REVIEW ARTICLE

TOWARD A NEUROPSYCHOPHARMACOLOGY OF HABITUATION: A VERTICAL INTEGRATION

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1. INTRODUCTION

This essay is a cross-disciplinary exploration of desensitization and habituation processes in the nervous system. The point of view and conceptual development represent a major focus of the effort: a reconfiguration of several kinds of data into a common language that emphasizes organizational dynamics among constituent elements as reflected by their statistical behavior. Our goal is not a conflict with mechanistic hypotheses developed from mean values but movement toward the development of a syntax for vertically integrative discussion of brain function using data from many levels of experimental observation[445].

In the early 1850s, Claude Bernard found that curare acted on the nicotinic receptor system of skeletal muscle, and he noted its remarkable ability "to extinguish the nervous properties of the motor nerves while retaining those of the sensory ones"[44, 45, 46]. Curare's action was regarded as competitive antagonism because it induced a parallel shift of the acetylcholine (ACh) log-dose-response curve[329] and interfered with irreversible binding of an α-bungarotoxin to end-plate receptors[465]. The time-dependence of the development of inhibition was observed by Miledi and Potter[465], and Manalis[440] subsequently demonstrated a slowly developing "noncompetitive" effect that was augmented at hyperpolarized levels of membrane potential and was associated with changes in the fluctuation pattern of membrane conductances[352]. This, in addition to other work, was suggestive of changes in what have been considered to be elementary values for single-channel conductances and rates of change of voltage-dependent channel lifetimes (twofold for each 100 mV)[646]. The inconstant quality of these elementary events is also suggested by their agonist-dependent diversity[118, 349], as well as by the early observation that the time-constant of end-plate current changes during desensitization[353]. Similar reports emerge from studies of the spectral properties of conductance variations after the administration of procaine[350], generally thought to mimic nicotinic cholinergic receptor desensitization[699].

To interpret variational data as statistical reflections of linear-deterministic mechanisms, as in the use of noise in the calculation of channel lifetimes, a number of assumptions are necessary: (1) the statistical independence of sequential molecular events; (2) relative stationarity and homogeneity in the population of their microstates; (3) an attendant deduction of ergodicity; and (4) application of a theorem relating fluctuations to relaxations in systems that are at or near equilibrium[385, 488]. Indeed, the hypothesis of Onsager[504, 505], which underlies such linear interpretations of phenomenological coefficients, is based on those kinds of assumptions plus the assumption of microscopic reversibility, i.e. time invariance, and it states that the wavelength of a spontaneously fluctuating process or the average rate at which a perturbation-induced fluctuation decays has the same linear dependence on thermodynamic forces that is observed in macroscopic

flows. Such was the basis of his derivation of the reciprocal relations of irreversible processes.

However, far-from-equilibrium conditions, which we argue below are characteristic of all sensitive, spontaneously active molecular and neural systems, as well as the presence in the brain of common electromagnetic and chemical fields, effectively destroy the notions of independence, time invariance, and microscopic reversibility; with them goes much of the justification for deterministic interpretation of apparently linear coefficients derived from variational data.

In this review, we approach desensitization and habituation as manifestations of change in the internal organization of systems. For example, the behavior of large charged particles, proteins moving autonomously but not independently, is viewed as subject to common electromagnetic fields as well as to body fluid composition and membrane structures, all of which promote perturbation-sensitive rates of intermolecular coherence[208, 362, 460, 515]. We will examine, as loci of pharmacological action, frequency and phase coherence and changing homogeneity in the behavior of aggregates among populations of autonomously fluctuating elementary units. For example, curare may create subpopulations of elements by redistributing the phases of variously coupled, autonomously moving, nicotinic receptor oscillators over time, reducing not the reception of the message or the capacity for the individual units to function but the potential for their concerted action necessary to realize the macro-event, conductance. In this context, rather than indicating values for physiological constants such as channel lifetimes, time-dependent parameters are seen to reflect the phase-frequency probability densities and interference patterns of quasi-stable solutions of a system of variously coupled nonlinear oscillators[14, 467, 517, 724, 725].

Defining habituation as a decrement in response that follows repeated elicitation of that response, we will examine that general class of drug-sensitive phenomena at several levels of nervous system organization and across disciplinary boundaries, seeking the possibility that, although each example may differ in mechanistic detail, its dynamics reflect a common ordering principle: habituation and its related phenomena, sensitization and desensitization, reflect the distributional reordering in time of the probabilistic actions of the population of microparticipants *within* the system generating the macrophenomenon.

Internal rearrangement of the spatio-temporal configurations of state can occur spontaneously in an open system of nonlinear oscillators in contact with a heat reservoir as a result of competition between the emergent order of autonomous coupling (increasing phase coherence) and the classical thermodynamic progression toward maximum entropy[397]. Without the influence of macroscopic deterministic mechanisms, over time a system will reach a quasi-periodic semi-stable state. Picture the almost clocklike regularity of the amoeboid rising and falling of the floating polymeric mass in the lava lamps that were omnipresent in the late 1960s. Similar self-organization has been well-studied in electrical, magnetic, and hydrodynamic systems[269, 270, 395, 722].

A Gaussian system of similar oscillators manifests a multi-determined, stable average frequency—the limit cycle[467]. Increased input of energy (e.g. increasing fluctuations), factors influencing the stability of individual elements or of the system itself, or frequency-phase coupling with an external periodic process (such as periodic perturbation in habituation trials) may bifurcate a population into two or more regimes[495]. If cooperative action by all or most of the ensemble is required to realize the macrophenomenon, then although coherent parts of the population may be very active, some remaining exquisitely frequency-tuned to the eliciting stimulus, the temporal coherence in the population necessary for the response may be lost. An example of such a situation might be the high-affinity desensitized state of cholinergic microsacs after prolonged exposure to ligands[279]. Likewise, the loss of electrophysiological sensory-motor connections over

habituation trials in *Aplysia* may be seen as the fractionation in time of a previously more coherently responsive neural population[95]. Temporal organization, coherence, may also be induced by periodic perturbation (phasing) of a population of oscillators so that the potential for concerted action is increased (before bifurcation) and that could explain first the increase, then the decrease, in the responses of some interneuron poplations to dorsal root stimulation in the feline spinal cord[256]. Probability density functions (pdf) of interspike intervals recorded from spinal interneurons that sensitize before they habituate reflect a single population before bifurcation, whereas those from interneurons that only habituate manifest multimodal populations[256].

Enzyme and receptor proteins, membrane conductances, postsynaptic potentials, single units, nerve cell nets, brain electrical fields, reflex behavior, and cognitive processes all manifest autonomous activity reflecting states of near-threshold instability. At any level, then, the elementary units can be viewed as nonlinear statistical oscillators with characteristic distributions that reflect their probabilities of response and temporal-spatial coherence. Perturbation or its inverse, isolation, can configure the distributional character of a population of spontaneously active elements with respect to their heterogeneity in frequency, phase, and coupling which leads to the manifestations of habituation and sensitization in the actions of the macrosystem.

The vertical mechanism of internal reordering will be recognized as alternative to the more horizontal thermodynamic processes involving changing receptor affinity and conductance states[2, 353, 435, 453, 485, 516, 558]; to the same-level, neurophysiological influences of homosynaptic and heterosynaptic facilitation, inhibition, and disconnection[88, 89, 95, 252, 254, 282, 335, 612, 632, 670, 710, 729]; and to the higher center memory-comparison-for-significance mechanisms involving neuronal assemblies, gnostic units, and descending inhibitory and facilitatory regulatory systems[289, 332, 628, 630, 685].

We shall review the literature relating to the pharmacology of the following experimental findings:

(1) Waning of the depolarizing effect of such quarternary ammonium compounds as ACh or carbachol in skeletal muscle associated with a decrease in nicotinic end-plate conductances[182, 348, 353, 558, 668].
(2) The desensitized, high-affinity binding state of cholinergic receptor preparations following prolonged exposure to ligands[541, 653].
(3) Changing synaptic efficiency following repeated elicitation of neural reflexes[65, 337, 419, 618, 670, 686].
(4) Changing EEG arousal and auditory evoked responses following their repeated elicitation[369, 566, 612, 629, 729].
(5) Alterations in acoustic and tactile behavioral startle during repeated stimulation[68, 133, 275, 550].
(6) The influence of selected cholinergic drugs and some psychopathogical states on human psychophysiological and behavioral response habituation[75, 261, 392, 685, 706].

At the outset, because they are essential to this analytic approach, time-dependent structural instabilities and autonomous motion in proteins and (in a nonmathematical way) theories of random process and oscillation will be reviewed.

Perhaps nowhere is the ubiquity, primitiveness, and distributed character of the habituation phenomenon better demonstrated than in protozoa, whose contractile response to mechanical shock disappears with repetition, where habituation generalizes to the bottom half of the organism when the top half is stimulated, whose rate of desensitization

increases inversely with the size of the area stimulated, and which manifests a long-term residual after partial spontaneous recovery. We hope to develop an image representational enough to apply to such phenomena at several levels of complexity: from the coronal withdrawal of a rotifer to a mechanism of psychological defense in man—similarities in what Richard Feynman[191] called "a rhythm and pattern between the phenomena of nature" that constitute physical law.

2. SOME DYNAMIC PROPERTIES OF PROTEINS

A protein molecule manifests multiple identities, depending on the technique with which it is examined. X-ray crystallography reveals an average structure with packing densities of groups within globular proteins as high as those in solid, crystalline amino acids and small organic compounds, which suggests that protein structure is compact and rigid[568]. Before the recent era of macromolecular dynamics, indeterminacy arising in such X-ray data with temperature-dependent blurring of images had been attributed to methodological error, lattice disorder, or simple thermal vibration[210].

Since the early 1950s, beginning with the observations by Linderstrøm-Lang[415] of rare, slow, nonlinear release of deuterium by a prelabeled protein, such techniques as fluorescence quenching and relaxation, fluorescence polarization, phosphorescence, tritium exchange, X-ray scattering for spatial variation, nuclear magnetic resonance for temporal variation, dielectric spectra, and temperature-jump experiments have suggested that globular proteins are fluid, dynamic structures whose multiple quasi-stable conformations have low energy barriers between them (as little as 5 kJ/mol), allowing autonomous conformational fluctuations to be observed across a range of time scales, depending on the resolution of the method and the size of the moiety being monitored. The periods range from 10^{-12} to 10^5 sec or longer[87, 209, 311, 344, 354, 424, 549, 657, 696, 717, 727].

Using a model globular protein with a molecular weight of 25,000 units with characteristic mass, volume, and heat capacity at constant volume and isothermal osmotic compressibility, Cooper calculated the ΔG_{RMS} fluctuations at 25° as almost equal to the mean enthalpy changes in protein denaturation[121], which implies that, at body temperature, structural fluctuations would have critical functional significance. Karplus and Mc-Cammon[345] empirically designed a computer model for the interactions among all the heavy atoms of a protein—the energy of the molecule being the sum of bond-stretching, bending, torsional, and non-bonded interactions. They monitored the plane of a tyrosine ring at a given temperature and found that the integrated classical equations of motion, grained from one to 100-plus picoseconds, revealed characteristic autonomous fluctuations. In his review of the binding energetics of protein, Weber concluded that in solution at physiological temperatures the globular protein is a "kicking and screaming stochastic molecule"[696].

The role of stability in the dynamics of proteins and the minimal energy required to alter their states are exemplified by the capacity of cholinergic ligands to induce reversible increases in sodium conductance in a system of cell-free mirosacs in the presence of azides, poisons of energy metabolism[541, 698].

The marginal stability of the macromolecule is thought to result from strongly interacting forces including internal and external (to solvent) hydrogen binding: hydrophobic interactions; and entropic, nonbonding (van der Waals), or solvent effects—all of which balance so delicately that the energy of very few uncompensated hydrogen bonds can destabilize the system[195]. As the result of random motion consequent to instability, amino acid side chains couple into clusters; clusters form domains; and domains cooperatively determine major folding–unfolding transitions[672]. The independence of separate contributors to structural variation is influenced by the dynamics of this thermally

driven coupling. The range of frequencies of fluctuation around the mean conformation is inversely related to the number of independent contributors, and increased structural coherence sums to both reduced variance and more regular structural fluctuations. Unstable structures hovering near their thresholds for phase transition[137] are more subject to synchronizing influences from weak long-range forces such as the brain's electromagnetic fields[30]. Supramaximal coherence among a population of nonlinear dissipative oscillators may lead to its bifurcation into two or more independent aggregates of elementary units[264, 265, 575].

Linderstrøm–Lang concluded that autonomous small rotational, vibrational, and translational motions of proteins gather cooperatively to produce slow, semicoherent movement[415]. Williams' calculations demonstrated that conformational (fold) instability correlates well with the ratio of charged (destabilizing) to hydrophobic (stabilizing) amino acid residues across characteristic protein types[717]. Kinds and degrees of crosslinking —S—S— bridges were also implicated. By applying the statistical mechanics of diffusion processes to protein folding, Karplus has evolved a kinetic scheme representing a diffusion-limited collision-coalescence of microdomains summing finally in the random coil-to-helix transformation leading toward tertiary structure [345].

We hope to illustrate how a changing degree of variational coherence among the constituents of a macrosystem determines its pattern of periodicities and probabilities for action and serves as a common regulatory dimension of neural systems, from a hydrophobic cluster within a protein monomer to the coordination of activity in the cerebral hemispheres.

In the literature of photosynthesis in the 1950s, there appeared reports of semi-systematic fluctuations in protein-mediated biochemical function; evidence for cyclic changes in the concentrations of phosphoglycerate and ribulose diphosphate led to a kinetic theory of oscillations[719]. Attendant studies in intact nonphotosynthetic cells showed overshoots and oscillations in intracellular components, most commonly in direct readings and continuous monitoring of NADH fluorescence[155]. One of the first cell-free oscillatory reactions to be demonstrated was in a soluble preparation of horseradish peroxidase/lactoperoxidase in the presence of a reductant and oxygen; there, changing concentrations of the oxidized state of iron manifested periods of slightly less than 5 min[732].

In the 1960s there appeared reports of continuous metabolic oscillations of glycolysis in a yeast system, *S. carlsbergensis*[100, 224, 298]; of ions and light scattering in mitochondria[86, 240]; and in various components of the respiratory chain in mammalian cells[101, 212, 313, 514]. On the basis of studies of yeast, muscle, and acites tumor cells, phosphofructokinase was speculated to be the controlling oscillatory enzyme in the eleven-enzyme glycolytic pathway[49], and a relationship was postulated between the capacity of oscillate and positive cooperativity, i.e. a Hill number greater than one[233, 285]. Several glycolytic oscillatory enzymes have been described since then, several of which manifest periods between 1 and 5 min, differing only in phase from other members of the sequence[48].

As early as 1952, there were suggestions of autonomous and frequency-sensitive periodic behavior in ACh concentration and release in the electric organ of *Torpedo marmorata* and in the frog neuromuscular junction that could couple with oscillations in nerve membrane potential[176, 293, 317, 318]. Likewise, cell-free periodicities in cyclic AMP generation and membrane binding have been demonstrated in the slime mold, in which cyclic AMP is seen as an organizing transmitter[364].

Three theoretical approaches that are not mutually exclusive have been used to describe oscillatory behavior in enzyme and receptor proteins. The first one involves nonlinear allosteric and feedback regulation. A two-component system in which the *self-coupling* effects are opposite (product activation, substrate inhibition); the *cross-coupling* effects

are opposite (the self-activating product of one inhibits the other and/or the reverse); the sum of the *self-coupling* effects is positive (a product flux of positive slope); and the product of the *cross-coupling* coefficients is greater than that of the *self-coupling* terms, will generate a system of partial differential equations in which the products will oscillate in concentration when their time-dependence is examined[286]. An enzyme candidate for such a system would be one that the substrate activated and for which the product was an allosteric inhibitor[234, 285].

The second theoretical approach is more general. It addresses the phenomena of relaxation/oscillation as manifestations of intrinsic instabilities (force-flux characteristics) in electrical, hydraulic, thermal, diffusional, chemical, and biochemical systems[205, 264, 476, 604]. States that are stationary but not necessarily in equilibrium behave differently during or after perturbation, depending on the dynamic nature of their neighborhood in a (time-independent) phase plane defined by its x, $\dot{x}$ axes. If the function crosses the origin with a negative slope the stationary state tends to return to stability after a disturbance. If the slope is positive the stationary state tends to be unstable. Functions with more than one crossing by x of the x-axis, i.e. those that fluctuate dynamically, are characterized by alternating zones of stability and instability[14, 467]. Over time, a system settles into a limit cycle[540], and driven to extremes, it bifurcates (with no memory) into other regimes[457]. Heat-capacity calorimetry[651] and other physical measures of conformational transitions, as well as allosteric enzyme kinetics, are consistent with this type of oscillation in, for example, a one-process system where the protein has two distinct stationary states with a nonstationary state between them and the transition is all or none.

Although such two-state models are manageable analytically, they are not consonant with the literature reviewed above, which suggests that the protein monomer has *multiple* statistically stable states, each with varying time distributions[32]. In addition, population dynamics involving a variable degree of frequency-phase coherence in this population of relaxation oscillators adds additional potential for nonlinear, quasi-periodic influences on both initial rate and equilibrium measurements. The receptor studies we review below indicate there are multiple singularities in ligand-binding functions. For example, stop-flow kinetics using cholinergic membrane fragments from *T. californica* with a fluorescent probe revealed at least three receptor ligand complexes with decreasing affinities[553, 554]. The capacity for multiple stable states in a single protein and multiple coherent aggregates in the population conveys the capacity for exquisite frequency and phase modulation in its function via superimpositional and interference interactions among the array of soft mode dissipative oscillators.

Whereas both the above approaches characterize the mechanisms of periodic behavior as intrinsic to the function of a system, regulated by its reactants and products and therefore specific, a third view involves a cross-modality mechanism in which physical-temporal proximity among charged globular proteins in a common membrane lipid pool, a heated dense fluid, and/or a common electromagnetic field will result in coupling of the autonomous physical motions of the macromolecules across their specific biochemical functions[47, 150, 374, 694].

In a denervated, supersensitive preparation isolated from randomizing environmental input, phase coherence would develop autonomously among proteins oscillating at comparable rates[517, 724, 725]. Increased statistical coherence, indicated by slower frequency in the aggregate[322], is associated with the longer autocorrelation lengths characteristic of critical systems, which are capable of large coherent actions from relatively small perturbations. Such mode–mode coupling, which is based on the physical motions of proteins rather than on biochemical mechanisms, could explain why, for example, denervated adrenergic nictitating membrane and salivary glands become very sensitive to both cholinergic and serotonergic stimulation[171, 591, 671].

A remarkable number of protein monomers have roughly comparable masses, from 40,000 to 60,000 daltons[401], and functional periodicities in minutes[559]. Just as identical pendulums on a common wall will move in phase after a random shock[467], independent of their specific metabolic functions, proteins with comparable masses may "breathe" together when subjected to the weight of common cause such as common electromagnetic fields, periodic perturbation, or drugs[625].

Studies of rat striatal tyrosine hydroxylase and ^{3}H-spiroperidol binding, rat raphé tryptophen hydroxylase activity, pure bovine pancreatic ribonuclease A and B, and luciferase activities[367, 368; Knapp and Mandell, unpublished observations] show kinetic oscillations in those preparations whose periods range from 3 to 25 min, even when exposure of enzyme protein to reactants is 2 min or less[444–446, 450, 733]. This suggests that, in addition to feed-foward and feedback regulation, the kinetic consequences of instability-based, thermally driven, coherent molecular movement changing catalytic probabilities generate quasi-periodic fluctuations in velocity. Metabolic intermediates may modulate their entrainment and phase[48, 284], but protein motions seem to be subject nevertheless to forces that physically couple across functional modalities.

3. A NONMATHEMATICAL REVIEW OF SOME ASPECTS OF RANDOM AND OSCILLATOR THEORY

As a group, biologists tend to distrust mathematical transformations of data, yet use them regularly in their work. The reciprocal rates of the Michaelis–Menten treatment or the dimensional normalizations and logarithmic transformations of Scatchard and Hill plots are common examples. Each brings with it mechanistic images of function: affinities, saturation of sites, positive and negative cooperativity. For example, the x, y plot of an allosteric substrate-velocity function is characteristically interpreted to mean that $\Delta[S]$ is *causing* rather than *sampling* a nonlinear distribution of enzyme activity states[376, 406, 471]. Fusion of an imagined mechanical property with its mathematical representation can become habitual, and its original symbolic purpose, phenomenological description, may be forgotten. New, unfamiliar treatments of data awaken us to the arbitrary nature of such approaches, and we react with suspicion.

From this point of view, even the mean is a transform with potential for significant distortion when used to describe a system that may never occupy its average state. For example, what does a mean kinetic value signify about the physical state of ribonuclease A when its microcalorimetry demonstrates peaks in negative heat capacity change at the extremes of the temperature curve, with no mean conformation indicated[160, 198]? The transition probability distributions from biased coin flipping and Markov chains or the frequency of fluctuations between quasi-stable states as in spectral approaches to noise may be as appropriate to the assessment of the behavior of such an enzyme as a linear or curvilinear function describing its only sometime average activity.

Moreover, biological data are seldom, if ever, strictly deterministic. Any equation relating independent and dependent variables now and forever can only be an approximation. Even the elegant differential equations describing the voltage-dependent properties of the nerve membrane in the Hodgkin–Huxley theory[293] do not deal with the local circuit currents that flow between different areas of the membrane and make membrane current geometrically and temporally heterogeneous. Under more realistic circumstances, even with the artificial temporal damping of the voltage clamp, additional equations are necessary[10, 35, 112, 302, 497], including many with periodic solutions[570].

The Langevin equation, used in many forms in statistical physics, describes the behavior of a dependent variable as a function of both its deterministic and its time-varying properties. With that orientation and because the data we work with are at best only quasi-

deterministic, we will review several techniques of description that do not require the assumptions of linear determinism, each of which evokes a different quality of the system being examined. Our descriptors range from the most deterministic, the mean, to the least, the average variational properties in the domains of frequency and characteristic exponents. These several kinds of statistical descriptions will make it possible to relate correlates of habituation and sensitization through common transforms, using biochemical data of neurotransmitter and receptor dynamics, electrophysiological data of membrane, synaptic, and electrical field phenomena, and finally, some distributional aspects of data from studies of human psychophysiology and cognition.

Mathematical transformation may not only be representational; at times it may be a direct expression of brain function. Consider, for example, how well the complex logarithm describes the translation of polar retinal coordinates into rectolinear visual cortical representation of images[175], or how a mass-spring oscillator with a forcing function describes aspects of gait transitions in motor coordination studies[358].

