efforts to treat PD with L-DOPA, a precursor of dopamine (dopamine itself does not cross the blood brain barrier). Over 80% of patients with PD obtain substantial benefit with L-DOPA therapy (Adams and Victor, 1993). However, its efficacy frequently wanes after several years, and disabling side effects including dyskinesias and hallucinations can develop. Before L-DOPA therapy, stereotactic surgery with ablative lesions in the thalamus or globus pallidus was commonly performed. In recent years, interest in stereotactic surgery has revived, with newer surgical methods yielding more control over the size and site of the lesions. Efforts have been made to treat PD with

transplantation into the brain of fetal cells from the adrenal medulla or from the fetal nigra. Several groups have recently shown that neural growth factors may improve the efficacy of transplanted tissues.

In Parkinson's disease the timing of the firing of agonist and antagonist muscle groups is dysfunctional. As a result, movements are slow and/or tremulous. To date, the mechanism by which dopaminergic deficiency leads to this symptomatology is not clear. Most investigators believe that dopamine deficiency leads to an imbalance of the direct and indirect pathways from the putamen to the internal part of the globus pallidus, but more precise mechanistic details are lacking.

Towards this end, Borrett and colleagues (1993) have studied the dynamics of a 4 layer neural network where the output layer feeds back to the input layer. They propose that such a network might model the type of calculations made by cortico-basal ganglia-thalamic-cortical loop that is dysfunctional in Parkinson's disease. Three types of stable states are possible from such nonlinear dynamic systems - a fixed attractor, a periodic attractor, or a chaotic attractor. Borrett showed that as the parameters of such a nonlinear system were gradually changed, the system suddenly reached a bifurcation point where output changed from a fixed attractor to a periodic attractor.

In their model, they simulated the effect of dopamine in cortico-ganglionic loops as a decrease in the threshold of excitability for units in the pre-output layer. They were able to show that as the threshold was gradually increased (simulating a decrease in dopamine levels) the output of the network first became slower and then changed from a fixed attractor state to a periodic (i.e. tremulous) state.

Even though Borrett's model consists of abstract units whose output is defined by a sigmoidal function, the model makes several points that underscore the role of computational models in understanding neurological disease. First, behavior results from the dynamic interaction of multiple units from different modular systems. Second, the model suggests that some behaviors such as tremor will develop suddenly when a bifurcation threshold is reached. The decrease in dopamine in the susbtantia nigra of Parkinson's disease occurs gradually over several years. It is likely that there must be very significant decrease in dopamine levels (some have estimated as much as 90%) before patients become symptomatic.

We believe that computational models will play an increasingly important role in understanding the pathophysiology of movement disorders such as Parkinson's disease. And a number of groups are beginning to apply methodologies used in understanding central pattern generators and

neuronal oscillations to the study of Parkinson's tremor. These studies may yield insights that will eventually lead to better treatments for these disorders.

4. Epilepsy

Over 1.5 million Americans suffer from epilepsy (Engel, 1989). Although over two-thirds of patients with epilepsy can be well controlled with medication, a sizable minority cannot, and medication side effects frequently limit patient's quality of life (Adams and Victor, 1993). Epileptic seizures are the clinical manifestations of excessive abnormal neuronal firings. Clinical phenomenology of seizures can range from brief lapse of consciousness without loss of posture to a generalized tonic-clonic (grand mal) seizure with loss of consciousness and prolonged post ictal state (Engel, 1989).

Many different pathological processes including trauma, infection, hypoxia, and stroke can lead to the development of a seizure disorder. Certain parts of the brain are more epileptogenic than others. For example, the hippocampus and certain neocortical regions are most epileptogenic. Seizures probably never originate in such structures as the cerebellum, basal ganglia, or brain stem (Engel, 1989).

Epilepsy results from the exaggeration of two normal neuronal processes - neuronal excitation and synchronization of groups of neurons (Engel, 1989). In patients with epilepsy, the EEG shows sharp waves, in contrast to normally occurring (8-13 Hz) alpha waves. The sharp wave represents the summation of the potentials of up to hundreds of pyramidal cells that are repetitively firing riding on a sudden depolarization wave (Engel, 1989).