Probability density functions

A completely probabilistic transformation of a set of measurements of the activity emitted by a quasi-stable system is represented by the probability density function (pdf). The total probability mass is distributed along the y-axis as percentages of the number of observations, with equal intervals of the particular measure arranged along the x-axis. The pdf describes the probability (y-axis) that at any instant the data will assume a value within a given range (defined on the x-axis). The function is usually highest near the mean and manifests a shape in which the relative size of the central region is described by the variance, the extremes by its characteristic exponent, and its asymmetry and spread by the higher moments, skewness, and kurtosis. Because the units on the y-axis are percentages of the population sampled, the integral of the function, the sum of the percentages over the x-values, is always 100, i.e. for discrete values, $\Sigma f(x) = 1$. Thus normalized, the pdf as a characteristic property of some stable systems maintains its general shape (symmetry, relative height, angle of the roll-off of the tails) with changes in the measurement interval[230]. That is, it is essentially invariant across scale. (If a balloon were shaped like a rabbit, inflating it or deflating it would not make the rabbit much less recognizable.) Whereas increasing N and/or the time of observation in a biological system, which is never absolutely stable, *may* lead to regression toward a Gaussian pdf, graining of the intervals on the observational axis dilates or contracts the function without destroying its shape in relation to those of other kinds of characteristic pdf treated similarly.

The *cumulative* distribution function (cdf), the increasing sum of the y-axis population percentage as increasing values for x are sampled, is the integral of the pdf. Kinetic saturation plots with hyperbolic, rectangular hyperbolic, or sigmoid characteristics look like cdf—which, indeed, they may represent. For example, relative to the *causing* versus *sampling* issue, increasing substrate may be seen as the cumulative sampling of the distribution of enzyme activity states. In that way, the shape of the cdf reveals changes in mean velocity with increasing substrate as well as the degree of homogeneity in the enzyme population. Setting aside for now the issue of mathematical continuity, the pdf of enzyme activity states sampled over substrate or time can be viewed as the plot of a derivative of the kinetic function; the trajectory inscribing the ratio between changes in the distribution of occupancy in probability space and changes in the value of the specific activity.

If a process is sampled repeatedly over time, its general intensity or total energy is reflected by the average of the squared values of the measurement, the mean square value, or its positive square root, the root mean square (RMS). This energy is given its specific distributional shape by the pdf. When bounded, time-varying systems are examined in

quasi-stable regions, that is, around their limit cycles[467], the total energy is a conserved property analogous to an angular momentum orthogonal to the direction of the system's velocity. That is, all other things being equal, low amplitudes of variation are often associated with high frequency.

Surrounding the mean or first moment, which is the most static, time-invariant aspect of the pdf, is a central region reflecting the relative size and shape of the statistical bounds limiting the more random behavior of the dynamic fluctuating qualities which, in turn, can be described by the higher moments. The second moment, the variance, is determined by subtracting the square of the mean value from the mean square value. For example, in a Gaussian distribution, the range of that variance, from below to above the mean, indicates the interval in which 68% of the population falls. The third moment, skewness, involves the third power of the square root of the variance and reflects the degree of symmetry to either side of the mean. The fourth moment, kurtosis, describes the relative height of the central peak.

Because the x-axis contains equal intervals over its full range, extreme values would change the shape of the function. If the extreme values were asymmetrically distributed around the mean, skewness would increase, and if they were symmetrical the portion of the central region along the x-axis would shrink, piling the percentage of the population higher there to produce a peaked distribution, indicated by a high kurtosis. Equally probable distributions or those with a narrow range would look relatively flat and have low values for kurtosis.

In contrast to skewness and kurtosis, variance is not very sensitive to changes in extreme values. In stable non-Gaussian functions[443] the shape of these marginal regions is maintained even as the sample size increases or more time goes by[230, 407]. This is one of the ways the "law of large numbers breaks down" in the behavior of critical dissipative structures[546] and non-Gaussian distributions reveal their nonequilibrium stability[408].

Whereas a Gaussian or normal pdf can be described completely by its mean and variance, there are other stable distributions that are not so characterized. One extreme of a non-Gaussian stable distribution, the Pareto, for example[230, 407], would be represented by the probability density of first-passage times in a one-dimensional random walk that begins some fixed distance from a goal[519]. Some of the times would be infinite, making the variance unbounded, and additional descriptive parameters would be needed to quantify the distribution function. One such parameter would be a *characteristic exponent* that describes the shape of the pdf tail. For instance, $e^{-x^{1/2}}$ represents the roll-off of the pdf of the number of steps to the goal in a random walk, a distribution that is known in closed analytic form and whose tail descends asymptotically more slowly than ones with higher exponents.

In another instance, when relatively rare events are studied over large samples where the number of occurrences in one epoch is unrelated to that in another epoch and where intervals between the events are likewise independent (a Poisson process), there will be wide-band noise and a pdf in which the convergence of the tail can be represented by the non-Gaussian e^{-x}. If the phenomenon under study is a linear superimposition of contributions from a large number of independent sources, if each variable is small compared to the sum, and if every finite set of variables in the process has a multivariate normal distribution, the process is Gaussian and the pdf has a tail described by the characteristic exponent e^{-x^2}.

As will be discussed below in the context of the time domain, using the Hausdorff dimension[277] and its sensitivity to the frequency of variation[441, 442], Mandelbrot[443] elucidated an array of stable pdf characterized by tails with fractional exponents that are between one and two[230, 407]. For example, a slightly constrained random process, the

self-avoiding random walk (in the process of polymerization the next monomer cannot occupy a place already taken), has a characteristic exponent of 1.66[202].

Thus far we have seen that exponents from $e^{-x^{1/2}}$ to e^{-x^2} represent increasingly bounded distributions of random events around the mean. We argue below that in the way that boundary conditions contribute to the shape of emergent periodic structures in the convection instabilities of hydrodynamics (e.g. Benard or Taylor) or in the spatio-temporal organization of an autonomously oscillating Belousov–Zhabotinsky chemical reaction[269], the boundaries of a pdf help determine the frequencies of center crossings or directional changes in time-dependent variational behavior[188, 567]. An example would be the near periodic limit cycle of the bounded Gaussian process representing narrow-band noise.

An almost maximally bounded pdf with periodicity resembling a sine wave is reminiscent of distributions associated with near critical point phenomena. Under suitable conditions of pressure and temperature, light scattering studies show critical opalescence as regions the size of microns—the wavelength of invisible light—fluctuate together. Likewise, having lost their magnetism from thermal randomization of the directions of their component electron spins, ferromagnets become partially magnetized abruptly as their critical temperature is approached from above, and that magnetization continues to grow to its maximum, the component spins having become coherent. The dipolelike electron spins have more free energy when they are parallel. Increasing nearest-neighbor interaction, emergent cooperative behavior, is the essential feature in the evolution of critical phase transitions[333].

Nucleations (coherence) and phase separation dynamics (subsequent bifurcation) in binary mixtures represent other critical phenomena. A system of identical random variables that are coherent in frequency and phase—for example, a large aggregate of coupled protein oscillators—manifests an undamped auto-correlation at the system's fundamental wavelength, and the characteristic exponents may be of high dimension[204, 426, 722]. Thus we see a gradual transition from statistical mechanical uncertainty to wave mechanical certainty reflected in a sequence of tails inscribing increasingly bounded pdf.

The existence of stable intermediate degrees of randomness rather than the statistical thermodynamic assumption of progression toward maximal randomness (entropy) may be more consistent with the varying statistical boundaries of, for example, an unsaturated kinetic system examined at physiological reactant concentrations (Poisson) than with the boundedness of an in vitro saturated kinetic system studied at manyfold the physiological concentrations of substrate (Gaussian). More important, such stable distributional states may reflect the degree of interdependence (frequency-phase coupling) among participants. We must remember that conditions promoting significant pair correlations exist between charged elements like receptor and enzyme proteins, nerve endings cells, networks and nuclei in common fluids, and electromagnetic fields. A variety of macro-ions including proteins studied under the influence of common field forces demonstrates just such short and long range temporal and spatial structure[67, 402, 533, 534, 552, 590, 703]. With its assumption of statistical independence, the ergodic hypothesis may not be as relevant to membrane noise analysis even in voltage-clamped preparations[646] as theories of critical phase transition or non-equilibrium stability, which take into account the variable coherence of the elements in a system and its reflection in both changing sensitivity and alterations in relaxation times.

Potentially parallel protein dipole gates in the membrane feel one another and would certainly become interdependent in their motion in a common electromagnetic field, caught in the dynamical interactions among membrane potential, membrane protein order, and the fluctuating dielectric properties of the membrane. The impedance function has been shown to be a composite of a distribution of variable relaxation times, and the

dynamics of dielectric dispersions modeling membrane mechanisms are seen as cooperative phenomena[114]. Sheridan and Lester's[615, 616] studies of voltage jump-induced relaxations in the action of cholinergic agonists on *Electrophorus* electroplaques demonstrate just such cooperative effects, opening to question the Gaussian assumptions behind using fluctuation spectroscopy to determine an elementary conductance event[735].

We therefore need not assume that the Gaussian and Poisson distributions are the only ones that are stable. It has been demonstrated analytically that the functional form of the Pareto distribution is invariant under convolution and manifests linearity through a change in the scale of the variable. Specifically, the distribution of sums of independent, identically distributed, stable Pareto variables is itself a stable Pareto distribution and has the same form as the distributions of the individual summands[443]. Its four qualities are location (along the x-axis), scale (size), symmetry (skewness), and tail-shape (characteristic exponent). These qualities permit descriptive flexibility and quantification of distributions with less bounded, non-Gaussian variance ($e^{-x^{-2}}$). It is important to reiterate that the skewness and characteristic exponents of these distributions are also invariant under addition. The experimental stability of these distributions as well as their time-dependent properties will be seen below in a re-analysis of ACh receptor desensitization studies from the laboratories of Katz and Changeux. We shall see, through the mediation of scalar invariance in tail-shape and skewness, how the characteristics of the pdf reflected in the patterns of frequency in membrane receptor fluctuation sampled in minutes demonstrate self-similarity when sampled in milliseconds. This suggests that, rather than changes in the wavelength of an elementary unit, what is being measured in studies of ACh receptor desensitization noise may be a general systems property such as a decrease in the degree of physicochemical interference with autonomous frequency and phase coupling across scale or its facilitation from periodic perturbation acting at several levels simultaneously. Across scale, the common physicochemical milieu may alter such indices of the dynamics of cooperativity as the coupling constant.

Indices in the time domain

Stationary processes as represented by stable distribution functions can be studied in the time domain as well. Stationary Gaussian or Poisson processes, made by linear superimposition of contributions from a large number of similarly distributed, independent sources, each with a characteristic frequency, may sum to a degree of temporal homogeneity called *almost periodic* (limit-cycle) behavior. The power spectral density function of a process represents its variance decomposed into contributions across a continuous range of frequencies. In the case of narrow-band (Gaussian) noise, multiple component frequencies sum to a single quasi-periodic process in which the amplitudes of different frequency components are independent. The spectrum can be visualized as the result of putting a time history of the data through a set of band-pass filters with sharp cut-off properties and computing the average of the squared outputs from the filters. It portrays the spectral density distribution of the function's mean square value. In practice, a profile of frequencies is obtained by representing the time series as an infinite sum of sine and cosine waves whose frequencies are integral multiples of the fundamental frequencies in the data. This transformation of the data into a Fourier series, the Fourier transform, is mathematically analogous to the output of the band-pass filters, and although theoretically it does not exist for unbounded processes (e.g. a random walk distribution with the tail of $e^{-x^{-2}}$), generalizations to Fourier transforms in the limit avoid some of the analytic limitations[57]. Because, on one hand, the power theorem requires bounded variance and, on the other, it will not allow the discontinuity of a line spectrum representing a pure

harmonic function, its application to some of the stable Pareto distributions with weak convergence or strictly periodic processes is only empirical. Fourier analysis of characteristic distribution functions[177] is beyond the scope of this review, but some general relationships are relevant to the data we examine in Sec. 4.

Without a set of particulars, there is no necessary relationship between the amplitude behavior of a pdf and its frequency characteristics. The Gaussian process is a random distribution of amplitudes across frequencies. However, for our model system (a group of similar nonlinear, dissipative, variously coherent, unstable variational structures with a random walk to an action followed by a refractory period—statistical relaxation oscillators with characteristic recurrence times), the relationship between the *changes* in these two transforms of the data is instructive, particularly in studies of noise and relaxation in binding and conductance of the ACh receptor during sensitization and habituation.

Power spectral density functions

We shall describe the shapes of a number of kinds of spectra and relate their forms to orderly and graded changes in the shapes of pdf without the usually necessary assumption of statistical independence, a step that may prove controversial[186, 328]. For example, it has been demonstrated for heart cells that increasing coupling among autonomously moving units progressively reduces their variance and slows their frequency[138, 139, 331, 582].

A remarkable and mysterious spectrum is one in which the power varies approximately inversely to the frequency, often without limit. The slower the frequency, the higher the power. Unbounded, such a process would manifest infinite variance and essentially no mean. Several physical and statistical models have been developed to explain such a spectrum[34, 299], and it draws our attention here because some nerve membrane noise may be an example of it[681, 683]. The boundless quality of the variance suggests that such a spectrum may be consistent with one of the weakly convergent Pareto distributions[443], for example, the $e^{-x^{1/2}}$ process described above which, like random-walk times to an absorbing barrier, may consist of a great number of elementary units whose relaxation times have very wide range and a hyperbolic (Pareto) distribution[154]. This scheme is also consistent with the distribution of a random walk with drift to the threshold of membrane depolarization[295].

A second kind of spectrum is commonly designated Lorentzian. It has a zero frequency asymptote (bounded variance) and an exponential decline at higher frequencies. Although they are made up of a number of independent contributors to variance, an essentially Gaussian condition, in such systems there is room for widely varying degrees of intermittent activity at low probabilities, which generates wide-band noise. Thus the wide-band noise of a Poisson process, e^{-x}, may spread over a range of frequencies, and its average frequency is usually characterized by the half-width of the Lorentzian power spectral density function.

A third characteristic spectrum represents the narrow-band noise of a Gaussian process with symmetric probabilities which also tends toward higher amplitude at low frequencies and lower amplitude at high frequencies. The quasi-periodic behavior (limit cycle) around which it is stable is represented by a peak rather than a half-width signifying its average. Just as the pdf of an e^{-x^2} (Gaussian) process is more bounded than one represented by e^{-x}, the average value of its spectrum is better defined. The stability of Gaussian quasi-periodicity is an experimentally verifiable statistical parameter of long standing[595] and is derived most clearly from the theoretical work of Poincaré and Liapounov on the orbital stability of limit cycles[467]. Consistent with this image, it has been noted that some noises put through a narrow filter (boundedness of pdf) come out like sine waves[567]. Increasing

the N participating in the coherent motions acts like a filter for variance, reducing the range of variation[136]. The graded steps from boundless variation to a limit cycle can be seen as the spectral equivalent of the progression in characteristic exponents representing pdf from $e^{-x^{1^2}}$ to e^{-x^2}. As coupling (i.e. frequency-phase coherence) increases in a system of almost identical random variables, the shape of the pdf changes, as does that of the power spectral density function. Beyond the Gaussian, there is the possibility of bifurcation of the spectrum into frequency-phase coherent subpopulations. Although in statistical fluctuations it is not energy but participants that are conserved[14], within definable regimes amplitude and frequency appear to be reciprocal. In data from the desensitization of the ACh receptor, we shall see that frequency parameters reflecting the temporal (and spatial) arrangements among these conserved participants are similar across five orders of time, reflecting scale-invariant distributional characteristics in the time domain.

A common distributional and spectral descriptor: D

It was Mandelbrot[443] who most thoroughly explored the scale-invariant characteristic exponent reflecting continuity in the progressive constraint of chance in stable Pareto distributions in relation to the behavior of the same process in the time domain, also invariant (self-similar) across scale. In brief, he found that the Hausdorff–Besicovitch dimension D[277] quantified the degree of entropy ''roughness' (frequency) in the time-varying surface of a random process and that the same index served as a characteristic exponent for the pdf of the time-independent ensemble measures of the same process. This measure has been used successfully in studies of emergent turbulence in critical physical systems[272]. or protein backbone structure from electron spin relaxation measures[639], and of the variations around mean velocity function in rat brain biogenic amine enzyme activity[449]. D appears to be more sensitive to fine grained frequencies like those that arise from thermal (shot) or Nyquist–Johnson noise. while the autocorrelation function (see below) appears to reflect the more general pattern of relatedness among events within the process. A system will relax through all available configurations or ensembles of configurations; the more possibilities, the longer the wavelength of the relaxations will be after either perturbation or autonomous fluctuation. Power spectral density functions reveal both kinds of order, and ''slows,'' longer wavelengths, can be generated by increased availability of either individual contributors with an average frequency representing a limit cycle and comprising a large, mass of phase-coherent oscillators (concomitant with low amplitude of variation) or a group of ensembles of contributors with multiple relaxation times (concomitant with high amplitude of variation). We have grained sampling rates using both kinetic data and progressively summed random number series[446] and found D to be stable across scale in the frequency domain, as it is as a characteristic exponent. Both spectral and exponential transformations of the stable Pareto distributions serve to relate probability density functions and frequency in a system across scale.

The autocorrelation function

The autocorrelation function of a time series of values describes the general dependence of data at one time on the values at another time. It serves as a measure of the degree and kind of temporal connectivity in an ensemble of values[737]. In contrast to the adjacent fine structure assessed by the Hausdorff–Besicovitch measure D, which may even resist shuffling of the sequential order in a time series, the autocorrelation measure is directed to more macroscopic characterization of the average sequential order in wavelengths of time across the data set. Values are multiplied by other values in the series at a system-

atically increasing time from the origin (which is chosen arbitrarily), and the system's variance (squared) is distributed over these lags. An estimate for the autocorrelation function between the values of $x(t)$ at time t and at time $t + \tau$ is obtained by taking the product of the two values and averaging them over the observation time T. The applications of autocorrelation functions in biology are varied. For example, it and its higher order moments are particularly useful in the analysis of nonlinear systems using white noise inputs[456]. Later in the text we tell how we used it, along with its Fourier transform the power spectral density function, to assess the changing degree of temporal connectivity and periodicity during the processes of sensitization, desensitization, and habituation.

Generally, the concentration of a particular protein molecule, carrying with it a fluctuating probability of catalysis or binding at some given substrate or ligand concentration, will oscillate around its mean value with a wavelength that depends upon, among other things, how many of the molecules are "breathing" together. In a Gaussian system, where amplitude is independent of frequency, the time it takes to return to the average after a perturbation-induced change reflects the same temporal connectivity among the participants as the time it takes to return to the average during spontaneous fluctuations in concentration. Reservations about the appropriateness of the assumption of this ergodic hypothesis have been discussed above. The autocorrelation length, showing how long repeated measures of the system are related, is an ideal measure of the wavelength of this relaxation[83, 246, 247]. In practice, the autocorrelation length in chemical kinetic systems near equilibrium is an average of multiple chemical and diffusive processes. A local excess of a quantity like catalytic velocity cannot disappear; it relaxes slowly as it spreads (in time and space) over the whole system with a time reflecting its average, characteristic wavelength. The relationship between the shapes of the autocorrelation function and the power spectral density function is generally as follows. When the autocorrelation function declines exponentially across lags the spectrum is Lorentzian, that is, it has a zero frequency asymptote (bounded variance) and an exponential decline in the region of the higher frequencies. When the shape of the autocorrelation function is Gaussian the spectrum is Gaussian. When the frequency measure yields a line spectrum the autocorrelation function shows a sine wave.

Unlike the small spontaneous fluctuations of the thermal noise in a Gaussian system, the coherent motion of a large number of particles in a highly cooperative system is reflected by slow autocorrelation roll-off, a periodic pdf tail, and a long-wavelength peak in the spectrum. This is the behavior of hydrodynamic, electrical, magnetic, and chemical systems near their critical points which is so stereotyped that "the details of the molecular structure become unimportant . . . the behavior (in this region) to a certain extent being universal"[137]. A similar image may well portray the cooperative interactions of the microdomains of a globular protein and be consonant with its emergent slow quasi-periodicity (in minutes) as well as the small amounts of energy necessary to evoke a dramatic change in state. Similar nonequilibrium critical behavior at the large-fluctuation, "high temperature" limit has been related to emergent order in a neural network modeled after Onsager's work with the Ising spin system[613]. The well-known reciprocal relationship between amplitude and frequency in the EEG suggests a comparable kind of variable cooperativity, and the dynamics of critical behaviors at an even larger scale in that measure have been associated with changes in spectral representations of autocorrelation function[25–27, 60].

In the case of the boundless distribution of a random walk or in wide-band noise, the autocorrelation function rolls off without revealing much of the periodicity produced when a recurrent process finds itself again over increasing lags. With narrow-band noise and strong average periodicity, the function reveals that periodicity over a progressively damped course, whereas the autocorrelation function of a sine wave oscillates undamped

over all time. A coherently coupled, variationally restrained system at its critical point may bifurcate into subsystems[204, 426, 722] and manifest multiple relaxations including strongly periodic components. We shall see this spectral transformation manifested in the receptor-membrane preparations of Katz and Changeux during desensitization.

Desensitization of ACh-activated ion channels leads to emergent periodicity, burst-kinetics[489, 585, Montal, personal communication, 1980]. Sensitization of central adrenergic receptors leads to stable oscillations in behavior and spinal fluid metabolites[543, 544, 601]. At a larger scale, electrical sensitization (kindling) in the limbic system leads to stable, coherent oscillations in electrical threshold behavior[219, 231, 707]. During the process of desensitization with local anesthetics, fluorescence-tagged cholinergic receptor fluctuations bifurcate into two populations: one strictly periodic; the other manifesting narrow-band noise (see later in text).

We come now to a brief discussion of periodic processes in the central nervous system, usually addressed under the rubric of the actions of ''central pattern generators''[720]. Like the progression from a random walk with unbounded variance to a Gaussian near sine wave, this subject lies at the border between random processes and the branch of deterministic wave mechanics in biology called oscillator theory.

Oscillatory phenomena: Periodicity in the central nervous system

The dynamics of frequency and phase coherence among a population of autonomously active, dissipative, nonconservative, unstable neural structures, from proteins to hemispheres, can be seen to be intrinsically involved in the determination of cross-scale symmetric indices of the shape of the pdf as well as the frequencies of time-dependent variation. Theories of the coordination of rhythmic events in the nervous system have, for the most part, been deterministic, the phenomena seen as the results of either feedback regulation from the periphery in recurrent loops or, more consonant with current experimental findings, or one[144, 605] or perhaps two[127, 355, 539] pacemaker neurons or networks. The possibility that statistical rather than deterministic mechanisms (transition probabilities and recurrence times) underlie rhythmicity in biology is currently being considered most seriously in the context of cell-cycle variability where division times distribute as e^{-x}[242, 371, 500]. Cooperative emergent properties of an entire system, not represented exclusively in any elementary unit alone, have not often been entertained as candidates for a role as the nervous system's central pattern generator.

In the mid-1600s, it was Huygens who reported that two clocks, slightly ''out of step'' with one another, eventually became synchronized when they were hung on a thin wooden board[467]. Spontaneous mutual entrainment of nonconservative oscillators can be visualized as the result of random variation of phase and frequency around average values by similar variational structures which, when they are a certain distance apart in frequency, produce beats as their vibrations move adjacent portions of the common medium (backboard, dense fluid, electromagnetic field) or generate interacting chemical frequencies to which they themselves are responsive. Two families of motions suddenly become one when a critical value in their difference is reached[560]. Absolute synchronization, then, is a critically valued, nonlinear phenomenon that occurs as an accelerating transition probability function over time, and it manifests both hysteresis and the possibility of bifurcational overshoot. A full range of joint interactions is possible. In a system of simultaneous simple harmonic oscillations each contributes independently to the vibration, any single point of which represents the algebraic sum of the wave function for each harmonic mode. This is known as the principle of superimposition, which can be thought of as an aggregation in time similar to crystallization in space, involving the dimensions of amplitude as well as orientation. The superimposition of oscillations involves vector

addition or, in the case of many oscillators, vector integration, whose magnitude is the product of the magnitudes of the two phase vectors and whose counterclockwise angle with the reference direction is the sum of the two angles. Constructive (resonant) and destructive interaction are possible. For example, appropriately phased, two identical organ pipes sounded together cannot be heard[560].

As the mass of the coherent aggregate grows, the more random variational properties of each element cancel out, leaving the average fundamental wavelength as a statistically strong value. Even in living oscillating systems, mass and frequency are inversely related, and the mass of the temporal aggregate slows as it grows. For example, as the mass of the isolated retina of *Aplysia californica* was reduced by sequential extirpations, its circadian period shrank progressively from 28 to 3 hours[322]. When the distance between the common frequency of the aggregate and that of new candidates for synchronization increases beyond the range of critical values for isochronous superimposition, the size of the aggregate is limited. In addition, as is the case for crystals, each growth process has a size beyond which it is unstable[669]. What was a single Gaussian quasi-periodic macroscopic collection of independent oscillators, with normally distributed variation in frequency and phase, *bifurcates* into two populations: often a more tightly synchronized aggregate with low variance and the remaining and retracting (parent) Gaussian population. The highly coherent smaller mass manifests an oscillating auto-correlation function, approaching a line spectrum indicating strict periodicity, and a characteristic exponent of 2 ($e^{-x^{2+}}$). These are exactly the properties of the two circadian "pacemakers" that emerge when mammals (including humans) are isolated from entraining light[539, 709], and here Kawato and Suzuki have elegantly applied the Hopf bifurcation model[355]. One pacemaker is tightly coherent and a little faster; the other is "loose" and slower. Similar splitting between temperature and activity rhythms occurs spontaneously in subjects kept in continuous light[708]. In a system of spontaneously aggregating and bifurcating similar oscillators in a heat bath, one can imagine the emergent organization in space and time that forms the phenomenological basis of Prigogine's application of nonequilibrium thermodynamics to living systems[545, 546]. As noted, the process of superimposition in time resembles aggregation in space, as is seen in the nucleation, growth, and cessation of growth in the process of crystallization[334].

Phasing and associated superimposition in frequency can also be facilitated by a commonly felt external perturbation, what has been called *the weight of common cause*[230]. The perturbation gathers (phases) near-neighbors into a coherent aggregate in the frequency domain. Such rhythmic perturbations as ligand concentration frequencies (a substance in solution has a frequency of variation as well as an average value), trains of electrical pulses, or regular loud noises make coherent a resonant aggregate that is limited in size by its mass-restricted frequency and stability. This aggregate moves out of the range of the driving fundamental or its integral harmonics as it bifurcates into two or more kinds of populations. In that context we shall show, from some data of Changeux, that during desensitization one population of ACh receptors bifurcates into two. In that context also, we suggest that during habituation trials[255] H interneurons in layers I to V of the feline lumbosacral cord, which are nearest the sensory nerve endings and already undergoing a steady state of random perturbation, only decrease their response with 0.5 Hz driving, while those farther from tonic random sensory input, the S interneurons in layers V to VIII, first gather (phase) more elements into a coherent variational pattern ("sensitization" of the macroscopic response) then bifurcate (habituate). The fractionation of the interneuron pool can be seen to reduce response probabilities in the way that a wider distribution of effort over time might reduce the collective strength below a critical level at any given moment if several men were trying together to move a heavy weight. Consistent with this view are the wide and variegated pdf of interspike intervals of H inter-

neurons and the narrow, almost coherent pdf of the S interneuron intervals (to be found in the data of Groves and Thompson[256].

Another aspect of oscillatory phenomena that requires some comment concerns the anatomical location of the observed coherence. Whereas in the critical behavior of magnets there is a local magnetic moment, and in liquids there is density, in systems like superfluids the fluctuating field can only be inferred. Forces between protein molecules that are fluctuating (breathing) as charged macro-ions in solution are influenced by and contribute to an interacting electromagnetic field, which in turn influences the behavior of the macro-ions[150].

To the possible chagrin of experimentalists, the source of the emergent periodic properties of such a system perhaps cannot be located in any of its participants or their point-to-point circuits, but reside in their common field which, in turn, configures the temporal-spatial order. A dynamical system serving as an example of that could be the voltage-sensitive ordering of membrane proteins, which changes the dielectric properties of the membrane, which in turn affects membrane voltage[112]. The emergent order is seen in the periodic behavior of the macrophenomenon, membrane conductance oscillations (see Section 4). Either in the volume or distributed over the interneuronal network, the behavior of common organizing and mediating fields of chemical and electromagnetic potentials and waves is inferred from the statistical properties (second order variations) of the macrobehavior of the system rather than its constituent parts[545]. So it appears that strict periodicities can indeed exist in the aggregate without an anatomically definable central pattern generator, and one way to visualize nonlinearities in the macroscopic behavior of our model population of relaxation oscillators is to see them as a sequence of quasi-stable quantum levels of spontaneous (thermally driven) or perturbation-induced organization. For example, as motion on the x-axis progresses linearly, the y-axis manifests a series of asymptotic growth curves followed by bifurcations into subpopulations.

Another image that is useful in thinking about oscillating, variously stable, dynamical systems is the phase portrait mentioned above[467]. The relationship between two time-varying parameters of a system can be represented on the x, y plane without time. For a variable with one degree of freedom, that would constitute a path traveled by a point representing the relationship between the two parameters at all times. Two parametric equations (representing x and y respectively as functions of t) are fused as the motion of the variables is described by the phase velocity and path of the point. The phase portrait of a group of harmonic oscillators is a family of closed ellipses in which the x-axis represents position and the y-axis represents velocity $(\dot{x})$. The stability of a system can be represented by parametric relations in the phase plane, with the periodic motions of a stable system (such as our multivariate, normally distributed Gaussian model) inscribing concentric closed paths, limit cycles, or spiraling inward toward the equilibrium states, which correspond to the degenerate path consisting of a point. Unconverging, unstable systems spiral outward. Bifurcation or its inverse, coalescence, can be represented by a single point splitting into a stable and an unstable limit cycle or by the fusion of a stable limit cycle and an unstable limit cycle into a semi-stable limit cycle[14]. This kind of behavior is well documented in the deviations from Ohm's law seen beyond the linear region in the relationship between current and potential in the squid axon membrane[110, 113, 459], which leads to temporal regions of "negative resistance" and a part of the parameter space where current "runs backward"[111, 659]. In another context, such circular relationships involving what were once perceived as positive linear functions (for example, Ohm's law for the membrane) led to Prigogine's concept of "excess entropy" in statistical thermodynamics[545, 546].

If, in addition to their specific receptor-mediated activities, psychotropic drugs as weights of common cause order populations of variously coupled, nonlinear relaxation

oscillators, then circular dose-response functions with a sequence of small linear ranges at higher and higher doses would be characteristic. Just such dose-response functions in clinical responses to tricyclic antidepressants have been documented by Asberg and others [see 229 for a review].

Nonlinear enzyme and receptor kinetic functions can also be addressed in this context. We have reviewed above evidence for the multiple stable states of a protein, with the same amino acid sequence. Each conformational enzyme oscillator fluctuates around its mean state and manifests a characteristic wave function: their joint output in the variational domain is a function of superimpositional dynamics. Measured as macroscopic properties, approach, binding, and dissociation are, in effect, time-dependent parameters of a variously synchronized population of nonlinear relaxation oscillators. When the parameters are related as x, y functions in the absence of time, one might anticipate re-iterative functions analogous to the bifurcational and phase-plane behavior of dynamical systems. It was Teipel and Koshland who first reported reiterative substrate-velocity functions for a number of regulatory enzymes[665]. Those functions can be seen as the result of sampling over a number of enzyme activity states or as characteristic of the behavior of successive functions progressing through zones of varying stability[467, 517, 724, 725]. We have observed reiterative saturation kinetic curves in the activities of both rat striatal tyrosine hydroxylase[449, 450] and rat raphé tryptophan hydroxylase[367, 368]. Changing substrate concentration frequencies interacting with the superimpositional dynamics of a population of enzyme oscillators would cumulate in reiterative, circular kinetics as substrate regimes were traversed. Thus the concentration of substrate or ligand, like a relatively nonspecific weight of common cause, could influence the coherence of the system. Hysteresis would represent a gradually growing time- or force-dependent synchrony. A high Hill number would reflect a zone of high homogeneity of enzyme forms or a narrow zone of resonance between the frequencies of reactant concentrations and protein motions. A negative Hill number would indicate a single very coherent population. As we shall review, the multiple affinities and diversity of shapes in the binding curves of the nicotinic ACh receptor[115, 167, 168, 279, 342] need not be seen exclusively either as sequential or concerted cooperativity (that is, a linear progression along x, causing y) or as an iso-enzyme diversity in conformations (that is, linear progression along x, sampling distinctive conformations as seen in the shape of y). They also reflect behavior typical of a system of variously coupled nonlinear oscillators sampled over unstable regimes characterized by positive derivatives, and then regions of negatively changing slope indicative of stable regimes[205]. In the changing statistical configurations of a collection of unstable, spontaneously active individual units, we find commonalities in the processes of desensitization, sensitization, and habituation across neurobiological levels. In Section 4 we discuss them at the molecular level.

4. A MOLECULAR LOCUS: THE DESENSITIZED STATE OF THE NICOTINIC CHOLINERGIC RECEPTOR-MEMBRANE CONDUCTANCE COUPLE

The dynamics of temporal-spatial order in instability-based autonomous motion of receptor-conductance proteins in nicotinic cholinergic membrane systems appear to be involved in the processes of excitation, sensitization, and desensitization, all of which can occur at physiological temperatures without additional (metabolic) energy. Because of the linear dependence of the amplitude of excitatory postsynaptic potentials (EPP) on membrane potential, Fatt and Katz conjectured that it was unlikely that energy-dependent charge separation was involved[183]. The finding that normal EPP can be observed in mammalian neuromuscular junctions in which the active transport of ions is inhibited[218] was consistent with their speculation. In addition, in a hyponatremic (5 mM), isosmotic

sucrose environment, calcium-free (chelated with 1 mM EGTA) metabolically poisoned microsacs from the electric organs of *Electrophorus electricus*[346] and *Torpedo marmorata*[541] manifest an array of responses quite comparable to those observed in vivo[653]; namely dose-related agonist excitation and blockade by antagonists; multiple-affinity ligand binding; responses to local anesthetics, "membrane stabilizers," dithiothreitol, gamicidin A, affinity-labeling reagents, and all known cholinergic ligands; and a reversible desensitization that can be modulated by temperature, calcium, "membrane stabilizers," or local anesthetics. In both the electrophysiological and neurochemical realms, neither calcium nor metabolic energy is required to desensitize a synaptic response at the molecular level, which suggests that recent theories that the molecular mechanisms underlying habituation involve cyclic AMP-dependent phosphorylation of channels of calcium channel currents at the synapse (if the process, although scaled up in space and time, is similar) are more about its modulation than its occurrence[89, 95, 335].

Molecular events related to habituation may be observed in the two-dimensional fluid matrix of the membrane lipid bilayer[196, 479, 622], wherein proteins, which we know to be in autonomous motion[1, 195, 727] can diffuse laterally, and wherein the aggregation and disaggregation of these variously constrained and coupled[477] relaxation oscillators can be described statistically through their joint actions over time. The membrane voltage-sensitive positions of the receptor-conductance proteins normal to the plane of the membrane[293] and the in-plane and "lateral" organizational dynamics influenced by magnetic fields[551] allow analogies with convection stabilities, nucleation, the organization of ferromagnet dipoles near their critical temperature, and other examples of nonequilibrium critical phase transitions[28, 269].

Ligands may aggregate multivalent[553, 554] nicotinic receptors into cell surface aggregates of increasing size whose physiological expression is distributed over time in quantal steps of increasing scale, from single incoherent fluctuating subunits, through a temporally coherent five- or six-member ring[94, 493], to the concerted action of aggregates of rings, as have been modeled mathematically for the receptor-ligand action of insulin[524]. These states of increasing motional coherence of ACh receptor proteins may correspond, respectively, to conductances that look like random noise, single-level autonomous quantal jumps, and finally multiple simultaneous jumps as seen in the spontaneous behavior of reconstituted purified ACh receptors with functional sodium channels in artificial bilayers[489].

The analysis of noise in membrane conductance has been directed for the most part at the temporal character of the elementary conductance event, the channel lifetime, and an agonist-induced configurational change in a statistical preponderance of the individual receptor-ion gate proteins has been assumed[488]. Consistent with the idea of a "channel lifetime" as a physiological rather than a systems constant is a report[12] of the failure to find, after desensitization, a change in the fundamental spectral wavelength of the fluctuations from which the channel lifetime is deduced. However, desensitization itself, and the action of procaine which imitates desensitization[699], have been reported by others to change the frequency spectrum[350, 352], which as we shall see, is more suggestive of a change in temporal-spatial order among the participants than of an alteration in individual molecular dynamics. For example, spectral bifurcation into two populations, one of which has faster frequency and a coherent spectral density, as will be seen in the data farther on, resembles aspects of the change in the noise spectrum after disaggregation of receptor subunits with dithiothreitol[394]. In our re-analysis of data from Changeux, the latter findings will be shown to be consistent with changes in temporal coherence among the elements rather than with simultaneous configurational change in individual protein receptors. In addition, as noted earlier, graining of the spectrum in minutes shows a bifurcation in the population represented by the emergence of two dominant spectral

frequencies, as Katz and Miledi saw in the time frame of milliseconds[350]. This represents the property of self-similarity across scale in the shape and the associated frequencies of stable Pareto distributions describing partially-ordered random processes[443]. The same kinds of changes in coherence emphasized by Mueller in the spatial dynamics of the receptor-conductance couple[477] will be seen in the time domain across levels during desensitization and habituation[28, 29].

The conflict between the mechanisms of agonist-induced conformational transitions in a receptor protein and agonist-induced alterations in temporal-spatial order among a population of autonomously fluctuating receptors resembles the previously discussed conflict in interpretations of nonlinear enzyme kinetics between sequential or concerted allosteric effects and various degrees of physicochemical environment-dependent autonomously emerging coherence in a heterogeneous population of ensembles of spontaneously fluctuating enzyme oscillators sampled sequentially[449, 450]. Threshold phenomena that require the concerted action of microparticipants may be regulated through the statistical mechanisms of frequency-phase coherence of the population; the macro-event emerging from the progressive organization in time of the actions of individual elements. Present emphasis in nonequilibrium statistical mechanics and thermodynamics on emergent order and temporal-spatial organization attests to the currency of these notions[269] and suggests that there may be a fundamental fallacy in regarding participants in the coordinated actions of biological systems as independent contributors to variance[271, 347].

The fundamental issue concerning mechanisms underlying the nonlinearities remains unresolved with respect to the cholinergic receptor-membrane conductance system. The *instantaneous* current-voltage relationships are reported as linear in such nicotinic cholinergic receptor preparations as the muscle end-plate[375, 436] and the *E. electricus*[403], comparable to the behavior of the sodium channels of nerve[293] and consistent with the concept of conductance channels as independently fluctuating Gaussian distributions of ohmic pores[488]. However, the dose-response relationships manifest sigmoid shapes with Hill numbers of up to 2.5, even at low concentrations of agonist where desensitization is minimized and high-resistance microelectrodes allow monitoring of the smaller currents in voltage-clamped preparations[148, 153, 522, 644]. Nastuk long ago noted that the rising phase of the end-plate potential was slow when ACh was applied through a microelectrode to a frog neuromuscular junction[484]. The electrophysiological expression of that type of time-dependent dose-response nonlinearity had been observed first by Cole in the squid axon when he studied current-voltage relationships beyond the linear range, that is, for longer times[109]. Before his later theoretical development involving emergent membrane organization, Cole had interpreted the nonlinearity as a manifestation of mechanical inertia in the coupling of electrical to mechanical events[110–112]. Those later studies focused on dissipative processes leading to internal reordering among the membrane elements that involved time-dependent interactions of concentration gradients and electric fields in solutions of electrolytes[490, 491, 506]. The nonlinearities, however, do not appear to be exclusively a function of organizational dynamics in the ionic-electrophysiological conductance mechanism; they are seen in receptor binding kinetics as well. Sigmoid functions with Hill numbers of 2 have been reported for receptor-binding preparations from the electroplaque of *T. marmorata*[168, 501, 653, 697].

The nonlinear ligand binding functions of cholinergic receptor preparations and similar current-voltage behavior in membrane conductances come together in studies of the voltage-dependence of the effectiveness of agonists released from nerve endings or iontophoresed onto neuromuscular junctions. Even when observations are restricted to the sites blocked by α-bungarotoxin, loss of the conductance response associated with slow shifts (bifurcation of the population) to multiple affinity constants (including high affinity ligand binding) is characteristic of the membrane voltage-sensitive process of desensitiza-

tion[102]. Perhaps an increasing amount or time of influence of a common field-sensitive mechanism is reflected in the nonlinearities in both binding and conductance functions that are evident during this process.

The concerted[470, 471] and sequential[376] allosteric kinetic models suggest that a sigmoid function over substrate or ligand, or hysteresis over time[213], derives from nonlinear actions of the x-parameter on y. An additional interpretation, just as consistent with the data, would be that the sequence in x, in units of substrate, ligand, or time, samples enzyme or receptor forms over a range of activity states indicated on y, and the shape of that function inscribes a *cumulative* distribution function (cdf) which can be differentiated into the system's pdf. For example, the sigmoid kinetic shape represents the integral form of a differential, a Gaussian pdf whose steepness is indicated by a Hill number reflecting the relative weight of the distribution at its average value. The more positive the Hill number in the kinetic cdf, the lower the variance of the pdf. In contrast, the kinetic curve resembling a more rectangular hyperbolic function with a Hill number below one in differential form displays a one-sided distribution function, as though only half the enzyme molecules or, more likely, half the time of the enzyme's oscillatory movement, is inactive catalytically. Perhaps what has been called "half-of-the-sites" reactivity[405] should be called "half-of-the-time" reactivity, as observed in a strictly coherent subpopulation of almost sine wave enzyme oscillators. Very coherent fluctuations between two states in time (active, inactive) among receptor oscillators is consistent with recent findings that suggest the maximal fraction of channels that can be open at the frog end-plate at any one time is 50%[5, 148, 153]. What is called the high affinity (low capacity) state of the desensitized receptor, a type of kinetics seen best at high substrate concentrations in enzyme studies and high "cold washout" concentrations of ligand in receptor binding studies, may represent the sine wave behavior of a "desensitized" post-bifurcation fast frequency subpopulation, oscillating between active and inactive conformers.

What has been interpreted as ligand-induced conformational change in the great variety of occupation-activation and hit-activation models[see 677 for an extensive review] or a statistical shift in preponderance of *independently* fluctuating forms[646] can also be seen as a kinetic-statistical portrayal of superimpositional population dynamics among variously coherent relaxation oscillators[517, 724, 725]. This would come close to a kinetic representation over ligand-time of the Mueller model of aggregation in space[477], with the additional functional dimension of a normal sequence of discontinuous first-order phase transitions, manifested by progressively temporally ordered emergence of coherent aggregates: from random motion-induced leaks in single protein gates, to quantal jumps in a single coherent rosette, to the multiple quantal conductance jumps of coherent aggregates of multiple coherent aggregates[489, 594].

It may be that a Lorentzian frequency spectrum, a Gaussian assortment of contributors to variance, portrays a necessary precondition for this normal organizational march across scale toward membrane activation[723]. Local anesthetics and desensitization segregate small coherent subpopulations away from the single Gaussian group in time (frequency), creating statistical "holes" in the Lorentzian spectrum[350] and preventing the normal sequence of first-order (discontinuous) phase transitions to membrane activation (see our re-analysis of Changeux's data farther on in text). Burst kinetics, which appear during desensitization, may represent the expression of the bifurcated subpopulation, spontaneously active but unable to participate in the integrated macro-event of a stimulus-induced change in conductance[585].

The temporal-spatial coordination of autonomous fluctuations in the receptor-membrane conductance couple may involve a variety of mechanisms. For example, Karlin reported a decrease in Hill number (which we interpret as increased heterogeneity among enzyme ensembles) after reduction of sulfhydryl bonds with dithiothreitol[342, 343]. The

statistical kinetic interpretation of the loss of excitability in this preparation and the reverse effect of oxidizing O-iodosobenzoate[141] would suggest that sulfhydryl bonds may play a permissive role in the spatial-temporal coordination of fluctuating subunits[557]. Their loss would distribute membrane receptor protein fluctuations less coherently over time and prevent their emergent order into integrated action. Sodium cholate eliminates high-affinity binding[280] and that effect can be prevented or reversed by a lipid membrane-like environment; temporal-spatial coherence among the elements may be facilitated by a common lipid membrane environment.