Some anti-epileptic drugs such as carbamazepine (Tegretol) and phenytoin (Dilantin) act by modulating Na (and Ca) ion currents. Other drugs including phenobarbital, valproate (Depakote), and benzodiazepines act by modulating the GABA-ergic system.

Computer models of single pyramidal cells have been used to study the effects of specific ion currents on bursting behavior and on repetitive firing. Lytton and Sejnowski (1991) developed a computer model to study the effects of inhibitory input on synchronization of pyramidal cells. In particular, they wanted to determine whether pyramidal cells receiving random afferent input could convert that data into regular repetitive output. They developed simple and complex models of pyramidal cells. The complex models had 406 compartments, and 11 types of ion channels were modeled. The simple models had 3 channels and 9 compartments. They were able to show that

IPSPs could entrain pyramidal cells receiving random input to fire at regular intervals.

Traub and colleagues (1992) developed models of CA3 in the hippocampus that contained 1000 pyramidal cells, 100 cells that simulated $GABA_A$ inhibition, and 100 cells that simulated $GABA_B$ inhibition. They attempted to adjust the density of intercellular connections to approximate that which occurs in vivo. Their models demonstrated that 1) recurrent excitation (in the absence of inhibition) can induce synchrony of the pyramidal cells; 2) in the presence of $GABA_A$ blockers, the network could produce synchronized bursts of activity; 3) with partial blockade of $GABA_A$ inhibition, the network could produce "synchronized synaptic potentials".

The use of such models has explained the basic mechanisms by which synchronized activity emerges. In particular, Traub and colleagues have been able to generate activity patterns, in realistic networks, that closely mimic epileptic activity recorded in vitro, and the types of EEG activity seen in patients. These models have been particularly useful in uncovering the roles of various cell types and connections in epileptogenesis, and in explaining the effects of various pharmacological agents. Traub's work serves as perhaps the best example of how detailed modeling can integrate neurobiological data, and serve as a means of generating testable experimental predictions.

5. Stroke and Neurological Injury

One clinical area in which there is an informative history of attempts to develop computational models is the reorganization of topographic maps in the somatosensory system as a consequence of injury. Over the last 20 years, a number of physiological experiments have been carried out to investigate in a controlled fashion, the central effects of peripheral nerve injury. Merzenich and his colleagues (Jenkins and Merzenich, 1987) made detailed mappings of areas 3b and 1 in monkey somatosensory cortex after a number of perturbations including nerve transections, nerve crush, digit amputation, syndactyly, and skin island pedicle transfer. They also studied the effects of focal correlated stimulation to a skin region under conditions in which the animal attended to the stimulus, or did not. Most relevant to stroke and CNS injury, they studied changes in representation as a consequence of focal cortical lesions. The general results of their extensive studies (reviewed in Merzenich and Jenkins, 1993) are that within the limits allowed by the anatomy, the cortical map reflects spatial relationships in the stimulus domain. Regions that are co-stimulated tend to be represented together. In addition, after a cortical lesion, skin sites formerly represented in

the damaged region can come to be represented outside of the damaged area. These studies suggest that cortical representations are plastic, and may be alterable through some combination of the pattern of stimulation, control of synaptic plasticity, and the general excitability of cortical cells.

Several neural simulations have been developed to test these ideas in a quantitative fashion. Kohonen (1982) developed the first algorithm to model how changes in input correlations can lead to reorganization of computational maps. Studies by Cowan, von der Malsberg, and others had earlier shown how topographic maps can arise in development. Kohonen's algorithm was not intended to model physiological experiments. Rather it was directed towards the problem of how relations in feature space (e.g., topographic adjacency) can be preserved through a series of neural mappings. For each stimulus applied to the network, the algorithm picks the most strongly activated unit in the network, and the synaptic weights of that unit (and its nearest neighbors) are adjusted so as to increase the response to the applied stimulus. Kohonen showed that this rule leads to formation of topographically organized maps and that such maps obey a magnification rule. As the frequency of stimulation of a particular input region is increased, the fraction of the map devoted to the stimulated region proportionately increases.