Addition of the dimensions of (a) autonomous protein fluctuations; (b) the in-plane lateral, mutual influences of dipoles in an electromagnetic field normal to the membrane potential; and (c) nearest-neighbor interactions capable of extending to large spatial-temporal correlations in a dynamic lattice model[655] suggests the relevance of an early mechanistic portrait by Changeux *et al.*, in which they described accelerating receptor coherence in the synaptic membrane as a lattice culminating in membrane depolarization[103]. That plus a nonequilibrium phase transition theory could represent the dynamics of the time-dependent nicotinic postsynaptic membrane during activation and would be analogous to the way random fluctuations can grow beyond a critical embryo size for nucleation in the process of crystallization[334] or the way spin couplings become coherent in a magnet near the critical temperature[723]. Presynaptic release of neurotransmitter could serve as a phase-organizing perturbation of receptor-conductance elements whose temporal coherence beyond a critical level would accelerate autonomously toward postsynaptic membrane activation.

The linear-deterministic use of noise analysis by Stevens[645, 646] does not emphasize changing temporal coordination among elements of the system (''the conformational change is rate limiting''), the dynamical aspects of polarization of the individual protein dipole moments as membrane voltage changes[111, 112], or the mutual influences of the magnetic fields of adjacent channels analogous to the critical coupling behavior of the spin lattice in ferromagnets near their critical temperature. Although Stevens' Gaussian assumptions permit analysis of noise for linear-deterministic values like channel lifetimes[34, 187, 427], they fail to permit interpretations relevant to changing population dynamics of elements, particularly their degree of coordination in a field of dense fluids, chemical ligands, and electromagnetic forces[694]. Both perturbation-induced temporal coherence and its exponential decay (time scattering) are consistent with organizational behavior in a population of nonlinear oscillators, varying in phase. Phase-response curves of ''central pattern generators'' to excitatory and inhibitory postsynaptic potentials supply straightforward analogical examples of such mechanisms[18, 20, 537].

In an early statistical approach to the nicotinic cholinergic synapse, Katz and coworkers addressed the issues of facilitation and inhibition of neuromuscular transmission by studying with intracellular recording electrodes the pattern of spontaneous end-plate potentials in relation to extracellular recordings during the elicitation of single and repeated nerve impulses[142, 143, 183, 184]. Using a low calcium, high magnesium Ringer's solution to hold the spontaneous EPP in a low probability, submaximal state (i.e. a Poisson process), they were able to demonstrate statistical recruitment of the quantal components—a second shock was followed by a higher response probability of the miniature units than the first, even when the first elicited no response. During tetanic stimulation, there was progressive increase in what they called ''fluctuations in a random manner'' at a single juction which at the extracellular ''whole muscle'' recording site was a smoothed, average increase in activity. They concluded that this kind of neuromuscular facilitation, recruitment, was a statistical process and, from the standpoint of mean firing rates, was the result of increased probability of activation of existing units, a state induced by prior stimulation which was not activating, but perhaps a phasing of elements generating subthreshold membrane con-

ductance oscillations. The temporal pattern of single junction discharges was characterized as random, their summation producing an increase in the activity as seen in the neuromuscular facilitation (potentiation, sensitization) first reported by Boyd et al.[56] and Feng[189].

When similar preparations were used to demonstrate what was then called *Wedenski inhibition* (depression, neuromuscular fatigue, desensitization) by prolonged nerve stimulation at a low rate for 10 minutes or longer, there was marked reduction of the evoked activity while "the rate of spontaneous miniature potentials was greatly increased"[143]. Although a qualitative correlation was observed consistently, the relationship between the reduction in EPP size and the increase in "random firing rate" was not linear. The same amount of EPP depression occurred at "random" firing rates from below 10 Hz to more than 200 Hz, which also suggests that refractoriness was not responsible for the phenomenon.

Our interpretation of these events is as follows: (a) the receptor-conductance elements of each end-plate are in autonomous motion with a less than maximal amount of phase coherence, so that ion conductance events are distributed quasi-randomly over time and the scaled-up behavior of the end-plate aggregate is similar over longer times; (b) facilitation (sensitization) by regular tetanic stimulation brings temporally adjacent oscillations into phase and results in larger, more coherent evoked activity at the micromolecular level, more coherently rhythmic activity in the spontaneously firing end-plates, and increased propensity for concerted action (sensitivity); (c) transitional sensitization and ultimately depression following prolonged stimulation may serve, finally, to bifurcate the responsive population into subpopulations uncoupled from each other and from the stimulus, with emergent autonomous rhythmicities. These islands of disconnected action analogous to the vortices of high flow rates in hydrodynamic systems have shifted their spectral position, creating statistical "holes" in the Lorentzian spectrum, Gaussian pdf of the oscillators and preventing the march toward the coherence necessary for the critical phase transition constituting the macro-event.

From these premises, we predicted that variational analysis of receptor-conductance fluctuations during desensitization would show: (a) that the baseline "random" activity of the miniature units manifests a specifiable degree of temporal order; (b) that the facilitated preparations manifest a single prominent spectral peak *not* similar to the tetanic stimulus frequency but a function of the elements creating the intrinsic periodicity (latency, refractory period, stability, etc.) in a system of macromolecular units now coherently rhythmic enough to produce more observable events above the random background at the end-plate; and (c) that the desensitized preparation manifests a bifurcated spectrum of autonomous activity indicative of functional disaggregation in time of the population of microparticipants, with resulting loss of temporally integrated behavior, that is, the evoked response, while demonstrating subpopulations with coherent autonomous rhythmicity.

Figure 1 represents the results of our digitization and analysis of an intracellular recording of the recruitment of EPP during nerve stimulation at 100 Hz producing facilitation of the response, as reported by del Castillo and Katz[143, their Fig. 2]. We established the trend across the fluctuating activity by linear regression analysis, expressing each point as a deviation from the mean voltage as normalized for slope and intercept, then calculated spectral and exponential transforms using techniques we have reported elsewhere[448, 449]. Quasi-periodicity in what had been called "random" activity manifested a spectral peak at 200 msec and a characteristic exponent of 1.66 reflecting both its frequency and distributional properties. Increasing macrobehavior, that is, activity at the extracellular electrodes on the muscle, was associated with increased spectral coherence and relatively slower frequencies.
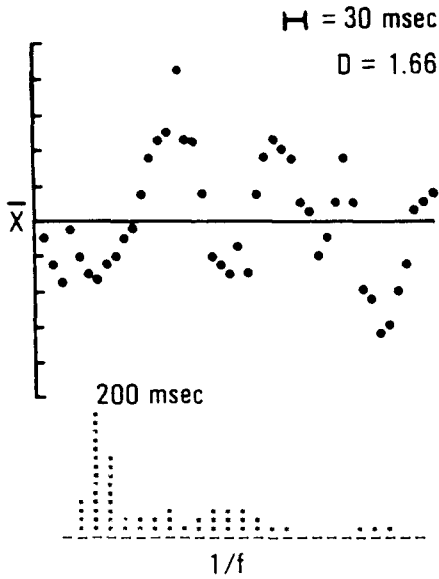
Fig. 1. Digitized data as deviations from mean voltage of end-plate potentials and their spectral and exponential representations. Original data from del Castillo and Katz (143; their Fig. 2).
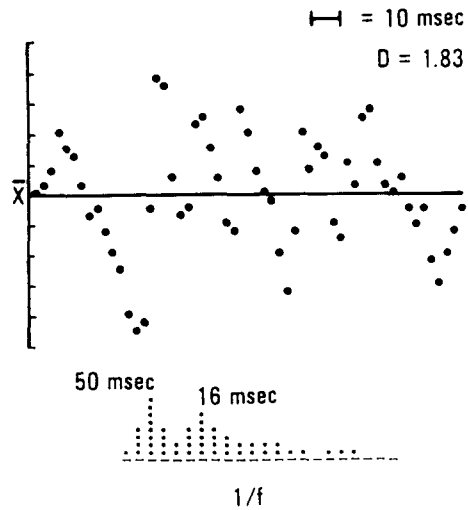
Fig. 2. As in Fig. 1, from del Castillo and Katz (143; their Fig. 4).

In contrast, Fig. 2 represents the results of similar analyses of the results of "fatiguing transmission" with prolonged nerve stimulation at 2 Hz over 10 min. The data are from del Castillo and Katz[143, their Fig. 4]. Bifurcation in the population is indicated by the two spectral peaks, and the characteristic exponent of 1.83 reflects faster frequencies; increased irregularity in the function consistent with the expression of interference patterns from two subpopulations of oscillators. The .25, .5, and .25 power distributions of single frequency peaks using the Hanning window[39] demonstrate two characteristic periodicities. It should be noted that just as the probability of response to the second shock in the stimulus pairs increased whether or not the first shock produced a response, the increase and decrease in phase coherence observed respectively in Figs. 1 and 2 were not coupled directly to the stimulus frequency. Table 1 illustrates the general consistency of these findings in additional data from del Castillo and Katz[143].

In Fig. 3, after both Maeno[432] and Katz and Miledi[350], increased dispersion over time similar to that of the aggregate activity of an end-plate potential can be seen in the

Table 1. Higher D and Bifurcated Spectra in Desensitized versus Sensitized EPP Preparations

	D	Spectral peak (1/f msec)
Sensitized		
Top	1.66	200
Middle	1.70	200
Bottom	1.73	200
Desensitized		
B	1.74	100, 50
F	1.89	100, 25
G_1	1.83	50, 16
G_2	1.75	50, 25

Data on sensitized and desensitized preparations were taken from del Castillo and Katz[143]. their Figs. 2 and 4, respectively.
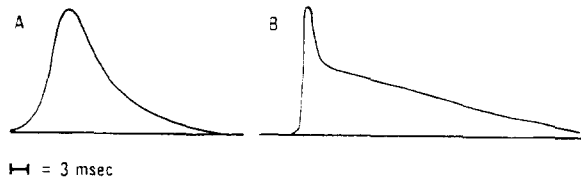
⊢⊣ = 3 msec

Fig. 3. End-plate potential after both Maeno[432] and Katz and Miledi[350]. A = control; B = after procaine.

representative change in evoked end-plate response from direct recordings in the presence of procaine, a condition resembling the endstate of desensitization[486, 699]. A single distribution becomes bimodal in going from A to B.

Regular 5-sec oscillations have been induced in ACh concentration in tissue from the *T. marmorata* electric organ by stimulation with 1–20 Hz. The fluctuations were in phase, mole-per-mole, with curare-resistant ATP generation and became desensitized in response to tetanic frequencies[317, 318]. Here, as in the frog neuromuscular junction, the quasi-periodicity of the behavior manifested a wavelength considerably longer than the stimulus frequency and was two orders of magnitude slower than the end-plate conductance fluctuations as seen in Figs. 1 through 3.

In Sec. 3 we developed the thesis that quasi-periodicities observable on the macroscale in physiological behavior reflect the degree of order among the microparticipants in a system, that is, deviations from Gaussian distribution that are due to aspects of interactional dynamics such as coupling, beats, interference, and resonance among the elementary oscillators. Changes in the frequency spectrum, then, reflect the changing character of the pdf and, as with Gaussian as well as self-similar Pareto distribution, will scale across both time and space. Thus we would view these 16–200-msec and 5-sec periodicities in the activity of the nicotinic cholinergic synapses as reflections of the same system dynamics whose appearance in smaller and larger descriptive dimensions depends on the graining of the observations.

For these reasons, we predicted that bifurcation of the spectrum occurring during desensitization, as well as the action of local anesthetics seen in the msec range, could be observed over longer times. We found an opportunity to examine this issue in studies by Grünhagen and Changeux[257, 258] in which they labeled membrane fragments from *T. marmorata* rich in nicotinic cholinergic receptors with a fluorescent local anesthetic, quinacrine, and examined the differential emission of fluorescence during and after relaxation following mechanical or pharmacological perturbation. Their published records of the fluctuations in fluorescence intensity following the relaxations were long enough to allow digitization of the noise (60–100 points), and we analyzed them as we had the electrical conductance data. Their fluorescence-difference technique allowed Grünhagen and Changeux to study the fluorescent energy transfer from the receptor protein to the ligand apart from the fluorescence of quinacrine activation itself. Figure 4 presents digitized data from a control preparation in the presence of a cholinesterase inhibitor and carbamylcholine[257, their Fig. 5]. The quasi-periodicity in the "random" variation is in the range of minutes, with an average wavelength of one minute.

Figure 5 illustrates a progressive dose-responsive bifurcation in the spectrum with increasing levels of the local anesthetic quinacrine in the presence of carbamylcholine, without the anticholinesterase. With increasing levels of quinacrine (which both eliminates conductance response and promotes high affinity cholinergic ligand binding), the spectrum splits and the faster, coherent spectral density with 1-min periodicity is seen to dominate the auto-correlation function.

These periodicities are 3 to 4 orders of magnitude slower than the conductance variations seen in Figs. 1 and 2, but they yield spectral reflection of the same population
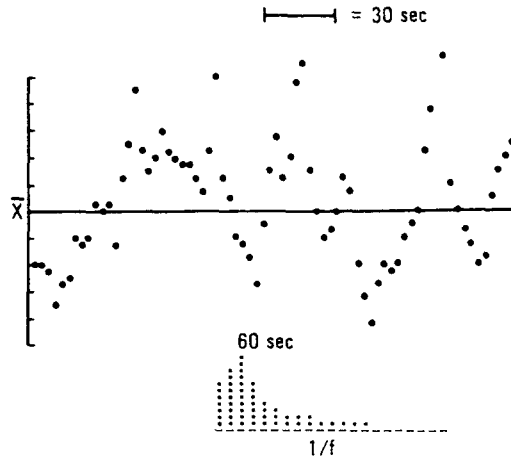
Fig. 4. Digitized data from fluorescence-difference fluctuations of quinacrine-bound cholinergic receptor proteins. Original data from Grünhagen and Changeux (257, their Fig. 5).
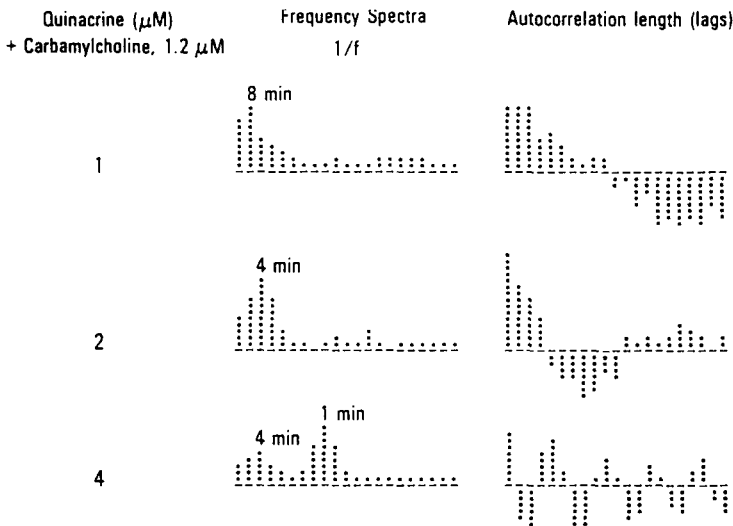

Fig. 5. As in Fig. 4, from Grünhagen and Changeux (257, their Fig. 6).

dynamics at larger scale. We see this as additional evidence that the desensitized state may represent a disaggregated condition in the population of receptor protein oscillators preventing a temporally and spatially coherent response in the face of what appears to be high-affinity ligand binding. Moreover, it seems very unlikely that the spectral peaks of these relaxation oscillators could represent biological constants, such as channel lifetimes, because the pattern of change in frequencies is similar across at least 5 magnitudes of time[12, 348, 349, 488].

This alternative explanation of the desensitized state may help undo confusion about changing channel lifetime constants following the application of local anesthetics or desensitizing procedures[350, 352] as well as the reported step changes in membrane potential with increasing ligand concentration[615, 616]. The latter have also been observed in analyses of conductance fluctuations[584]. In addition, the similarity in the time-dependent dynamics during desensitization to stimulation, to high ligand concentration, or to local anesthetic action suggests that electrophysiological conductance responses and

fluorescence-tagged receptor protein motion may be mediated by the same time- and field-dependent population dynamics.

The spectra in Fig. 6. re-analyzed as described above from the data of Grünhagen and Changeux[257, their Fig. 5] demonstrate that with increasing concentrations of the local anesthetic prilocaine there is an increasing tendency for the population of fluorescence-tagged cholinergic receptor proteins of *T. marmorata* to disaggregate into separate ensembles as observed in the frequency domain, and the tendency is more pronounced in the presence of increasing concentrations of the cholinergic agonist carbamylcholine. Bifurcations and a more even distribution of power over the frequency bands are consistent with the loss of the integrated temporal order of a single Gaussian group of receptor protein oscillators and the emergence of coherent subpopulations.

This suggests that the local anesthetic effect may be to facilitate the course of agonist or ligand-induced temporal disaggregation among the elementary units in the way prolonged and/or repeated exposure to ACh does. A later paper by Grünhagen *et al.*[258] gave us an opportunity to examine this issue directly. Fluctuations in quinacrine-bound receptor fluorescence-difference measurements were analyzed from an experiment in which the effect of ACh (5 μM) was examined over 60 minutes in the absence and presence of the cholinesterase inhibitor Tetram[258, their Fig. 5]. Figure 7 illustrates that during
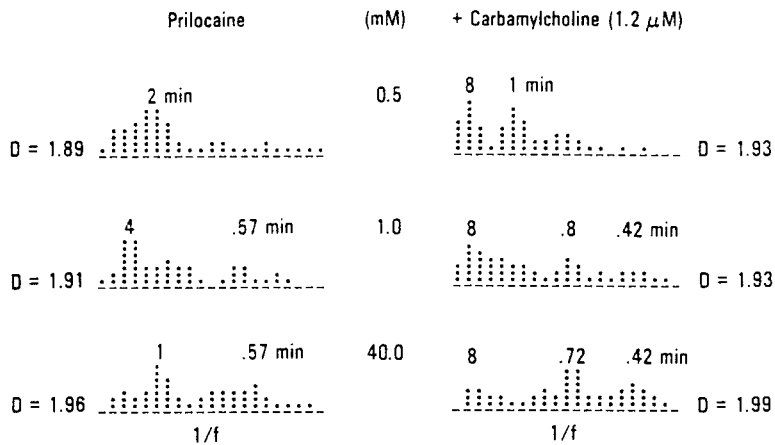

Fig. 6. As in Fig. 4. from Grünhagen and Changeux (257, their Fig. 5).
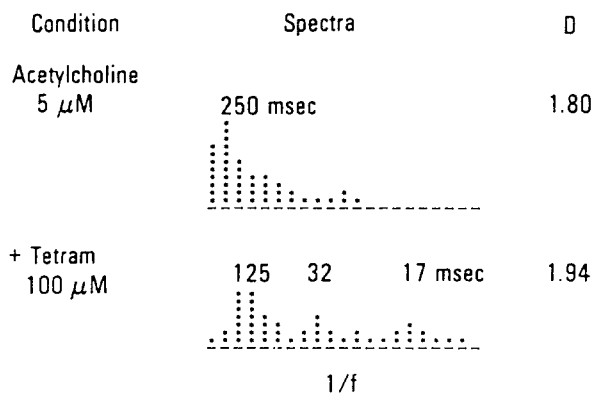

Fig. 7. As in Fig. 4. from Grünhagen *et al.* (258, their Fig. 5).

60-minute incubations. ACh alone (which has a short biological half-life) yielded a spectrum with a single Gaussian peak. whereas prolongation of ACh action with Tetram produced the same kind of bifurcation in the spectrum that was seen in the presence of the local anesthetics quinacrine or prilocaine alone or in the presence of the agonist carbamylcholine, or after prolonged nerve stimulation. Note also that the statistical dynamics of these populations of cholinergic receptor proteins, as reflected in the frequency domain. were similar across temporal scales in wavelengths of milliseconds. seconds. and minutes.

That patterns of population dynamics underlie the kinetics of desensitization in the activation-conductance event, as well as the subsequent loss of peak conductance values during membrane inactivation maintained by voltage step techniques, was suggested by Hodgkin and Huxley[293], although they considered the latter phenomenon to be a separate, voltage-dependent process that was governed by an additional set of differential equations. They perceived the voltage-dependent gating characteristics of what may generally be called *translocators* as reflecting the time-dependent position of these charged moieties normal to the plane of the membrane, and several of them had to act in temporal-spatial coherence for the activation-conductance kinetics to be observed. A "cooperative" mechanism was also suggested by the time-dependent, sigmoid shape of the curve of conductance in response to an applied potential step (a) by the sodium and potassium currents in physiological membranes[9]: (b) by the behavior of translocator polypeptides in artificial bilayers[478]: and (c) by the pattern of responses to agonist ligands by reconstituted purified ACh receptor proteins from *T. californica* in planar lipid bilayers[489. 594].

Consistent with mechanisms involving nonlinear population dynamics is the dependence of the time course on exponential voltage[293] and translocator concentration with powers greater than 1[478]. especially in view of the actions of other variables with potential influence on temporal and/or spatial aggregation dynamics in the membrane. such as the lateral diffusion constant reflecting varying lipid fluidity[29].

In contrast, then, to the assumption of the independence of the gating mechanism from all but its most immediate past history, allowing the use of deterministic linear equations implicit in the Hodgkin and Huxley analysis as well as the noise analysis techniques of Stevens[646]. Mueller has demonstrated that with polypeptide translocators in lipid bilayers at high negative holding potentials, the initial delay of the current rise becomes so long that the exponential factor in one of the Hodgkin–Huxley equations has to be raised from 4 to 24[477]. In addition, when more physiologically representative (nonsteady state) starting conditions are used (for example. two voltage steps in sequence. in opposite directions), the conductance follows the initial direction for a while before it reverses, no matter which direction came first. Here we see that the gaussian assumption of independence among sequential events, or Markov chains of stable transition probabilities which underlie the use of linear coefficients of noise to establish constants for channel lifetimes, is at odds with a body of evidence indicating the cooperative nature and time-dependence of activation and inactivation in the conductance mechanism.

A phenomenon directly analogous to cholinergic receptor desensitization during the action of agonists—as demonstrated, for example, in the permeability response of microsacs from *T. marmorata*[654]—can be seen over a shorter time scale in neural sodium conductance after a voltage step: the conductance increase passes through a maximum that is followed in time by what was called "membrane inactivation"[9, 477, 483]. The rate and degree to which the membrane inactivates is a function of the voltage step, time. temperature, calcium concentration, and (in artificial bilayers) the translocator concentration. Except for translocator concentration. these "field" variables, including membrane hyperpolarization. in addition to low sodium. other multivalent cations in addition

to calcium, and, as noted above, local anesthetics, facilitate desensitization of the muscle membrane response to ACh. See Heidmann and Changeux[279] for a recent review.