In 1987, Pearson, Finkel and Edelman proposed a slightly more complex network specifically directed at modeling cortical map reorganization. The network contained excitatory and inhibitory cells, with a topographically organized set of inputs from a sensory receptor sheet (corresponding to the hand). Only excitatory cells in the network received an input from the receptor sheet, and these connections as well as the excitatory-excitatory connections within the network were plastic according to a voltage-dependent synaptic mechanism. Repeated stimulation of the receptor sheet led to the formation of clusters of strongly interconnected cells, neuronal groups. Cells in these groups had highly overlapped receptive fields. Each excitatory cell received equal numbers of inputs from receptors on the "glabrous" and "dorsal" aspects of the "hand". Thus, initially, all cells had receptive fields on both front and back of the hand. However, after neuronal groups had formed, all the cells in each group exhibited a receptive field either on the front or the back of the hand--but half of the input connections were weakened to subthreshold strengths.

Pearson and colleagues were able to demonstrate a number of reorganizational properties in the network that corresponded to those observed physiologically. Increased stimulation, manifested as tapping of a small skin region, led to an expansion of the representation of affected skin surface in the network--at the expense of the representation of adjacent skin

regions. Resumption of a more balanced stimulation, was followed by a contraction of the map back to a representation similar to that originally found. A converse experiment involved transection of inputs corresponding to cutting the median nerve (which mediates touch perception for digits 1-3 on the glabrous surface of the hand). After transection, a representation of dorsal aspects of digits 1-3 emerged in the network locations formerly devoted to the glabrous representation. There were also silent regions in the network which could not be activated. But with tactile stimulation of the receptor sheet, these silent regions gradually shrank away, leaving an intact, topographic map of the back of the hand--just as is described experimentally.

In 1990, Grajski and Merzenich described a similar network model, which incorporated an intermediate "thalamic" stage. They were able to account for an additional important experimental finding, namely, that as the size of a cortical representation increases, the receptive fields of the cortical cells decrease in size -- the so-called inverse magnification rule.

More recently, Reggia and colleagues (Sutton, et al, 1994; Armentrout, et al., 1994) have shown that a competitive activation rule can also account for these findings. In addition, they have been able to account for the changes in representation seen after cortical lesions.

Thus, one can account for many, if not all, of the types of cortical reorganization seen after stimulation, deafferentation, and other manipulations by changes in either synaptic connection strengths or competitive distributions of activity in networks of interconnected cells. However, several recent experimental observations suggest that additional processes to those considered in these models may be at work.

First, in 1991, Pons and colleagues reported on the cortical effects of de-afferentation in a set of monkeys who had survived over 10 years after deafferentation. Whereas the effects Merzenich and others had observed had been limited to cortical shifts on the order of hundreds of microns (up to 1 mm in the most extreme cases), Pons reported map shifts on the order of 10-14 mm. In these animals, the cortical areas formerly devoted to representing the hand and arm were now occupied by a representation of the face. It was as if the representation of the lower face, chin and cheeks had been stretched, as if on a rubber sheet, over the centimeter of cortex formerly devoted to the arm.

Ramachandran (1993) has recently demonstrated similar findings in humans. He examined a set of patients who had recently undergone arm amputation, and were experiencing "phantom" limb syndrome. Ramachandran found that all of these patients had topographic representations of the missing arm which could be elicited by stimulation of a site on the remaining stump. And in several of the patients, there was a

second site of representation of the missing hand, located on the lower portion of the face. Thus, in their cortices, the representation of the face must have expanded into the region formerly devoted to the hand. When the face was stimulated, it activated two sets of cells; the original, intact representation of the face, and also cells in the cortical region formerly devoted to the hand. Higher centers, viewing this latter activation, may "interpret" it as arising from the hand.

Further documentation for this view comes from combined MEG-MRI studies of these patients (reviewed in Ramachandran, 1993). The normal representational spacing of the face-arm-hand is observed in the hemisphere contralateral to the intact arm. However, in the affected hemisphere, the representation of the face is seen to shift towards the site of representation of the missing arm and hand.

In perhaps the most striking finding, Ramachandran had amputee patients view a mirror image of their remaining hand from such an angle that it visually appeared to be the missing hand. Patients were instructed to move both "hands" symmetrically through a range of motions. Remarkably, patients reported the disappearance of painful phantom sensations, and eventually, the disappearance of the phantom limb perception itself.

Ramachandran has also studied patients with right parietal lobe strokes who experience varying degrees of left hemisthesia, hemiparalysis, and hemineglect. Some of these patients also undergo somatoparaphrenic delusions, a syndrome of confabulation in which they deny the existence of their condition. Following earlier studies by Rubens, Bisiach and others, Ramachandran found that application of cold water to the external ear canal of these patients resulted in amelioration of their condition. Several minutes after cessation of the cold water, the temperature returns to normal, and the neurological deficits (and delusional state) return.

Cooling of the external ear results in a unilateral decrease in vestibular activation, and thus a shift of the perceptual "midline". Behavioral experiments confirm that after left ear cold water stimulation, when normal subjects with eyes closed are asked to point straight ahead, they instead point off to the left. Frackowiak and colleagues (Bottini, et al., 1995) have used PET to identify sites at which vestibular and somatosensory inputs are colocalized in the brain. They report that co-activation is found in secondary somatosensory cortex, in the putamen, insula, premotor cortex, and supramarginal gyrus. A patient with right parietal stroke (whose lesion spared putamen and insula) was found to have maximum PET activation of these regions when touch and vestibular stimulation were combined.

These observations are provocative and fascinating, and they imply that additional mechanisms to those considered in the above models must be

at work. The anatomy underlying the shifts seen in Merzenich's data is limited to branching thalamic arbors, which can extend over 1-2 mm^2 in cortex. There is no way in which these arbors can account for shifts over 15mm. Given Darian-Smith and Gilbert's (1994) results on plasticity in striate cortex it is likely that these long-term effects result from new anatomical connections which are made in cortex. The consideration of sprouting adds a new dimension to the parameter space of modeling, but more importantly, to the possibilities for rehabilitation after neural injury.

A second set of recent experimental observations also calls for re-evaluation of some of the modeling assumptions.

Working in the cortex of the Australian flying fox, Calford & Tweedale (1988) studied changes in the hand representation that immediately followed digit amputation or application of local anesthesia. They found that, in addition to shifts in the location of receptive fields, there was an large and immediate expansion of the receptive field size. These changes were reversible when the anesthetic wore off. These results are analogous to those observed in visual cortex by Gilbert and Wiesel (1992) following creation of a focal scotoma.

The magnitude of these receptive field changes are large compared to the anatomical scales of the thalamo-cortical connections in the early models. More importantly, the fact that the change occurs before any significant stimulation of the skin takes place, suggests a mechanism different from that mediating the chronic map changes due to altered patterns of stimulation. And the immediate nature of the expansion leads these investigators to suggest that the change may be due to an alteration in the balance of excitation and inhibition, rather than due to synaptic plasticity, per se. In their article, Calford and Tweedale point out that the Pearson, et al. model is limited by the assumption that only excitatory cells receive a direct thalamic input. Thus, deafferentation affects excitatory cells directly, but inhibitory cells only indirectly, through the loss of inputs from local excitatory cells.

Some insight into the mechanisms responsible for these immediate changes in receptive field size come from an experiment by Pettet and Gilbert (1992) involving the creation of an "artificial" scotoma. The artificial scotoma is formed by a dynamic textured stimulus that has a small, homogeneous grey region whose luminance equals the average luminance in the surround The stimulus is placed such that the homogeneous region covers (and extends somewhat beyond) the classical receptive field of the recorded cell. Ramachandran and Gregory (1991) had shown psychophysically that when such a stimulus is viewed for several minutes, the texture appears to "fill-in" the homogeneous region (color also fills in with a slightly faster time course). Pettet and Gilbert reported that in cat cortex, there was a 5-fold expansion of

receptive fields located within the scotoma region. This expansion was immediately reversible when the scotoma region was stimulated.