Development of a functionally representative system of artificial bilayers[472] which, like real membranes, represents a planar liquid 20–30 Å in width has been combined recently with reconstitution and insertion of ACh receptors[489, 594]. Like real membranes, these preparations are variously penetrable by leaks of ions and water generating the baseline conductance noise that some think is also responsible for the frequency-dependence of the capacitance[112, 249]. The artificial bilayer preparations have provided an opportunity to examine Mueller's time-dependent polymerization-aggregation hypothesis for both conductance and membrane inactivation processes[477]. He speculated that under the influence of the impressed voltage difference, the ACh receptor-conductance elements in what has turned out to be a pentameric complex with m.w. of 40,000; 40,000; 50,000; 60,000; 65,000[489, 557] would move from a flat to a transmembrane position normal to the membrane plane[650] followed by lateral organization into N-mers of various sizes, creating functional channels. In an analogous (β-adrenergic) system, it has been shown that inhibition of lateral mobility of intramembrane proteins prevented the receptor-transduction of the neurotransmitter-induced effect[19].

Mueller has hypothesized that nonconductance states occur at low levels of order, that is, where monomers and dimers could not complete a channel (accounting for the time- and ligand concentration-dependent hysteretic limb of the voltage-dependent sigmoid conductance function) as well as at high levels of order, oligomers aggregated beyond five or six members resulting in channel blockade[477]. A mechanism for such emergent order is suggested by recent work explicating the nonlinear statistical mechanics of nearest-neighbor, pairwise hydrophobic interactions in proteins, which can be generalized from the internal relations of amino acid residues to protein molecule dimerizations and beyond and are consistent, within physiological range, with the dynamics of the temperature-dependence of the desensitization process[40, 354]. Sensitivity to weak field forces is conferred by the intrinsic structural instability of globular proteins in solution[121], making them responsive to the organizing influence of magnetic fluxes with axes normal to the conductance channel created by the flow of ionic currents[551].

Spontaneous electrochemical potentials fluctuating across the membrane, causing and caused by ionic leaks[145], may begin, via their associated magnetic fields, to align dipoles normal to the planar surface. As much as 30% of the population of ions may be involved in nonactive transport membrane leaks[Ehrlich and Diamond, personal communication]. and beyond a critical value of the leak, the resulting laterally-oriented magnetic fields and diffusion combine with hydrophobic interactions to create an accelerating trend of polymerization of receptor-protein gatekeeping dipoles toward and through an optimum. Finally, a reduction in phase boundary potential through ion concentration changes and/ or a blockade of the ionic current leads to a loss of the organizing fields along both axes and, with them, a loss of the emergent molcular temporal-spatial order, which is dissipated by the entropic influence of the thermally driven randomizing motions of the proteins. Over a short time, this organizational process can be seen as a "quantal" conductance event; over a long time, it can be seen as desensitization and/or membrane inactivation. In contrast to the simple exponential decline of the desensitization phenomenon, the complex kinetics of accrual are consistent with multiphasic ordering and its subsequent single exponential loss from thermal randomization[279, 486, 558, 652]. A more stable (stationary) homogeneous system of aggregates yields a Lorentzian spectrum in the conductance domain[488] *when the voltage-clamp method prevents or reduces the voltage-, time-, and field-dependent development of the critical phase transition toward bifurcation of the population and functional disorder.* Without the voltage clamp, the preparation

becomes capable of manifesting the heterogeneity of ensembles characteristic of the functionally inactive system in measurements of both electrophysiological and fluorescence-tagged receptor motions (Figs. 1–7).

Alternative explanations of the desensitization process include the possibility of a shift in the reversal potential[382] which, in light of other studies, appears to be more the result of complex concentration-time interactions of ACh iontophoresis leading to alterations in the membrane diffusion-space constant[149, 439] than the result of desensitization. In addition, it has not been confirmed by direct measurement[351].

An optimal temporal-spatial order of receptor-channel proteins ("active conformation") alternating with "resting" and desensitized "nonconducting" arrangements (the latter like the phase II blockade induced by such drugs as decamethonium[433]) is generally consistent with the dominant theories of desensitization, which include a role for secondary "internal" sites[353, 434, 486, 558]. Those studies, however, tend not to emphasize temporal-spatial disorder in a population of elementary units as much as they stress the creation of an abnormal conformation, anatomical micropathology, such as the entrapment of agonist (or drug, like a local anesthetic) inside the channel[2, 3, 11, 125]. The high levels of spontaneous activity manifested by desensitized preparations argues against even transient morphological damage.

The conversion from single to multiphasic decays by local anesthetics (analogous to spectral bifurcation into two or more populations) has been seen directly in miniature end-plate currents and by means of fluctuation and voltage-jump relaxation methods in several laboratories[4, 31, 168, 350, 487, 581, 585, 643], and the implication is that the inactive integrated system is composed of multiple active subsystems. This also is consistent with the suggestion that the conduction failure in the face of normal resting potential derives not from blocked channels, but from abnormal temporal-spatial arrangements in the population. Desensitization to agonists leading to a bifurcation of the spectrum into a slower, more random and a faster, more regular component (bursts) has been directly demonstrated very recently[585, their Fig. 2-C].

Time-dependent emergent temporal-spatial disorder within a population of variably dependent nonlinear receptor-conductance proteins in autonomous motion may underlie what have been seen as ligand-induced slow conformational transitions in cholinergic receptor proteins[55, 353, 553, 558, 621]. The Ising bidimensional lattice representation of the ferromagnet near its critical point models a system of variably coherent randomly oscillating dipoles which, through a temperature-dependent coupling constant acting via nearest-neighbor interactions, slowly accelerates toward a state of temporal coherence among the microparticipants that results in the macrophenomenon, magnetization[426]. After a sudden change of applied fields from one constant value to another, the initial fast change in magnetization of solids is followed by slower additional changes, observable over intervals ranging from seconds to days[69]. Cole's classical studies of membrane impedance[112] suggest that there is a relationship between time-dependent nonlinearity and internal reordering in the system, and it is the energy-induced reorganization of microparticipants gathering finally to be reflected in the macrophenomenon that is the common element in nonlinear, far-from-equilibrium, critical phase transition behavior as seen in electrical, hydrodynamic, and solid systems[63a]. The entropic rearrangement in a system of subsystems that alters or prevents its normal integrated behavior while maintaining the normal level of its available energy, the same mean membrane potential, is consistent with low energy, critical-order requirements of information processing thermodynamics in systems like the brain[712].

The vertical symmetry of the desensitization-induced bifurcational behavior of the frequency-labeled population of receptor-conductance nonlinear oscillators across scales of time, as seen in Figs. 1–7 and in the multiphasic decay of miniature end-plate currents

in the literature, fits the model of frequency as a reflection of the scalar invariance of the Pareto pdf of quasi-ordered random processes that we developed in Sec. 3. Karplus and his group[344, 345], having programmed Newtonian forced and molecular masses at physiological temperatures, simulated macromolecular dynamics on a computer to reveal autonomous, time-dependent motions, spontaneous transitions from one potential minimum to another, and positional distribution functions that were not Gaussian. When faster fluctuations were damped by coarse-grain averaging, longer-lived fluctuations emerged. Larger (slower) motions would emerge without limit as longer periods of averaging were exploited. That kind of self-similarity across scale is characteristic of partially ordered Brownian random processes[443].

A simulation exemplifying the appearance of longer periodicity with coarser graining is seen in nonrandom activity in Fig. 8. A sine wave of arbitrary amplitude and a wavelength of 4 was sampled at 0.1 unit increments and then "coarse-grained" at observational intervals of 2.1. Larger wavelengths of 40 units, composed of 10 small sine waves, can be seen with the longer sampling intervals. Anatomically defined spatial units of various sizes (molecules, membranes, muscle end-plates, cells, nuclei, nets, hemispheres) manifest in parallel larger emergent structures in time. Changes in the environment of the smallest unit would alter its statistical periodicity reflecting the entropy of the microsystem and would influence the patterns of behavior at several larger scale-defining magnitudes of sampling intervals.

A temporal-spatial disorder in the population of microparticipants induced by prolonged stimulation or contact with high concentrations of agonist ligand and/or over long times, reflected by bifurcations in the spectra of conductance and fluorescence-tagged receptor protein motions, could explain the "slow conformational transitions" to multiple affinity-constant binding states (higher and lower) across milliseconds, tenths of seconds, seconds, and minutes in studies of nicotinic cholinergic receptor preparations[23, 54, 55, 258, 553, 554, 555, 621, 697, 699, 700]. The conditions of almost all agonist binding studies promote

Nested Periodicity and Graining
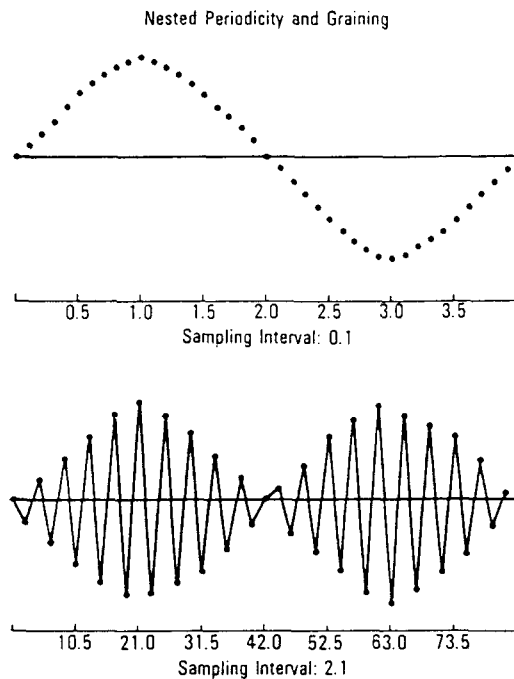

Sampling Interval: 0.1

Sampling Interval: 2.1

Fig. 8. Sine-wave simulation. See text.

the desensitization phenomenon: high concentration of ligand (of which only a very small fraction is bound) and equilibrium, not rate, binding measures requiring long times. Because most ligand binding studies are performed on functionally desensitized preparations (i.e. high concentrations of cold ligand are used to swamp the "nonspecific" binding functions), the multiplicity of agonist affinity constants spanning 3 or 4 orders of magnitude[116, 117, Colquhoun's Table 4] and reports of a range of multiple contemporaneous affinity constants[554] are consistent with the temporally disaggregated spectrum of conductance and receptor phenomena seen above, as well as with our statistical mechanical view of the desensitization process. "Slow transitions" then would not represent the changing configuration of the dense, coherent silhouette of a single protein profile but the long-latency dynamics of a population of oscillators reordering in space and time into multiple ensembles—each with a characteristic frequency and binding constant[112, 517, 724, 725].

The spatial-temporal disaggregation of a Gaussian population of receptor proteins, with a single average ligand-binding isotherm, into coherent subpopulations with differing binding constants may explain why other neurotransmitter systems as well (such as polypeptides, β-adrenergic ligands, dopaminergic, serotonergic, and other "drug receptors" manifest a multiplicity of affinity constants[59, 170, 225, 273, 294, 356, 361, 562, 627, 666]. It should be noted that heterogeneous agonist binding with high affinity, associated with an inactive membrane transduction mechanism (as seen in nicotinic cholinergic preparations—see previous references) may not be the same in all neurotransmitter systems. For example, a recent statistical resolution of β-adrenergic average binding slopes indicated that desensitized frog erythrocyte cells manifest an *impairment* in high affinity binding[361].

In addition to defining multiple autonomously fluctuating protein substates, the report of a recent series of studies by Fraunfelder and colleagues[32], in which they used flash photolysis followed by rebinding of carbon monoxide to protoheme and of oxygen and carbon monoxide to myoglobin as they varied solvent viscosity, portrays the ligand-protein interaction as follows: "A protein is not like a solid house into which the visitor (the ligand) enters by opening doors without changing the structure. Rather it is like a tent into which a cow strays." Over time, the potential for multiple protein substates and high concentrations of ligand may select and/or configure protein conformations underlying what has been called specific binding as well as order the receptor population into subensembles which appear to be responsible for the multiple affinity constants for single neurotransmitter-ligands. Along with classical conformational transitions, a key-into-lock image of protein-ligand binding may be seen eventually as considerably less specific and even artifactual if ligand-induced conformations and population dynamics among variously coherent protein oscillators are responsible for the data[221, 263]. For example, we have noted that, in cholinergic receptor and conductance desensitization, sodium concentration affects the rate of spectral bifurcation into functional subgroups, apparently rendering the aggregate incapable of coherent action; the same population dynamics may be reflected in the differential effects of sodium concentration on drug-receptor ligand binding isotherms[245, 530]. A report that high affinity, low capacity binding of TRH takes longer to saturate than does the low affinity, high capacity binding[78] suggests to us a process by which an increasing number of high-affinity states emerges over time in a process that concurrently creates (by bifurcation) and measures the resulting high affinity binding phenomenon.

The statistical mechanics of fluctuations among multiple protein states and their mutual interactional behavior in larger systems augurs reinterpretation of biochemical kinetics, transition-state thermodynamics, and site specificity, much as earlier linear and curvilinear deterministic theories have given way to probabilistic considerations[32]. We have used

the statistical dynamics of desensitization as reflected in conductance changes, fluorescent reflections of receptor motion, and receptor binding kinetics to model what may represent at the molecular level a common statistical mechanical mechanism for habituation. In Sec. 5, we examine the phenomenon in simple synaptic systems.

5. HABITUATION IN SIMPLE SYNAPTIC SYSTEMS

We have reviewed the evidence that the autonomous motions of globular proteins in solution at physiological temperatures make agonist-receptor-conductance interactions probabilistic beyond the statistics of simple collisions. Likewise, the statistical ordering of spontaneous fluctuations in probability and latency of neural responses to stimulation, made measurable by the use of the oscilloscope, introduced similarly nondeterministic dimensions into considerations of the function of more complex neural systems[51, 52]. In an early statistical treatment of fluctuations in excitability, the coefficient of variation (CV), the normalized variance, was treated as the inverse of the square root of the number of ions necessary for excitation. When adjusted for fiber size and an ion's sphere of influence, the CV in the range of 0.01 was consistent with a Gaussian distribution of thresholds. Using this approach, Landahl[300, 393] generated a Gaussian distribution of response times with a small normalized variance, and from that distribution function he predicted linear relations between response and stimulus intensity and decreasing latency of response with increasing intensity of stimulus, both of which fit the data then available[520]. The statistical orderliness in the "random" variations in excitability threshold as well as statistical mechanical dynamics for their regulation were also suggested by the work of Erlanger et al.[173]. They demonstrated that cooling increased the amplitude of the spontaneous oscillations in neural excitability (increased coherence suggesting the expected inverse relationship between the coupling constant and the temperature) and that strychnine altered the configuration of the spike. As seen in Fig. 9, strychnine, which facilitates habituation of the flexor response in the spinal rat[428], was associated with temporal disaggregation of the integrated evoked event almost into two, along with increases of several hundred percent in the amplitude of fluctuations and increases in threshold as well. When stimulated externally, the disaggregated and autorhythmic components of the response behaved more variably than the control.

This finding is generally consistent with statistical models of spontaneous neuron firing in which rhythmic regularity is inversely related to sensitivity to stimulation[172]. Bremer's description of the electrical activity of the cord during tetanus induced by strychnine also emphasized emergent synchronization of rhythmic elements associated with loss of normal integrated function[61].

As indicated in Sec. 4, fluctuations in membrane voltage were first systematically analyzed by Fatt and Katz[182, 184]. Spontaneous depolarizations of less than 1 millivolt manifested the same "irregular intervals" between them as the end-plate potentials. Although observable frequencies ranged from 0.1 to 100 Hz, the range of observation was limited by excluding from analysis both high frequencies with potential for summation
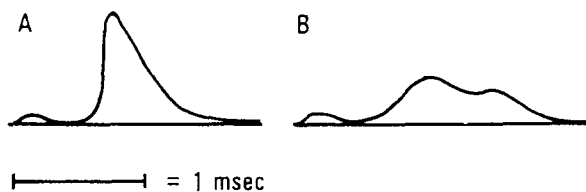

= 1 msec

Fig. 9. Action potential of nerve before (A) and after (B) strychnine. Adapted from Erlanger et al.[173].

and coincidental firing and low frequencies with very few data points. Both the inter-event interval histogram with a simple exponential curve and the cumulative distribution function, $P(\tau) = 1 - \exp(-\mu\tau)$, suggested a Poisson process of intervals with a mean rate μ. In addition to an exponential interval distribution function, this finding both suggested stationarity and precluded simultaneity[152]; that is, it implied the independence of a Poisson process. However, later re-analysis[409a] of Fatt and Katz's data using statistical tests of the significance of this hypothesis (see also van der Kloot et al.[675]) showed reliable deviations from the Poisson point process. Moreover, further studies[105–107] with various Ringer's solutions and temperatures have demonstrated that the intervals between spontaneous discharges of the end-plates are not exponentially distributed and that adjacent intervals are not independent. Cohen et al.[105–107] demonstrated increased power (variance) at low frequencies, long autocorrelation lengths, and significant simultaneity, that is, clustering. Recent models of the action of multifunctional ligands on aggregating cell-surface receptors deal with similar dynamics in spatio-temporal nonlinear cluster point processes[140].

Direct measurement of electrical noise from membranes has not only demonstrated frequency-independent spectral density distributions of the fluctuations (i.e. Johnson–Nyquist noise of thermal agitation and Brownian motion reflecting independence of contributing events); in addition it has shown evidence of the heterogeneous phases more characteristic of nonequilibrium, voltage- and time-dependent systems including $1/f$ ("excess" or "flicker") noise[681, 682]. Although the mechanism of $1/f$ noise remains a mystery, anomalous noise from singularities[702], multiple simultaneous relaxation times[299], diffusion of charge carriers[241], paramembrane turbulent convection[414], and other models bespeak internal reordering and nonlinearity in the system, that is, variable dependence among contributors suggesting coupling and other aspects of self-organization[278]. Thus, spontaneous fluctuations in membrane parameters and their reflection in thresholds and latencies to activation strongly imply varying degrees of temporal-spatial order among the microparticipants.

At the next level, the single neuron manifests sequences of "random" spikes with unidentical responses to successive presentations of the same stimulus[17, 386, 387]. As was the case for autonomous activity in receptor proteins, membrane current and voltage fluctuations, here also various classes of dependency are evident, including those of direct interactions and shared inputs[474, 527]. More direct evidence of spontaneous self-organization can also be found. For example, Kuffler et al.[387], Hughes and Maffei[307], and Rodieck and Smith[571] describe the increasing emergence of rhythmic firing patterns in cat retinal ganglion cells with longer periods of darkness, reflecting increasing frequency-phase coherence among the elements. This circumstance is comparable to the isolation from perturbation and evolving self-organization, coherence, that we speculate generates denervation supersensitivity (see Sec. 4). Correlations between spike train parameters among neighboring neurons are well-documented for the retina[283, 572], lateral geniculate nucleus[647], cerebellum[33], auditory cortex[146], and many other systems[64, 370, 642]. In addition, emergent temporal-spatial order in networks of interacting neurons manifesting hysteretic, limit-cycle, critical phase transition, bifurcational behavior are ideally suited for analogy to their counterparts in electrical circuit theory[174, 602, 603, 613, 721]. It should also be noted that interactions of slow field electrotonic potentials that do not involve action potentials have also been implicated in the organizational dynamics of cell syncytia in systems such as the heart[588].

Gerstein and Mandelbrot suggested a productive way of thinking about spike generation in a single neuron as a random walk to threshold followed by instantaneous reset[222]. Despite some simplifying assumptions, their model generated representative quais-peri-

odicity and scaling properties of interspike interval variations, which they demonstrated would become more and not less ordered when more bounded by physiological conditions. Their model and its relation to Einstein's deterministic analysis of the randomness of diffusion[166] and Poincaré's insights into recurrence time in processes involving multiple ensembles[540] serve to demonstrate aspects of intrinsic order in what have been regarded generally as randomly active neural systems. Using the scaled interspike interval histo-gram (wherein intervals could be the sums of any 2^m adjacent intervals, where m is a small positive whole number) they derived from the spontaneous activity of single auditory neurons studied by Rodieck *et al.*[573] examples of self-similarity across scale in asym-metric pdf. Because the scaled interval histograms had the same general shape as the interval histogram, it can be said that the (skewed) pdf was invariant under convolution, that is, it was stationary. Because the distribution was not Gaussian and its spectrum was not Lorentzian (despite the convolutional invariance), it belonged to the class of stable Pareto distributions of asymmetric density with a fractional order (see Sec. 2). Gerstein and Mandelbrot saw their populations of interspike intervals as limited by the refractory period (''retarded action'' generating periodicity[467]) and reflecting a limit cycle like that of Gaussian populations even without convergent (bounded) tails. Neurons with asym-metric distributions about the mode that manifest long positive times can be seen as making random walks to a threshold at which some trajectories never arrive. The tails of these pdf, with boundless variance, do not converge as N increases. Called formally a random walk to an absorbing barrier[188], a finite state Markov chain with a stationary distribution, this has also been analogized to statistical ''birth and death'' processes[420]. These pro-cesses manifest characteristic wavelengths or recurrence times.

Reflecting the composition of incoming elementary excitatory and inhibitory postsyn-aptic potentials and resetting without memory to the resting potential after discharge, Gerstein and Mandelbrot's model demonstrates invariance in distributional shape and associated characteristic probabilistic quasi-periodicity. As the step-size of a random walk decreases, the sample path might be thought of as approximating a smooth function rep-resenting diffusion and, as noted, the systematic quantifiability of diffusion processes in Brownian systems was first demonstrated by Einstein[166]. If this process in a particular system can be seen to reflect the amount of its spatial (or temporal) variation from a starting location or value and analogized to the distance from an expectation such as the mean ($\mu = 0$, the mean net distance traveled in a one-dimensional random walk equals zero), the size of the variance can be viewed as the boundary condition for the more random (thermal) variations around its zero mean.

Another source of quasi-periodicity of longer times is determined by the number of ensembles of states (arrangements of the participants) available for occupancy. From that point of view, a Gaussian independent system with only one kind of ensemble would be reflected by narrowed variance (lower amplitude) and the slower periodicity of its limit cycle. The bifurcated system with varying subpopulations of coherent ensembles of ele-ments would be reflected in a higher amplitude of variance, the recurrence time—the time necessary for the system to occupy the increased number of ensembles and begin again[540] generating its slower fundamental periodicity. Thus it appears that relatively stable non-Gaussian statistical wave processes with potential for many variational fre-quencies (thermal, limit cycle, recurrence times) mirror the changing pdf of even a single neuron firing under different probabilistic conditions. Although such a system with a reset mechanism is considered memoryless, the capacity to collect and be governed by a char-acteristic ensemble of inputs (not necessarily time-ordered) in which the relaxation time of the macrophenomena is long compared to the input ''collision'' frequencies, represents an averager very much like a primitive memory[238]. Without time ordering, such sta-

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tistically stable ensembles of inputs as protein motions, membrane fluctuations, or single-cell discharges will produce quasi-periodic phenomena that scale via such a temporal step-down averaging or counting mechanism.

Thus intrinsic instability in mean function of elementary units and the capacity to become quasi-ordered individually and progressively frequency-phase coherent as populations over increasing scale are equally evident with regard to receptor proteins, neuromuscular end-plates, membranes, and individual nerve cells. We shall now review evidence that the negative entropic progression from randomness through order to bifurcational disaggregation (frequently associated with an emergent element of strict periodicity) accompanies habituation in networks of simple synaptic systems the same way it does in receptor desensitization and membrane inactivation. We continue to develop the hypothesis that regular impingement by a suitable frequency attracts[711] and phases populations and then subpopulations of autonomous nonlinear oscillators, organizing them coherently in space-time, although not necessarily at the wavelength of the perturbation. (The reciprocal of the frequency of a ligand's "activity" could be called the wavelength of its concentration fluctuations; for an external stimulus, that would be the interstimulus interval or ISI.) The coherently rhythmic oscillations of a subpopulation may come to dominate the baseline activity; examples would be oscillating hyperpolarizing potentials of the membrane, "burst" kinetics of membrane current, or periodic bursting patterns of single units. The implied assumption is that the normal function of a system of this sort requires a normal degree of randomness. The temporal-spatial ordering accompanying desensitization and habituation makes statistical "holes" in that Gaussian aggregate, and the absence of some elements (now organized and acting autorhythmically) prevents its normal cooperative behavior. In thermodynamic terms, instead of the input of energy of the habituation process producing action *of* the system, it promotes reordering *within* the system. Iberall has analogized this dynamic to the vertical transport of some of the energy of collision into the bulk viscosity of the "particle" which, by dissipative processes, reorders its internal state[312]. After a hysteretic lag during which collisions are collected, a fundamental, stylistic change in its kinetic identity and function may emerge.

It was Sherrington who first reported neurobiological studies of the habituation process, demonstrating a decrement in digital flexion in the monkey in response to closely-spaced stimuli[617]. In later demonstrations of the phenomenon in the spinal dog, he worked to differentiate it from "fatigue"[618], and Pavlov called the phenomenon experimental extinction[518]. Among the early studies, the repeated evocation of a response leading to its decrement was explicated in neurobehavioral terms by Humphrey[309] and was variously demonstrated by others in spinal reflexes[203]; the knee jerk[421]; auditory startle and spinal reflex[550]; postrotatory nystagmus[248]; the galvanic skin response[120, 134, 542]; EEG arousal[369, 566]; and the orienting response[373]. It was related generally to behavioral theories of learning and memory of the time by Harris, in 1943[275].

Prosser and Hunter[550] used electrical and mechanical stimulation of the legs, tail, and hindlimb nerves to demonstrate the fundamental phenomenology in the chronically spinal rat. Habituation of the leg and tail responses requires stimulus frequencies in the general range of 4 to 6 per minute, an ISI of about 12 seconds. The effect was associated with electrical recordings in the muscle indicating a decrease in the number of participating units and in the duration of the after-discharge, with either no decrease or an increase in the latency for the response of a given unit. In addition, spontaneous recovery, dishabituation by a strong extraneous stimulus, and faster habituation of responses to weaker stimuli than to strong ones were observed. That the frequency range required for this kind of habituation may be a more general neurobiological property is suggested by several similarities of temporal dimension in the literature ranging from the demonstration of the extinction of motor cortical responses at ISI of 13 sec by deBarenne and McCulloch[135]

to the ISI of 16 sec by Davis[131] studying behavioral startle in the rat. This stimulus frequency also differentiated habituation from synaptic "fatigue" evoked at much higher frequencies[618]. The potentially long time dimensions of all these effects on spinal reflex mechanisms were demonstrated after section of the thoracic spinal cord in week-old kittens[378]. Toe-fanning and the cross-scratch reflexes habituated exponentially with daily sessions of 20 min with a $t_{1/2}$ of 2.3 days. The effects were manifested by the progressive shrinkage of the skin area from which the reflexes could be elicited. It took a week or longer for the reflex to return. The same general time parameters were observed in similar studies with chronically spinal dogs[492].

Development of the microelectrode and better electronic recording techniques plus exploitation of the large identifiable neural elements in invertebrate preparations like the marine gastropod *Aplysia* led to a more direct approach to synaptic habituation, response inhibition, and hyperpolarization following the repeated induction of excitatory (in contrast to inhibitory) postsynaptic potentials. Synaptic habituation, "inhibition" through the activation of excitatory nerves, was called "long lasting inhibition" by Tauc, to contrast it to the direct influence of inhibitory input[660, 661]. Hughes and Tauc noted in recordings from the abdominal ganglia of *Aplysia* that compound EPP in the right giant cell decreased upon repeated stimulation of the skin[305, 306]. This suggested a specific neural location in which to study Humphrey's classic observations of both behavioral habituation and dishabituation in the snail[308]. The relationship between the shift from random spontaneous neural discharges to rhythmic, oscillating membrane hyperpolarization waves (characteristic of the post-bifurcation dynamics described in the previous sections) and neural response inhibition was demonstrated in 1961 by Holmgren and Frenk after low frequency mantle nerve stimulation and microelectrode recording of parietal ganglia giant cells in the *Helix*[296]. In an investigation of the generality of the desensitization phenomena induced in the end-plate region of vertebrate muscle fibers by Katz and Thesleff[353], which was discussed in Sec. 4, Tauc and Bruner iontophoresed small amounts of ACh and carbachol onto the somatic membrane of ganglion cells and demonstrated a gradual loss of response in the neurons, which occurred more quickly at smaller intervals between applications and took as long as 20 min to dissipate[662]. Bruner and Tauc related this kind of effect to the loss of tentacular contractions after repeated elicitation, noting a similarity between the kinetics of the loss of their amplitude and the disappearance of EPP in the giant cells[71, 72]. The same effect was demonstrated by Kandel and Tauc with electrical stimulation of afferent fibers[337].

That mammalian spinal cord systems manifested the same neuronal dynamics over habituation trials was suggested by reports from Spencer *et al.*[632] and Buchwald *et al.*[76]. The first group showed that acute spinal animals manifested a decrease in EPP amplitude and spike activity in motoneurons, and in the latter study, already rhythmically bursting units demonstrated only response decrement, whereas tonically (more randomly) firing units manifested an increase in activity. Analogous to the gill-withdrawal reflex in *Aplysia*, which manifests both habituation and dishabituation[538], is the flexion reflex in spinal cats, rats, and dogs[619].

A classical series of studies by Spencer *et al.*[633–635] was aimed at elucidating the mechanism of the response decrement and its return by strong stimulation in spinal cats and kittens. Stimuli were delivered to the skin or a cutaneous nerve at 4 to 6 per minute, and recordings were made of muscle tone, electrotonic ventral root activity, intracellular activity of motoneurons, and dorsal root potentials. Prosser and Hunter's rejection of inhibition as a cause of reflex decrement due to the time course (⩾300 to 500 msec, longer than any presynaptic inhibition known[157]) was confirmed and found to be consistent with the little change observed in the N wave of the cord dorsum potential used to reflect the degree of presynaptic inhibition. This surmise was consistent with the inability of

picrotoxin or strychnine to alter the process. Because presynaptic inhibitory fibers very quickly inhibit themselves during repetitive stimulation. Eccles *et al.*[158] thought a presynaptic afferent mechanism for habituation of spinal cord reflexes was unlikely.

There has been a general lack of correlation between reflex decrement and the inhibition of cutaneous primary afferents. interneurons. or flexor motoneurons[162, 253]. In the studies of Spencer *et al.*[635]. either a normal or a facilitated monosynaptic reflex and no change in the intracellularly recorded membrane potential indicated that motoneuron depression was probably not involved in flexion reflex habituation. Recordings in the dorsolateral and ventral columns showed no correlated changes. and that is consistent with a recent examination of extrasegmental (descending and ascending) influences on habituation processes by means of comparisons among intact. spinal, and decerebrate preparations[429]. Homosynaptic depression[528] of primary afferent fibers[611] was ruled out because of the generalization of the phenomenon across segmentally related afferents[633], and because of the difference in the time constants of habituation and homosynaptic depression[419]. The role of what Bruner and Tauc[71, 72] called the episynapse, modulatory interactions between afferents[462]. was considered.

Spencer *et al.* suggested that the evidence pointed to the effect residing within the dynamic organization of the network of spinal interneurons[635]. Homosynaptic depression through alterations in the temporal-spatial order of information transport through a common, autonomously active neuronal network (whose pattern of autonomous background activity was also being configured by the input) would fit the hysteretic buildup and slow decline of the effect as well as both its generalization and summation across input channels. A decrement in a macroneural event associated with homosynaptic depression of spinal interneurons had been observed in some invertebrate systems[268, 360].

Characteristic of the inertial properties of most processes involving the dynamics of emergent order, evidence presented by Lethlean indicated that the flexion reflex in the chronically spinal rat continued to habituate for many minutes after the stimulus was withdrawn[404]. Eccles *et al.* suggested that what we might now call "ringing" in the interneuron network could account for the continued depression of the flexor reflex after a single cutaneous afferent volley[157]. That the changing order induced progressively by repeated stimuli might reside between input and output in an intermediate network organization manifesting inertia (information storage through a maintained pattern of activity) was also consistent with the finding that weak "disinhibiting" stimuli only temporarily restored response amplitude and that the disinhibiting effect that facilitated control responses, also habituated[400]. Indications that habituation and dishabituation were separate phenomena included evidence that strong stimuli went beyond reversing the response inhibition[670], and spike contours with shorter latencies than those induced in controls were evoked by disinhibiting stimuli[635]. Response facilitation may be a more appropriate term than disinhibition for such events.

A direct approach to the relationship between response habituation of spinal motoneurons and dorsal horn interneuron activity was made by Wickelgren[710]. She demonstrated an optimal frequency for the elicitation of response depression with skin and proprioceptive afferents, nonlinear (both hysteretic and oscillating) time-dependence (stimulus train length) of accrual. and exponential-like decreases reminiscent of the complex dynamics of both receptor and membrane desensitization and its simple exponential decay. She also confirmed that neither the behavior of primary sensory afferents nor a depression of membrane potential and spontaneous firing rate of the motoneuron was involved, pointing to the dynamics of the interneuron pool. Both interneuron habituation (which was not monosynaptic) and recovery manifested the same frequency and time parameters as the motoneuron response. The effect of repeated stimuli on this ensemble can be viewed as similar to that of electrotonic or low-frequency depression disaggregating

a Gaussian population into one or more subpopulations of autonomously oscillating coherent membrane proteins, creating a defect in ordering potential and resulting in membrane conductance burst kinetics[585].

Spontaneously active, mutually interacting, variously coherent interneurons in a normally random network contain the same potential for self-organization, limit-cycle oscillation, hysteresis, critical-phase transitions, bifurcations, and the evolution of long range order from a progression of nearest-neighbor interactions that hydrodynamic and ferromagnetic systems do[174, 211, 509]. Such dynamic cooperativity may not be exclusively neurotransmitter-mediated, for electrotonic coupling between spinal cord cells has been reported[250, 631, 695]. The directionality of information transport through the random network serves as the same source of irreversibility and emergent order as convection in the Benard instability[315, 556]. Spatial and temporal variance evolves normal to the direction of the "carrier" velocity of the information transport process and is analogous to the way magnetic fields organize receptor proteins at right angles to the direction of ion-mediated conductance current. Wickelgren caught this image in her speculation that the mechanism of response inhibition might be a "polysynaptic analogue of low-frequency depression." The possibility that an appropriate stimulus frequency creates a temporal-spatial statistical hole in the normal randomness of the mediating network and thus prevents its normal emergent order is consistent with Wickelgren's findings that motoneuron response habituation was maximal at the test frequency used in its induction and that transfer of habituation between two sets of afferent fibers implicated small common receptive fields[710]. Focusing on the dynamics of organization, rather than the dominance of facilitation or inhibition as monotonic influences, it can be seen that Wickelgren's hypotheses explaining depression of motoneuron response (synaptic depression versus inhibitory buildup) could be alternative descriptions of the same kind of interneuron network dynamics. In comparative studies of two cutaneous afferents with partially overlapping receptive fields, induction and test effects were not always symmetrical when the order was reversed; Wall interpreted that as indicating there were different pathways through a partially shared interneuron network[687]. However, comparable studies by Glanzman et al. showed more symmetry[228].

Habituating interneurons manifest high-frequency bursts along with random activity, longer latency to response, and a wide dynamic range—all suggestive of a heterogeneous and partially temporally ordered population[206, 252, 686, 710]. In systematic studies of the interneuron correlates of habituation and desensitization using the hindlimb flexion reflex in the acute spinal cat, Groves and Thompson[255, 256] demonstrated an H (habituating) type cell in dorsal layers I to V[565] and S (sensitizing before habituating) cells in ventral layers V to VII. H cells, like the interneuron population of Wickelgren, manifested both high frequency bursts and spontaneous activity of irregular character, and during repetitive cutaneous stimulation they only habituated. The S cells manifested either fewer or a longer train of more regular discharges, and their response increased before it decreased during repetitive stimulation. During response sensitization and before the onset of habituation, spontaneous rhythmic activity in the S cells increased; that may be analogous to the "storms" of spontaneous activity reported by Hill[287] to be associated with habituation of the frog spinal cord ventral root response and to the burst kinetics of membrane inactivation[585] discussed in the previous sections.

The habituation hypothesis being developed here would suggest that the distribution function of a dynamic parameter in the population that was prebifurcational (here the S population) would be unimodal, whereas that of the H population would manifest post-bifurcational heterogeneity, analogous to the spectral dynamics noted above. Figure 10, after Groves and Thompson[256, their Fig. 6] portrays just such pdf for the interspike intervals of spontaneous activity in those two cell types. We speculate that the population
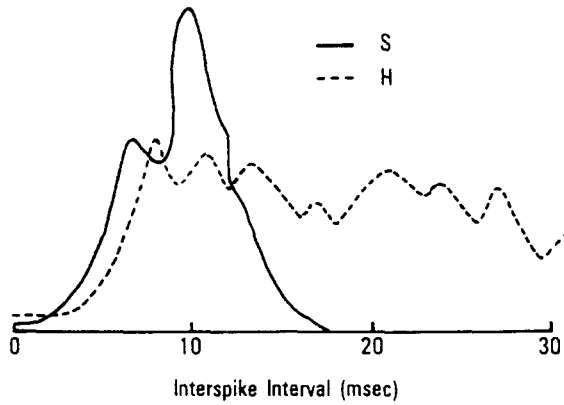
Fig. 10. Distributions of interspike intervals from two types of interneurons, after Groves and Thompson (256, their Fig. 6).

of H neurons, more dorsal in the cord and closer to tonic sensory afferents, has already undergone bifurcational transition.

Although the elementary units in the populations differ (receptor proteins in an electromagnetic field versus interneurons in a network), Sharpless' suggestion that habituation and membrane desensitization are analogous[611] may have been correct from the standpoint of the similarity in the dynamics of quasi-ordered random systems. The same characteristics of the habituated state appear at several levels of neural complexity. For example, the crayfish neuromuscular junction[70] habituates without changes in its electrical excitability, evidence of transmitter depletion, or inhibitory modulation. A more recent examination of the neurotransmitter-depletion hypothesis of response habituation[390] using calcium and magnesium also failed to find any relationship between transmitter stores and ventral root response inhibition[574], although calcium-induced facilitation of the process has been reported in some systems[41, 50, 667].

The entropy among rather than the functional status of individual elementary mechanisms or their potential energy appears to be critical. In the same way, habituation of the gill-withdrawal reflex in *Aplysia*, although presynaptic, may involve a reordering in the population of elementary units as reflected in the temporal pattern of response probabilities—Kandel's parameter m, the mean number of quanta of neurotransmitter released per unit time[335]. The entropy of the system would be better seen in the variance, covariance, autocorrelation and frequency properties of the time-dependent behavior of m[547].

Except for the mammalian spinal cord, the neurobiological substrates of habituation have been studied most extensively in three invertebrate preparations: the crayfish[379, 736]; the locust[508]; and *Aplysia*[71, 72, 97], although the characteristics of habituation as defined by Thompson and Spencer[670] are present in many other phyla as well[122, 730]. In the most programmatic series of studies in the field, Kandel and associates elucidated an identifiable neurological system, sensory nerves from mechanoreceptors to the L7 motor neuron, as one of the neural pathways underlying the *Aplysia* gill-withdrawal reflex. It manifested both short[97] and long-term[95] habituation, spontaneous recovery, and dishabituation. The anatomical specificity of the effect has been challenged recently by studies indicating that depression of motoneuron responses with the same dynamic characteristics as were observed in L7 occurs in LDG1 and LDG2 [323]. In addition, habituation of the response in the absence of the gill ganglion[525] has been demonstrated although when the ganglion is present its control is clearly prepotent[526]. The potential for the involvement of network dynamics in the response habituation of this system is

suggested by the large number of elements underlying the "simple" gill-withdrawal reflex: 6 motor, 24 sensory, and 3 interneurons[80, 389].

Distributed influences reflected in altered network dynamics of varying size are well suited to a vertically self-similar statistical thermodynamic systems approach to the habituation phenomena. As in Sherrington's and Jackson's concepts of neural organization, similar patterns of order reach from lower to higher level processes, adding changes not in the fundamental character of relations but in their scale (and, of course, complexity in detail). The self-similarity of entropic status across scale suggested by comparable spectral dynamics in different time frames (see Sec. 4) may also explain the symmetric relationship between induction test frequency and duration of habituation which operates across temporal magnitudes. In *Aplysia*[97] a short session of tactile stimuli to the siphon skin leads to habituation lasting minutes to hours, whereas coarser grained conditioning at intervals of 1.5 or 24 hours leads to habituation lasting days to weeks[88]. This scaling property involving the wavelengths of induction and test phenomena was also demonstrated by Davis using the rat startle response: habituation trials to the same critical endpoint with an ISI of 16 sec led to longer lasting response decrements than those with an ISI of 2 sec[131].

The extensive studies by Kandel's group on the simple neural circuit in *Aplysia*, which may or may not involve parallel network dynamics, were designed to demonstrate features of "monosynapticity"—one-for-one following, short and constant latency, and no further reduction in latency with pharmacological facilitation of the presynaptic spike[335, 336]. Kandel perceived response habituation as a progressive reduction in the efficacy of the synaptic connections of the sensory input to L7 (functional disconnection) and believed a decreased incidence of detectable EPPs would mirror the development of homosynaptic depression of excitatory transmission[335], an idea somewhat similar to those of Spencer *et al.*[635] and Sharpless[611]. Elementary EPPs induced by sensory input to L7 decrease in amplitude with repeated stimulation. The distributional character of this process can be followed in the amplitude histograms of consecutive EPPs from the L7 motoneuron during repetitive stimulations of the sensory as in Fig. 11, after Castellucci and Kandel[96, their Fig. 3].
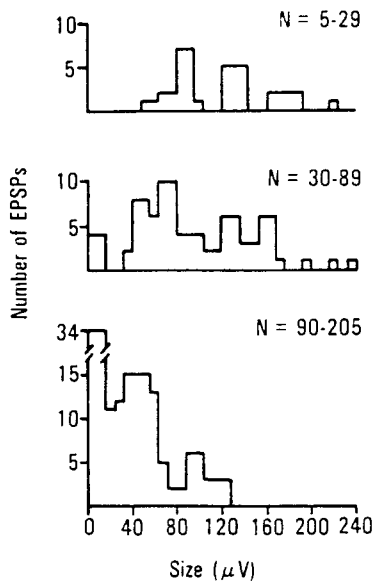

Fig. 11. Distributions of elementary EPP amplitudes from L7 motoneuron of *Aplysia*, after Castellucci and Kandel[96].

The histograms reveal an initial distribution reflecting multiples of contemporaneous quantal conductance events from trials 5 to 29 at an ISI of 60 sec. That suggests an initial small baseline degree of coupling, elementary units acting together. In passing, it should be noted that evidence of this simultaneity makes the assumption of Poisson independence underlying Kandel's parameter m less tenable[152]. From trials 30 to 89 more chunks of large amplitude are realized, signifying an increase in coupling. Despite an increased sample, N, which the central limit theorem relevant to independent elements predicts would lead to a reduction in dispersion, there is an increase, indicating a changing degree of cooperativity[269]. Over the last 105 trials, the apparent disaggregation suggests a final trimodal population distribution: (from left to right) failures, a "hole" in the distribution, a Poisson-like distribution with an average amplitude of about 40 μV, and a smaller group at 100 μV. A statistical systems approach to this phenomenon would indicate the transitions from a more equiprobable distribution, reflecting a relatively random array of coupled chunks, through emerging cooperativity, to final bifurcations associated with a left shift in mode.

These dynamics are not inconsistent with those seen by Katz in membrane conductance (Figs. 1–3), by Changeux using fluorescence-tagged receptor proteins (Figs. 4–7), in Erlanger's strychnine-disaggregated nerve conduction spike (Fig. 9), and with Groves and Thompson's H and S neuron spontaneous activity (Fig. 10). The pattern of changes in the distribution, as in Fig. 11, suggests that response failure is associated with changing entropy, cooperativity, in the temporal-spatial patterning of elementary units in the sensory-motor synapse. EPP amplitude histograms from studies of long-term habituation demonstrate the same population dynamics[95]. Time-series analysis of the deviations around the mean exponential conductance regression line over habituating stimuli using spectral, autocorrelation, and exponential approaches would be a way to explore these population dynamics further. It is worth noting that in this population changing entropy gathers and is maintained the way that the changing character of the random behavior of a protein from averaging impingements serves as a primitive memory; both are coarse grained in time relative to the unsequenced inputs and tend to persevere.

Although the phenomenon of sensory-motor response inhibition as seen in the pattern of EPP at L7 lasted as long as three weeks[95], a single sensitizing electrical stimulus to an area outside the sensory field of the habituated behavior restored the response[89]. Associated with this dishabituation was a return of the density distribution of EPP amplitudes to its prehabituated, more equiprobable form—a more random array of EPP chunk sizes, similar to the top histogram in Fig. 11. We speculate that, in this system as well, habituation orders in a way that destroys the random field required for the normal pattern of self-organization underlying the gill-withdrawal event. A large dishabituating perturbation entering the system from multiple, nonhabituated paths may act like a "quenching" injection of randomizing noise. It remains to be explored whether these population dynamics refer to entropic changes in the population of presynaptic conductance units, to temporal-spatial disorder among postsynaptic receptor proteins, to changes in the pattern of spontaneous activity indicating a reordering of the network that involves all 33 neurons, or, as we suspect, to changes at all 3 levels of organization. For example, the simple absence of inhibition as might be inferred from the normal resting potential of the motoneuron or its normal response to a nonhabituating input does not mean that the receptor conductance mechanism underlying the habituating sensory-motor connections is not disordered in space-time; i.e. locally "inhibited" by an ordered defect in a normally random field.