More recently, Freeman and colleagues (DeAngelis, et al, 1995) used reverse-correlation techniques to precisely determine receptive field changes during conditioning with similar artificial scotoma. They reported that many cells show no change in receptive field properties, and those that do change appear to have undergone a change in response gain. The overall responsiveness of a cell might be expected to change through contrast gain-control mechanisms as a result of decreasing the local contrast versus that in the surround. If response gain is increased, then inputs which were formerly sub-threshold, can become supra-threshold, and thus weak distant inputs can now be included in the receptive field. DeWeerd and colleagues (1995) present data consistent with this interpretation. They recorded from cells during the conditioning phase of the artificial scotoma, and found that cells in the scotoma region gradually increase their firing rates.

The explanation offered for these results (DeAngelis, et al., 1995; DeWeerd et al, 1995; Chapman and Stone, 1996) is that the conditioning stimulus (the texture surrounding the homogeneous "hole") leads to an adaptation of the inhibition onto cells in the scotoma region. Reduced inhibition translates into increased gain response. Restimulation in the scotoma region itself activates local inhibition which reduces the gain. The long-distance inhibition could be mediated by horizontal cortico-cortical connections, or by basket cell networks, or by a combination of both. This is consistent with the model of Xing and Gerstein (1994) who found that adaptation of inhibition can account for the types of receptive field expansions observed.

It is in fact conceivable that these immediate changes are solely the result of the decreased stimulation to the receptive field center, in the context of surround stimulation. Contrast normalization or gain control mechanisms would then up-regulate cell responsiveness--independent of any changes in inhibitory adaptation. Changes in gain control may have interesting effects particularly when considered in the context of the differential time courses of excitation and inhibition following cortical stimulation. For example, in the model recently proposed by Douglas and Martin (1991; 1995), thalamic inputs comprise a small fraction (on the order of 5%) of the connections received by cortical pyramidal cells, whereas the vast majority (85%) of those connections are from other pyramidal cells. Douglas and Martin therefore propose that the thalamic input serves more as a "trigger", unleashing a cascade of recurrent excitation that amplifies and sharpens the thalamic signal. Inhibitory cells are activated earlier than excitatory cells due to a faster, highly myelinated set of inputs (Somers, et al.,

1995). The extent of cortical activation is therefore a race over whether excitation can reach threshold levels before inhibition "wipes the slate clean". Receptive fields will tend to be localized as a consequence of the limited spatial domain over which excitation spreads before inhibition prevails. However, under conditions of deafferentation, and resulting changes in cell responsiveness, the balance between excitation and inhibition is changed. Stimuli which excite distant cortical locations are now capable of exciting cells in the deafferented region, due to a net increase in the positive feedback within the local recurrent circuits. Thus, the effect of a distant input is not merely strengthened due to increased cell responsiveness, but also as a result of the local recurrent excitatory circuits.

A number of other mechanisms are also possible, including effects mediated through inhibitory networks. Regardless, these results illustrate how the assumptions of the original models constrain their possible responses to altered stimulation conditions. Furthermore, it illustrates how the failure to incorporate a particular detail of cell physiology--in this case, overall cell responsiveness or gain--can have important implications for the ultimate success of the model.

It is possible that immediate changes in cell responsiveness can be translated into longer-term changes in synaptic plasticity. Increasing postsynaptic cell responses will lead, through any Hebb-type mechanism, to increased synaptic strengths. And it is further possible that these synaptic facilitations play a role in the even longer-term axonal sprouting processes that underlie the system's response to altered input stimulation. Thus, there may be a continuum of changes, over different time scales, that allow the system to measure the permanence of the alteration in input characteristics.