Mean values are not indicators of either the entropic status of systems or of their potential for an as-yet-unrealized response. For example, Klein and Kandel have demonstrated a cyclic AMP-dependent increase in calcium current[365], which could also

have been a decrease in potassium conductance[267], that did not change the membrane potential (an average value) but did sensitize the sensory neuron's presynaptic terminals. Their deterministic explanation involved increased responsivity (conductance) by calcium channels secondary to their phosphorylation. A statistical mechanical explanation would recall that with repetitive responses the impedance loci for the opposite condition, low calcium concentrations, approached an undamped oscillation[207, 310], suggesting an increase in coherence. Evidence should be sought for the behavior of a pathologically ordered (bifurcated) population in the presence of increased calcium. The ion has been shown to modulate the conductance changes induced by procaine in the lobster axon[235], and we have observed a spectral bifurcating effect of calcium (following the induction of coherence) on the statistical kinetics of brain neurotransmitter enzymes[367]. The changed latent status of the system, seen by Klein and Kandel as a mechanical mechanism, could be a field (voltage)-dependent rearrangement within the population that both affects calcium dynamics and is affected by them. An approach to these questions could be made through studies of the variance properties of spontaneous activity, especially in the frequency domain.

Recently, studies in mammalian spinal preparations have confirmed that single-cell interneuron inhibition evoked by cutaneous stimulation does not accompany the habituation of the flexion response[428, 429]. Like membrane desensitization in the presence of a normal resting (or hyperpolarized) state, that finding is consistent with a rearrangement in the temporal-spatial order, cooperativity, in a network of elements rather than a change in their individual potential for function. There have been descriptions of changes in the activity of a population of dorsal horn cells responsive to stimulation of the central pad of the cat hindlimb[163] that parallel the ventral root response in the lumbosacral cord, first sensitizing and then habituating[161, 162] and resemble the S neurons of Groves and Thompson[255, 256]. These cells belong to a large group of the dorsal horn with wide central latency distributions to peripheral stimuli, consistent with membership in a complex interneuron network[377, 688]. That the transition from sensitizing to habituating effects in single dorsal horn interneurons correlated well with similar changes in the ventral root suggests that a theory based on two types of interneurons may be unnecessary[256], and is consistent with studies in the frog spinal cord[180, 181] and in *Aplysia*[96, 96a] which suggest that the same synaptic systems may mediate both sensitization and habituation.

Several features of transsynaptic response habituation suggest the role of the reordering of an autonomously fluctuating, variably coherent, multiparticipant system at several levels: (1) the greater influence of frequency than of intensity of the stimulus parameters on the process; (2) a defective depolarization mechanism in the face of a normal amount of potential energy to drive the system via a normal or even increased resting membrane potential; (3) a homosynaptic mechanism indicating a fundamental internal alteration in function without the recruitment or elimination of other systems; (4) hysteresis indicated by time-dependent accrual with nonlinear kinetics, inertia reflected in continued development beyond the arrest of initiating stimuli, and spontaneous single exponential decline of the habituated state—all dynamics consistent with those of a system with potential for the development of cooperative order and its thermal, diffusive decline; (5) the emergence of semicoherent autorhythmicity in segregated subpopulations associated with a defect in integrated function; (6) the critical and scalable (resonance) relationships between elicitation and test frequencies; and (7) evidence from both pdf and spectral analyses that at several levels of nervous system function desensitization and habituation processes are associated with bifurcations in previously more homogeneous, randomly distributed populations.

The statistical thermodynamics of nonequilibrium, multi-element systems manifesting

complex developmental kinetics and critical phase transitions is a burgeoning frontier in statistical physics[269, 426, 480, 494]. Closely related to catastrophe theory and bifurcation theory[589], the many-body status of these systems[496] makes the models and their differential equations leading to direct solutions intractable, even on high-speed computers. In place of deterministic equations are approaches that involve various techniques of transformation: the moments, probability densities, autocorrelation functions, spectra, and characteristic exponents used in this essay as well as many other available transforms (LaPlace, Melon, Green function, etc.) which describe dynamical characteristics of physical quantities without definite values for the quantities themselves. One can imagine lawfulness as manifested not by the prediction of a precise value for a parameter but by a consistent style of statistical motion in a system under similar changing circumstances. Without being able to follow the Hamiltonian trajectory of each participant, having only the statistical aspects of the macrobehavior to monitor, men like Wiener[711], Katchalsky[347], and Prigogine[545, 546] saw the power of transforms and random theory for the description of patterns of inner order in biological systems. These approaches contrast to earlier applications of the deterministic differential equations of mechanics to biological processes by such pioneers as Thompson[669] and Goodwin[237].

The autonomous development of organization in a random system involves single steps of describable transition probability of a Markov type and, in addition, a sequence of nearest-neighbor interactions that culminates in long range order in the population. This process reflects the influence of field conditions. The magnitude of the coupling constant, an ordering parameter describing the efficacy of common field influences, is usually inverse to the temperature, a randomizing influence[426]. When temperature, the classical probe of statistical thermodynamics, was applied to the synaptic depression problem to analyze the contribution of temperature dependency of transmitter secretion in the rat neuromuscular junction, inverted U-shaped functions for fractional release and mobilization were found[303]. The view of sensitization and habituation involving the development of order among subpopulations that creates defects in the random field from which normal self-organization arises would predict that lowering temperature (increasing the coupling constant) would facilitate habituation. Five studies have demonstrated this effect. Although confounded by small decreases in conduction velocities and amplitudes and prolonged duration of evoked events, cooling consistently facilitated the development of response depression, and that effect was poorly correlated with the effect of decreased temperature on stimulus intensity[189, 303, 409, 577, 701].

As the temperature of a ferromagnet is decreased from the critical point at which the orientation of the component dipoles is random and there is no macroscopic magnetization, there begin to emerge regions, patches, in which the net fraction of spins lines up. The exchange of negative entropy, which is the dissipative ordering mechanism, operates on neighboring spins, the coupling constant being an index of the efficacy of the exchange. In contrast, thermal noise turns spins randomly. As the temperature is decreased and the sizes of the patches grow, a longer time is needed to approach equilibrium after a disturbance. This increase in temporal-spatial connectivity is seen in the lengthening of the autocorrelation function and the increased prominence of spectral slows. At such a point, in another example, as the temperature is decreased below 647°, at 218 atmospheres of pressure, a phase without a discriminable difference between the physical state of water and vapor bifurcates into separate identities in a phase transition[638].

In an analogous circumstance, where the habituating ensemble is repeatedly perturbed by stimuli, the frequency modulates and phases through shared periodic input an increasing fraction of the population of autonomous fluctuating soft-mode oscillators. In turn, this creates longer (autocorrelation) relaxation times for the return to baseline and decreases the amplitudes of response to succeeding stimuli, i.e. habituation develops. The

wavelength of an effective ISI serves to induce as well as to reflect the degree of temporal order in the system in the way that ligand binding functions both create and measure the bifurcated high-affinity state of desensitized receptor preparations. This approach is roughly analogous to the perturbation-relaxation techniques used to probe the equilibrium arrangements in enzymatic systems[165]. Continuing the stimuli beyond this temporary action, which would decay spontaneously under the time-dependent, single exponential influence of thermal randomness, leads to a bifurcation into two or more coherent sub-populations and a longer lasting habituated state. By reducing thermal randomness, i.e. increasing the relative ordering influence of nearest-neighbor exchange and field forces, a decrease in temperature has been known to facilitate the development of long lasting habituation.

6. FIELD ELECTROPHYSIOLOGICAL AND ENCEPHALOGRAPHIC CORRELATES OF HABITUATION

Application of the concepts and techniques of random theory to electroencephalographic data ("incessant fluctuations" in electrical potential over the brains of animals and humans[98]) began with discovery of the stability over time of the alpha rhythm by Berger[42] and its confirmation by the more systematic studies of Adrian and Matthews[7]. Modern statistical techniques have established individual differences in the average frequency of rhythms in the alpha range[564] known to be stable in individual subjects over years[128]. The spectra of the EEG were related to persistent features of personality style as early as 1943[689].

Norbert Wiener[711], who had long been interested in the harmonic analysis of continuing random processes, explored the extent of latent order in the EEG using techniques analogous to Taylor's applications of the autocorrelation function to Brownian motion and turbulences[664]—themselves derived from the early work done on time-dependent random processes by Smoluchowski[626]. Both the degree of inter-correlation and the periodic aspects of a time-varying random function can be observed if over an increasing number of temporal distances (τ), the value of the function at that point is multiplied by its value at the beginning, i.e. $f(t)$ by $f(t + \tau)$ over increasing τ, generating an autocorrelation function. A more random system will show less autocorrelation length; the degree of coupling (frequency-phase coherence) among the participants generating correlations between adjacent values will demonstrate an increase in shared power (variance) over increasing lags (τ). Harmonically varying processes will be signified by variably damped waxing and waning of positive and negative power. If this function is decomposed into its two frequency components, the sum of its sine and cosine functions representing, respectively, its amplitude and phase, a power (frequency) spectrum is generated (see Sec. 2). An image of the mathematical process is represented by the mechanics of an early autocorrelation technique: a frequency-modulated magnetic tape of the EEG was played through a machine with two variably distant playback heads in which the products of their current densities (power) over time were determined using square-law rectifiers, the averaging performed by integration using a resistor-capacitor network[22].

Wiener attributed the stationarity of the spectral density distributions of the EEG to the stability obtainable in a collection of multiple, similar, mutually dependent nonlinear oscillators in a common field. Frequency coupling ("nonlinear binding of frequencies") generates the system's average spectral peak, with a statistical "hole" separating the peak from the unbounded frequencies on either side. This statistically weighted frequency, the alpha limit cycle, varies remarkably little; in a specified set of circumstances, insensitive even to the effects of temperature (as in the case of other limit cycles such as circadian rhythms[724, 725]. As an instructive analogy, the stable nonlinear orbital behavior of a

population of asteroids does not manifest a continuous spectrum, but shows stable power peaks that are rational multiples (with surrounding gaps) near the frequency of the dominant field forces emanating from Jupiter[476]. Wiener saw the capacity of selected flicker frequencies to drive the EEG spectrum, the hysteresis in this process, and the sensitivity of EEG frequency to amplitude as indicative of the operation of cooperative nonlinear statistical mechanisms[711]. This kind of system generates dominant oscillatory frequencies representing "attractive" clumps of self-organization, reflecting sums and differences (the interference patterns) of the participant contributors. The image of stable, nonequilibrium distributions of variably cooperative, fluctuating dissipative elements which has been used in the analysis of the behavior of proteins, receptors, membranes, and interneuron nets, is equally applicable to the dynamics of brain field potentials. In studies of random fields of partially coupled oscillators in contact with heat reservoirs, the signatory precision of the parameters and the stability (stationarity) of nonequilibrium distribution functions persist in the face of an N so large that the central limit theorem would have predicted their loss in Gaussian randomness. It was a phenomenon like the remarkable persistence of (nonconvergent) distribution functions of random variables that facilitated a revolution in the theory of nonequilibrium processes begun by Boltzmann and Onsager[504, 505] and continued by many others[43, 83, 384, 473, 548, 676, 691]. The variable dependence of N, coupling, leading to frequency-phase coherence, changes stable non-Gaussian variance and is seen over time-dependent fluctuations as amplitude.

Whereas direct electrical stimulation of the cortex produces traveling waves of electrical fields[498], and studies of spatial EEG patterns over time show a limited degree of directionality[398, 399], more recent work suggests that the EEG may be better viewed as a coalescence of potentials that travel in various directions and fuse into stable standing waves whose characteristics are partially determined by such variables as their physical boundaries. For example, in smaller human heads, alpha rhythm is faster (denser)[498, 499].

Nondissipating waves, called solitons, require for their existence particular nonlinearities in periodicity (which Wiener had shown to be characteristic of the EEG[711]) that compensate for the dissipation term in their wave equation. Under these circumstances they can persist relatively undamped for long times and distances[220]. Solitons maintain their character while traversing and being traversed by other waves[561] and generate wave equations that allow exact solution[291]. Frölich, the proponent of a physiological role for long-range, low-frequency coherence in the electromagnetic wave processes in biological systems, has shown how long wavelength vibrations could extend throughout the system of oscillators of the human body by means of nearest-neighbor interactions that sum to long-range Coulombic order[215].

In Sec. 2, in the discussion of the relationship between distribution functions and their expression in the frequency domain using the characteristic exponent D, we saw that the shape of the pdf of a random function could be reflected in the quality of "roughness" in its stochastic surface over time. Coupling constants, sensitive to general field conditions, can generate characteristic critical exponents describing the state of the system both spectrally and probabilistically. From this point of view, the EEG could represent standing probability waves reflecting the kind and extent of self-organization, cooperative order, in the brain as a *distributed* property. The tendency for similar nonconservative oscillators to become phase coherent over time suggests that characteristic interference with this process may be the field influences that lead to scalar self-similarity.

The tendency for nearest-neighbor self-organization of the cortex in the direction of increased coherence was suggested by the regular synchronous burst/silence cycles created by isolation of small cortical islands from internal and external randomizing input, either by undercutting[62] or from tumors[159]. In addition, even the earliest work dem-

onstrated that traveling waves of abnormal activity induced by convulsants[8] or stimulants[411] were transported across cuts in normal synaptic connections. It was Adrian who first noted the spread of surface positivity in all directions, without attenuation, after an initial negative response to stimulation of the cortical surface[6]. The characteristics of these nonsynaptic field electrical wave phenomena may mirror the nondissipative transport of entropy across interacting chemical, electrical, and mechanical potentials in the brain as an open system[347]. A recent conference on neural communication and control provoked considerable discussion about field potentials as emergent properties of the statistical state of microparticipants as well as influences upon them[431].

Workers in solid state physics have long dealt with wave propagation in periodic structures[65], emergent structure among probabilistic components[13], and how general (distributed) properties of materials at microscopic levels determine macroscopic shape and function[21, 77, 124]. The brain's electrical wiring and "cable" properties[293], the electrical engineering equipment used in its study, and the tracks and pathways of neuroanatomy have focused attention in the brain sciences away from the long-range order achievable through field-dependent probabilistic nearest-neighbor interactions. Phasing by electrotonic slow waves rather than action potentials has been recently emphasized in studies of the mutual synchronization of heart cells[324]. Neuron networks are just one of many likely locations for these dynamics in the nervous system[174]. Kenneth Cole was rare among the pioneers in neurophysiology in his applications of the principles of solid state physics to neural membrane phenomena[112]; speculations he made in the 1930s sound very much like the modern efforts to apply nonequilibrium statistical mechanics to biological systems.

An instructive issue with respect to the EEG involves the general state of order, temporal-spatial connectivity, reflected by either the slow waves of sleep (delta waves) or the low voltage, fast waves of "arousal" (beta waves), two component quasi-stable states which Wiener thought coupled to form the alpha rhythm[711, 712]. Recent studies of the 40-Hz beta band in man have shown that its appearance is associated with the disappearance of alpha and an increase in 1- to 2-Hz delta waves, suggesting that the alpha can split into its two previously coupled components[412]. In electrophysiological studies, a state of high voltage, slow wave activity has characteristically been called "synchrony"[363, 437, 726] because, compared to a condition in which phase is randomized, frequency-phase coherence among a population of nonlinear oscillators was imagined to increase the observable amplitude. However, the spindle bursts that characterize slow wave sleep are like those observed in islands of disconnected cortex as seen with undercutting, tumors, brainstem lesions, and deep anesthesia[417]. The same "disconnected" state is associated with bursting autorhythmicity in single units[38, 292, 304]. The suggestion is, then, that EEG slow waves do not represent the synchrony of a coherent whole but express the disaggregation of the larger population into subpopulations, i.e. distributions over time and space of multiple coherent clumps manifested in time by the composite wavelengths of autonomous relaxations through a heterogeneous group of aggregates, an increase in Poincaré's recurrence time through multiple ensembles. The increase in amplitude then reflects the increased variance, deviations from the mean, in a multimodal pdf. It should be noted that this circumstance approximates the statistical mechanical end-state of the desensitization-habituation process at all the levels of nervous system function we have discussed thus far: a bifurcation into coherent subpopulations. That the habituation process involved a distributed alteration in state mimicking slow wave sleep was first suggested by Pavlov who noted "internal inhibition" manifested by drowsiness, lassitude, and sleep emerging at the end of habituation trials of the salivary reflex in dogs[518].

In contrast, a homogeneous, randomly phased population of a dissipative oscillators

would manifest the low variance (amplitude) associated with a random distribution of parameter values and the associated frequency of centercrossings like that of Johnson–Nyquist noise. In EEG terms, this state of low voltage, fast waves (the organism in aroused readiness) which is associated with continuous rather than bursting single-unit discharge[99, 126, 304], seems consistent with the electrophysiological representation of a single, nonbifurcated population with a random distribution of phase, which Winfree[725] has described as being characteristic of a sensitive system near a phase singularity. For example, the North Pole (a phase singularity) is a place where a few steps (little energy) make radically different categorical changes in time zones. The low voltage, fast waves of arousal[437], their presence on the motor cortex subsuming a voluntary action[521], and their association with fine visual discrimination and fast response[217, 301], are representative and suggest both the homogeneity and sensitivity necessary for the evolution of organization toward the critical phase transition of macrobehavior that we have ascribed to the normal state of a single random population. Perturbation-induced relaxations are short during low voltage, fast wave activity, as indicated by fast recovery cycles after evoked activity[416, 726].

In contrast, a multimodal distribution with coherent subpopulations would lead to the high amplitudes of low phase variance and the increased recurrence times of multiple ensembles, consistent with the slower relaxations following perturbations in slow wave sleep. Such an unintegrated population would be consistent with the failure of attentional and integrated actions during slow waves[437] which, as noted, are associated with bursting unit activity[126, 304] comparable to that seen in the "desensitized state" at all neurobiological levels.

Pavlov's discovery of the behavioral parallels among habituation, "internal inhibition," and sleep may have been mechanistic as well as phenomenological. More recent work has shown the same relationship between arousal level and response habituation (see farther on in the text). Although the phenomenon being habituated may involve specific sensory-motor neural mechanisms, the changes in state engendering and engendered by habituation appear to be more general, distributed properties [197, 637]. We propose that the low voltage, fast (beta) wave state of sensitizing arousal may represent a single population of responsive, continuously active elements with a random phase distribution and maximal sensitivity; the slow (delta) waves of habituation and sleep, the neural population bifurcated into multiple disconnected, phase-coherent subgroups (bursting ensembles), would be represented by wide variance (amplitude) and slow relaxations through multiple ensembles. Whereas stimulation of the rostropontine reticular formation[475] and the thalamic reticular formation[327], respectively, evokes these two states, both the radically different stimulus parameters required and the different conduction properties of the two pathways to the same population of cortical neurons[16, 623] suggest that temporal-spatial dynamics as well as neuroanatomical connections may be responsible for the observed duality in function.

As pointed out earlier, a measure of the degree of order as well as potential for order in a system is the time-dependence of its return to stationarity after a perturbation alters its equilibrium conditions. In general terms, having no order to rebuild (and perhaps having less capacity to build it), a system of independent particles relaxes quickly to its old equilibrium after, for example, a temperature jump. In contrast, a system with both existing and potential capacity for dissipative reordering expressed as temporal-spatial coherence, coupling, will take longer to return to equilibrium after an energy imparting or a disruptive change in baseline conditions. This reflection of the degree of present and potential intercorrelation in function among microparticipants in a system can also be seen in an analysis of their spontaneous noise using the autocorrelation function (see Sec. 2). Systems with more internal order demonstrate longer autocorrelation lengths, from

which Fourier transformation produces spectral slows. The dissipative aspect of the process following perturbation or autonomous fluctuation involves what might be seen as an entropy exchange in the transport of order. In this context we shall examine the auditory evoked potential (AEP) as a probe of central dynamics by perturbation, not simply in an effort to bring something measurable out of the EEG "jumble" of electrical potentials, as was suggested by Callaway[81], but to elicit data that may converge with the EEG itself with respect to both its existing capacity and potential for entropic alteration. In this way, an effective ISI, frequency, in relation to habituation rate (the gathering of incomplete relaxations culminating in bifurcation) is a deep probe into both the existing and nascent order of a statistical system. As Worden has noted, such factors as refractory periods, recovery cycles, and changes in the dynamics of populations of neurons are the major revelations of differential responses to the temporal characteristics of habituating stimuli[728]. Although definitional differences have been constructed to discriminate "rate effects" from habituation[670], beyond the encroachment of the ISI upon the immediate refractory period of mediating neural pathways for the earliest events, the symmetrical scaling of interval induction in relation to the duration of the phenomenon suggests that the boundaries between these two kinds of "rate effects" are less than definite [see earlier in text and 131, 438].

As might have been anticipated by findings that the long-latency components of the AEP, the auditory vertex potentials (P_1, N_1, P_2, N_2 from 50 to 250 msec after the stimulus) change with alertness, drowsiness, and sleep[130, 715], it is only the N_1-P_2 waves that manifest long-term habituation in a systematically predictable way[288, 535, 536, 579]. A changing attentional state has been viewed as a source of experimental artifact in studies of habituation of the vertex response; for example, drowsiness decreases the amplitude of the N_1 wave[704]. However, it has been clear from the time of Pavlov that habituation itself involves similarly distributed changes in state[518]. The habituation mechanism, the loss of a unitary random field via bifurcation, distributed diffusely both over the system under observation and vertically across many levels of neurobiological function, may involve the process underlying changes in the attentional state itself, both constituting reflections of the same underlying statistical conditions.

If the habituation process involves a distributed change in state, one would predict cross-modality interactions in the evocation and habituation of the vertex potentials[232, 357], especially since some share cortical fields[690]. Davis et al. demonstrated generalization of the recovery interval when mixing repeated auditory and visual stimuli[129], and Butler described spatial and frequency specificity and pitch periodicity generalization within one modality[79], suggesting the involvement of both distinctive and overlapping neuronal populations. Similar dynamics involving overlapping neuronal fields have been suggested by others[529, 678] and recall the generalization of flexion reflex habituation across spinal cord segments. Generalization of habituation to decreased responses to disinhibiting stimuli across modalities is also consistent with the development of a more general, distributed property[216]. The dynamics of short- and long-term habituation of evoked potentials with respect to these longer latency waves are very similar in all the sensory modalities that have been studied so far[151, 227, 289, 535].