This graduated response to deafferentation suggests new approaches in neurological rehabilitation. In cases where deafferentation is not permanent, i.e., where input will be reestablished after some time, it may be beneficial to try to prevent synaptic facilitations and cortical sprouting. In cases where the lesion is irreversible, we may want to encourage whatever plasticity is possible. In either case, modulation of cell responsiveness through pharmacological means may serve as either a boost or a suppresser to intrinsic gain control mechanisms. It is conceivable that stroke patients might be given neuromodulatory agents (including those affecting cholinergic, adrenergic, serotonergic and other systems) to increase cell responsiveness, as a means of encouraging plasticity. And given the effect of vestibular stimulation in parietal strokes (Ramachandran, 1993; Bottini, et al., 1995) it may be possible to modulate neuronal responsiveness through stimulation of alternate anatomical pathways. Of course, increasing metabolic demands during a period when cortical regions remain ischemic

may be counter-productive. But models can track the time course of both neuronal activity and cellular metabolic state, and in such a way, possibly suggest windows for therapeutic intervention. The development of treatment strategies may then be addressed through detailed simulations in which the anatomical, physiological, and pharmacological properties of cortical networks are studied under conditions emulating neurological disease.

6. Conclusions

The success of applying computational methods to understanding neurological disease will depend upon a number of factors. Models should be sufficiently detailed to capture the effects of the major contributing anatomical, physiological and pharmacological processes. However, once an understanding of the system is gained, the model should be simple enough to allow interpretation of its results. Whereas most modeling efforts culminate with reproduction of some subset of the known data, it is more valuable to use the model to try out new experimental predictions.

One of the most difficult initial decisions in constructing a model is the choice of level of detail to be considered. In any simulation, there is a trade-off between memory and speed, and thus a compromise must always be made between the level of detail (number of channels, anatomical structure, temporal resolution) and the number of units simulated. Should the network contain 5 different cell types with multiple channels and compartments--or is an abstract, artificial network sufficient to test the ideas behind the model. In general, the advantage of incorporating more biological detail into a model is the level of detail at which predictions can be made. The major disadvantage is the increase in model complexity as it becomes more realistic.

The choice of level always depends upon the particular problem, however, for many problems, a safe choice may be to construct the model at the level of integrate-and-fire units. Such units sum their inputs and generate an individual spike of activity whenever the firing threshold is exceeded. A growing body of evidence suggests that the temporal dynamics of cell activity is critical to neural function.

However, a major problem with modeling at the single spike level is that one is confined to a millisecond time scale, and thus behavioral events may require thousands of iterations to simulate. To model events transpiring over seconds or minutes, or to make correlations with MRI or MEG data, one may wish to move to a higher-level model in which only mean-firing rates are simulated. Neural models built of rate-coded units use a (usually

nonlinear) transfer function to convert the summation of their inputs into a mean-firing rate. Such models are capable of representing the spatial aspects of network processing, but are not realistic in terms of the temporal aspects of network dynamics because they do not represent the instantaneous firing properties of cells.

Detailed models which simulate the actual Hodgkin-Huxley type dynamics of cell firing have the advantage of accurately computing these temporal dynamics, but introduce such a degree of complexity, and require such specific assumptions about channel properties as to be of limited use except in those cases where sufficient experimental evidence exists. The integrate-and-fire level model represents a reasonable compromise between these extremes. In addition, effects such as after-depolarizations, or transition to bursting modes, can be incorporated by appropriate terms in the equations of state. Most importantly, effects of various transmitters, modulators, and drugs can be modeled by their effect on cell excitability or firing characteristics. Understanding the detailed behavior of such interactions may require a channel-level model, but once the effect is understood, it may be sufficient to represent its effects on firing characteristics.

Perhaps the greatest challenge to the computational approach is to begin to explain how functional behavior emerges from the operation of cellular-level processes. A model constructed at the level of Ca-channels and NMDA receptors, which was also capable of high-level behavior--perception, memory, or motor action--would provide an invaluable illustration of how the system as a whole might work. Lesions to such a model, particularly if they can be made to resemble in some detail the pathologic changes in actual disease processes, can occur at the cellular level, but be manifested functionally. This approach may reveal unsuspected common mechanisms operating in different disease processes (relations between Parkinsonism and schizophrenia, or related problems in synchronization in Alzheimer's disease, epilepsy, and dyslexia). The goal is to move from the current situation, in which the "standard model" for a disease process is a flow chart of interconnections between brain regions, to a conceptual model that integrates, through simulations, the wealth of information at the molecular, cellular, network, systems, and behavioral levels.

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