An elegant theoretical examination of the brain as a population of variably coherent relaxation oscillators whose degree of frequency-phase coupling is manifested similarly in the spectral features of spontaneous field potentials and in relaxation phenomena after evoked auditory activity, comes from the studies of Basar and associates of simultaneous EEG and evoked potential data[25–27]. Generalization of effects of evoked potentials in time across frequency bands (8–25 Hz) and across neural structures (auditory cortex, medial geniculate, inferior colliculus, reticular formation, and hippocampus) demonstrated the importance of intrinsic spatial-temporal connectivity as a dynamic and distributed

dimension of brain function. The magnitude of the evoked response to an auditory stimulus could be relatively well predicted from the spectral properties of the preceding spontaneous activity. Parametric excitation indicative of multiplicative interactions among fluctuating nonlinear oscillators[614]—strong resonance—was suggested by the considerable enhancement of amplitude in evoked activity when the response signal contained frequency components that existed in the spontaneous activity. This is the same kind of coupling in the domain of electrical fields that we described in the context of receptor-conductance proteins and dynamic networks of interneurons with the additional demonstration that degrees of coherence among wave mechanisms may be responsible for nonlinearities in thermodynamic functions involving parameters like energy and its derivative entropy[347].

Whereas efforts with repeated low stimulus frequencies have failed to reveal a voluntary attentional influence on the long-latency AEP waves that habituate, i.e. N_1-P_2[288, 593, 714], denser stimulus trains evoked significant increases in N_1 when ear tones were attended to, versus when they were not. Increasing the rate of stimulus presentation (facilitating the gathering of unrelaxed emergent order) made attentional effects more robust[596, 597] and, as might be expected because habituation dynamics are facilitated at low intensities[670], the influence of attention on N_1 amplitude was more marked with faint or partially masked stimuli[598]. Whereas sensitizing stimuli disorder a system (cf. the reversion to a random phase distribution of EPP amplitudes after strong "sensitizing" stimuli, Fig. 11) and strong stimuli retard habituation, faint inputs with short ISI are fairly easily incorporated into perturbation-induced alterations in the autonomously emerging pattern of temporal-spatial connectivity, and attention appears to facilitate that incorporation[289, 535]. The "conservation of attention" suggested by intermediate N_1 amplitudes when attention was split between two competing acoustic channels[290] may exemplify the bifurcation in the neuron population during habituation, which is also associated with an N_1 decrement. When multiple cues or properties are attended to, their N_1 correlates are all augmented[599], which again testifies to the distributed character of the underlying mechanisms. The N_1-P_2 complex begins small, is augmented, and then is reduced as novelty turns to habituation that may be explained by the probabilistic and spectral sequence developed in the previous sections: equiprobable to Gaussian to multimodal.

It was William James who most assiduously tried to capture the subjective dynamics of the attentive and inattentive preconscious stream using literary images reminiscent of statistical wave processes[325]. He pictured autonomously increasing and decreasing coherence emerging from random thoughts via the confluence and then disaggregation of moving summations of multiple common causes. In the language of modern biological oscillator theory, the pulsations of increasing coherence of the phase-locked nucleus expand along the frequencies to engulf a band width[724, 725]. James imagined the emergence of an ordered sequence of "wave crests and hollows" that are not exactly the same, but over a given short time display a statistical stability characterized by "feelings of relation, cosubstantial with our feelings or thoughts of the terms between which they obtain"[325]. Other times are not integrated or stable, forms change without continuity, jumping from one to another with "magical rapidity."

It may be that the aroused state is an expression of a single population of relaxation oscillators with their phases nearly random in distribution, with the sensitivity to perturbation of near critical-phase transition status[724, 725]. The awake, relaxed state represents a Gaussian distribution with significant phase coherence, a stable limit cycle with low amplitude that can be fractured by strong or startling stimuli into the equiprobable distribution characteristic of arousal. Without ordered "defects" in this random field, the

attentional machine can self-organize into quasi-stable states of cognitive, conative, and affective integration, moving between equiprobable and Gaussian states of consciousness.

In contrast, the habituated state, "internal inhibition"[518], represents a bifurcated population of multiple, coherent autorhythmic subpopulations. defects in the random field eliminating the normal avenue for emergent order to move toward a critical phase transition, lacking both the sensitivity of a system of oscillators with distributed phase and the integrated condition and phase coherence of a Gaussian limit cycle. The multiple ensembles manifest slow relaxations, multimodal distributions, and islands of coherence leading to high amplitudes in the EEG. The population that normally orders into the $N_1 - P_2$ complex is bifurcated, reducing the N_1 amplitude. The N_1-P_2 complex could also be reduced if the ordering properties of attention or short repetitive stimulus trains failed.

To illustrate how the descriptive parameters and dynamics of statistical wave mechanisms might be applied to integrated brain function in a clinical syndrome, in Sec. 7 we discuss the phenomenology of the habituation failure in schizophrenic patients[261]. We review evidence suggesting that the defect may result from an already disaggregated, bifurcated state among a population of neural elements. Pavlov referred to "the destruction of the normal unification of the activity of the whole cortex" in schizophrenia[518]. In the discussion, we consider the low N_1 in the AEP of schizophrenic patients which does not increase with stimulus repetition[330, 609]; the apparent symmetrical relationship between statistical distributions in time and their representation in disordered spatial mappings[239]; the functional anatomically-based separation between affective activity and cognitive work in the hemispheres of such patients[147], perhaps a concomitant of the destruction through bifurcation of normally harmonic anterior-posterior and bilateral hemispheric oscillations[366, 444]; and the repair of both the habituation defect and schizoprenic symptoms in some patients by either 1- or d-propranolol[259], both of which order through spectral unification the diffuse dysrhythmias in denervated cardiac atrium[468].

7. BEHAVIORAL HABITUATION AND THE EEG AS PARALLEL PROBES OF CHOLINERGIC, ANTICHOLINERGIC, AND PSYCHOPATHOLOGICAL INFLUENCES

The representative drug actions addressed here do not emphasize receptor-site specificities, linear or nonlinear interactions with kinetic saturation functions, or dose-response curves, but field effects on the interactional dynamics of populations of elements leading to new cross-modality and distributed variance properties.

The Langevin equation describes the effects on a function of both deterministic and statistical influences and is represented by the classic stochastic differential equation of motion for a Brownian particle. Over time, that particle both experiences "random" hits by smaller particles which generate its motion and encounters viscosity, a force that slows it down at some constant rate as a linear function of its velocity. Thus the particle's motion is a joint function of random and deterministic influences. Deterministic approaches emphasize expectations, treating deviations from mean function as measurement error. Nonequilibrium statistical efforts treat alterations in mean function as growing out of changes in population dynamics seen first as reorganization in the variational properties of the system.

The approach to the behavioral pharmacology of habituation made here does not assume the existence of two competing independent deterministic processes such as the H and S spinal interneurons of Groves and Thompson[255, 256], the homosynaptic versus heterosynaptic serotonin-calcium-cyclic AMP mechanisms of Kandel[335], or the competing pontine versus thalamic reticular systems of Jasper[327] and Magoun[437]. The mechan-

istic image is closer to that of Sokolov[628–630], who viewed the brain as a continually-varying statistical field manifesting probability-wave processes. The temporal and spatial patterns of input (statistical wave processes) interact with the brain's temporal-spatial network (periodic probability structure) and the results of their meetings range from constructive to destructive interference: attraction, repulsion, resonance and/or bifurcations among the members of the network.

Cholinergic drugs

ACh is known to be of functional importance in the regulation of neural systems at all levels of our analysis. In the interest of maintaining the vertical continuity, behavioral habituation in relation to EEG-defined states will be discussed in relation to the actions of cholinergic agents, although myriad studies have demonstrated significant influences by many other neurotransmitter-relates classes of agents. See Davis[132] for a review. Whereas only the nicotinic cholinergic receptor mechanism underlying ionic conductance mechanisms has been discussed[372], similar sensitization and desensitization dynamics have been demonstrated for the muscarinic receptor as well [169, 281]. With respect to synaptic dynamics in simple neuronal systems, in addition to answering completely the definitional requirements for a neurotransmitter[381], ACh has been shown to be involved in motoneurons, Renshaw cells, and other small spinal interneurons nearby[156, 326, 718], which partially explains the significant concentration of ^{3}H-quinuclidinylbenzilate binding and ^{3}H-choline uptake, choline acetyltransferase and acetycholinesterase activities in the cervical cord[731]. With respect to the potential role of ACh in flexor response habituation, it is known that anticholinergic compounds depress and cholinergic compounds enhance the flexor reflex[458, 679]. *Aplysia* interneurons with widely differing actions have been shown to release ACh[335], and there is pharmacological evidence (as well as the biochemical findings noted above) that cholinergic interneurons exist in mammalian spinal cord[341]. Krnjevic[380] has suggested that the rapidly responding, probably nicotinic Renshaw cell system in the spinal cord may not be typical of the diffuse fine fiber, slow conducting, polysynaptic, older phylogenetic cholinergic pathways suggested by the distribution of their markers in the central nervous system. Rather, he characterized the central cholinergic system as more muscarinic, populated by variable, slow (hysteretic) responders whose reverberations far outlast their stimuli, and very state-sensitive[380, 381]. This is precisely the kind of system that is capable of manifesting the nonlinear dynamics we have been describing.

A number of findings are consistent with a cholinergic neuroanatomy of systems whose organization has been shown to regulate the morphology of spontaneous and evoked EEG phenomena: (a) histochemical and neurochemical demonstration of the diffuse ascending cholinergic tegmental-mesencephalic-cortical system of Lewis and Shute[410, 523, 620]; (b) less clear indications of a cholinergic role in the diffuse thalamic-cortical projections[649], although significant choline acetyltransferase activity has been found in the nucleus important in the generation of recruitment waves, the centre median of the midline thalamus[482]; (c) classic evidence for the existence of a cholinergic septal-hippocampal track[410]; (d) new data suggesting that there are septal-cortical cholinergic projections[388]; and (e) enzymatic, turnover, histochemical, and pharmacological data suggesting the presence of diffuse ascending cholinergic pathways including septum, hippocampus, and hypothalamus[523, 656].

Perhaps analogous to their facilitating influence on the polysynaptic network supporting the flexion reflex (randomization of phase may increase a system's sensitivity[724, 725]), cholinergic agonists produce low voltage, fast patterns in the EEG that resemble those

of arousal[466] (<25 V and >40 Hz)[63]. Conversely, anticholinergic agents generate high voltage, slow waves more marked than the hypersynchronous waves of slow wave sleep[422]. Spectral examination of the influences of these agents on the EEG in animals[178, 179] and humans[319] indicates that the agonist-induced pattern is a bit unlike that of the awake state, nor does the antagonist-induced pattern exactly resemble that of slow wave sleep. These drug-induced disparities are consistent with the dissociation of EEG patterns from their expected accompanying behavioral states: anticholinergic, high voltage, slow waves are associated with increased motor activity (of an abnormal sort, see later in text) and cholinergic, low voltage, fast waves are associated with what appears to be behavioral sedation[58, 338, 713]. Anticholinergic drugs restrict and change both the range and spectral composition of EEG synchronization[104] and alter the facilitation of auditory, somatosensory, and visual evoked activity in the thalamus and cortex that usually occurs after reinforcement in learning tasks[455], even though consummatory performance may be unaltered[454]. What may be most significant is that elements of evoked activity associated with irrelevant (unreinforced) performance and emotional excitement are increased by atropine and scopolamine, but not by peripherally acting methylscopolamine[454]. Such a finding is consistent with the possible impairment of the inertial role of an unbifurcated Gaussian random distribution of cholinergic-sensitive elements, one that might normally bury rare, unsystematic, and irrelevant stimuli in the mean weighted Gaussian noise and stable limit cycle of the population. Carlton[91] has characterized the major effect of anticholinergic drugs on behavior as the facilitation of the "intrusions" of low probability behavior that "have previously been excluded from the population of active responses available to the animal." Similar conclusions were reached by Macht[430] about the return of maze errors into his animals' repertoire after anticholinergic drug administration. In addition to the speculated loss of normal randomness, anticholinergic drug-induced bifurcation of the population may evoke behavioral driving by islands of autonomous neural activity insensitive to modulating input.

Rather consistently, cholinergic agonists and anticholinesterase compounds retard the evolution of learned responses to unnaturally restrictive and repetitive stimuli (for example, self-stimulation in "reward brain regions[503, 640]), but at low doses they facilitate the learning of tasks that require, in statistical thermodynamic terms, access to a fuller range of available states (for example, maze learning, discrimination tasks[123, 692], and spontaneous alternations in a T-maze[636]. Cholinergic agonists will be seen to regulate the reversible interconversion of equiprobable to Gaussian states without evidence of progression to bifurcation, with the exception of one spectral EEG study in man[531]. Resonance with tasks involving strict spectral periodicities appear to be reduced.

Dynamics typical of a population of relaxation oscillators expressed in the frequency domain are reflected in manifestations of cholinergic function at many scales of time. Frequency-sensitive periodicities of ACh levels and release in minutes have been seen in the electric organ of *T. marmorata* and at the frog neuromuscular junction[176, 317, 318]. Diurnal rhythms in ACh can be observed in several mouse and rat brain regions[214, 150a, 583], and at larger scale, seasonal variations in concentrations of ACh can be found at frog spinal cord motor and sensory roots[469, 496, 705]. From a pharmacological perspective, it is important to restate that autonomous periodicity defines a dynamical system that, independent of time, inscribes circular relations between parameters in the phase plane[14]. It is this statistical property that is consistent with the "inverted U-shaped" functions representing circularity in many cholinergic and anticholinergic drug dose-response relationships. In sum, observations of nested periodicities, hysteretic inertia, the generally inverted U-shape or biphasic (oscillating) character of dose-response functions, and diffuse network representation throughout the brain—including regulation of ion con-

ductances at the molecular level—make the cholinergic system a useful one in which to examine organizational dynamics as distributed statistical properties of neurobiological function.

Cholinergic drug effects will be examined in the context of the dynamics represented in Fig. 12, which summarizes indices of the statistical configurations and their transitions speculated to underlie the processes of desensitization and habituation at several neurobiological levels.

The "ring" of the phase distribution portrait[724, 725] represents one full cycle of periodicity of a dissipative, nonlinear oscillator and the lines indicate the distribution of phases in the population. If one imagines that the organizing influence is periodic perturbation as in the case of habituation trials (or concentration fluctuations in a chemical system), phases become progressively more coherent over time and then are seen to bifurcate as the main probability mass pulls toward the mean, away from a group of unbounded frequencies[711]. Changes as seen in the distributions of parameter values in the pdf and the population as labeled by their frequencies, indicated in the power (frequency) spectrum, behave similarly. The autocorrelation function demonstrates increasing length as it approaches the bifurcation, known as "critical slowing down" representing the increasingly heavy limit cycle[269]. The subpopulation of coherent, rhythmic elements (autonomous bursting) which separate from the main probability mass as seen in the satellite spectral peak, are mirrored in the undamped periodic behavior of the autocorrelation tail. The potential energy plot and the graph of equilibrium coordinates are classical portraits of behavior of the mean during and after bifurcation[266].

If we assume that the EEG represents probability waves mirroring distributed qualities of organization in contributing populations of neural elements, and note the influences
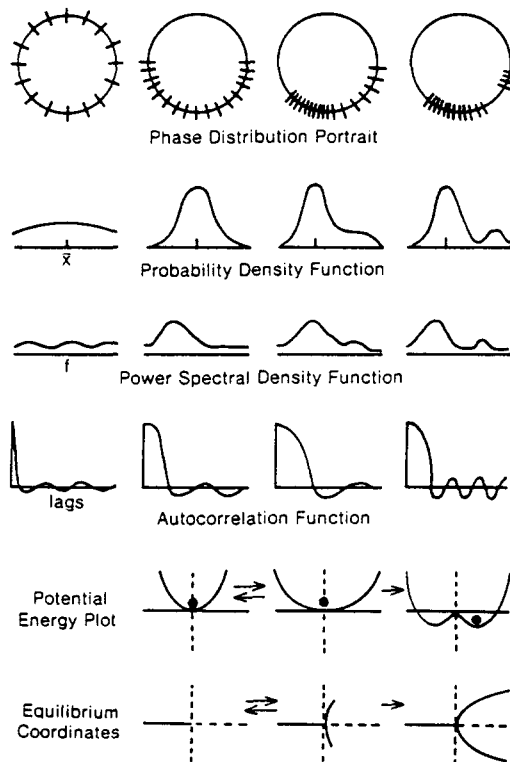

Fig. 12. Multiple representations of transitions in state over the processes of desensitization, inactivation, and habituation.

on this measure from cholinergic and anticholinergic drugs as reviewed above, the agonists appear to induce a *circular* dose-response sphere of influence on population dynamics, whereas the anticholinergics act in only one way. Administered at the lowest doses (like low energy stimulation of physiological pathways), cholinergic agonists can shift an equiprobable distribution toward a normal Gaussian population with an average frequency, and at higher doses may then re-randomize phase to an equiprobable distribution. Perhaps ACh molecules as circulating positive charges in high concentrations are like white noise reducing the potential for electromagnetic coupling and emergent coherent organization in the field. As field influences, low doses of anticholinergics appear to promote or sustain coherence and increased levels create disaggregated islands of autonomous function, insensitive to external input.

That anticholinergic EEG coherence (slow wave) reflects the relaxation oscillations of multiple ensembles in a post-bifurcated state is consistent with a number of studies that demonstrate impairment of normal habituation processes by scopolamine (the system can be viewed pharmacologically as already habituated)[92, 93, 192, 193, 244, 464, 658] and the perseveratory character of increased locomotor behavior (autonomous bursting). This hyperactivity should not be viewed as exploratory behavior because of its lack of spatial randomness [Flicker and Geyer, personal communication] and its resistance to shaping[15, 194], analogous to the unresponsive moving stereotypy following administration of high doses of amphetamine[600, 601]. The insensitive, disarticulated character of behavior generated by anticholinergic drugs is reflected in their attenuation of the transfer of startle habituation between trials even when the first habituation trial was not affected[243, 693]. As might be predicted from the character of time-independent behavior of quasi-periodic systems, nonlinear dose-response functions are characteristic of anticholinergic effects on behavior[463, 648], and the frequency and duration of both stimuli and responses (wave mechanical parameters) are critical aspects of experimental paradigms[190]. It thus appears that the ordered disorder of the anticholinergic bifurcated state is associated with increased motor activity of the autonomous variety and with high voltage (coherent subpopulations), slow waves (the relaxations of heterogeneous ensembles) in the EEG. In contrast, cholinergic drugs in larger than minimally effective doses produce the fast frequency and low amplitude of a population of oscillators with widely distributed phase and behavioral inertia characteristic of a system with decreased capacity to organize. Whereas anticholinergics induce the loss of an integrated random system with the emergence of autonomous, fixed, coherent subsystems that impairs both goal oriented behavior and habituation, cholinergic agonists regulate the degree of randomization most commonly short of bifurcation including increasing resistance to the organization underlying integrated motor behavior.

Both Carlton[90, 92] and Stein[641] suggest that the dose-responsive facilitation of many kinds of learning[339, 481] by cholinergic agents involves a process by which extraneous stimuli are made trivial; in this context, one might suggest that an increase in the background of randomness from cholinergic ligands serves to heighten the contrast between signal and noise and therefore the discrimination of influence would also retard the progression of the ordering process toward habituation in behaviors that require selection of relevance from an array of background stimuli (e.g. exploratory or maze behavior) more than it would affect extrinsically bounded tasks like startle habituation[66, 693, 716]. However, recently retardation of acoustic startle habituation has also been reported following administration of anticholinesterase inhibitors[510].

Studies under the rubric of "state dependency" offer another potential approach to cholinergic influences on variational aspects of brain function[119, 226, 511]. The properties of frequency and amplitude of the brain state (its periodic probability structure) could scale the incoming stimuli in units of variance. For example, transfer of training is sig-

nificantly impaired if acquisition and test trials are conducted under two different types of drugs or under drug/nondrug conditions, and there are over 20 differentiable pharmacological categories within which cues generalize[513]. With "state" representing the dynamical condition of the neural substrate, stimulus-response connections may travel like wave processes through the drug-configured periodic brain structures[65], their final internal representation appearing in the patterns of their mutual interference. That these pharmacologically sensitive functions of state have representational significance in addition to their modulatory quality is attested to by research indicating them to be discriminative stimuli[24, 276]. As might be anticipated from our model of the differential ordering effects of the two classes of cholinergic drugs, the antagonists are consistently active in both transfer of training and discriminative stimulus paradigms[24, 383, 512] whereas good evidence for the stimulus properties of the cholinergic agonists is not present in the literature. For example, even cholinergic nicotine failed to generalize as a discriminative cue to nicotine-related drugs[592]. The absence of symbolic function of drug state is consonant with the hypothesized randomizing role of the cholinergics.

The influence of cholinergic agonists on the EEG in man as seen in many studies is consistent with their engendering a more equiprobable random statistical state. The anticholinesterase compound diisopropylfluorophosphate engendered significantly increased low voltage, fast activity that was reversed by atropine[251]. Repeated daily administration of the drug lowered EEG amplitudes early and increased them later as behavioral tolerance developed[580]. The EEG of patients poisoned with cholinergic organophosphates were continuously desynchronized and flat[563], a frequency-phase randomizing effect that fits with the suppression of attention-sensitive late somatosensory evoked potentials by physostigmine[624], as developed in Sec. 6. The most instructive EEG study in man to date involved repeated spectral measures over time after acute administration of physostigmine which demonstrated the complete sequence portrayed in Fig. 12: a loss of alpha, an increase in fast activity followed later by the emergence of delta rhythms and then still later an intermixture of both beta and delta, reflections of the expression of at least two subpopulations in the bifurcated end-state[531]. This study uniquely suggests that a full progression through Gaussian order to bifurcation may be observed when the effects of cholinergic ligands are monitored over long enough periods of observation. The high amplitude, slow waves induced by anticholinergics have been observed in cats, rabbits, rats, monkeys, apes, and humans[319, 340]. This post-bifurcated state, we think, may underlie long-term response habituation in that atropinics, like the irreversible nondissipating phase of evoked-response habituation itself, prevents or attenuates EEG arousal in response to sensory stimuli or even reticular formation activation[58, 423, 569].

The schizophrenic syndrome

Just as the effects of cholinergic agents permitted observation of consistencies in relationships between the EEG and statistical configurations of the contributing population of elements, behavior, and response habituation, studies of a psychopathological condition appear equally informative. The schizophrenic syndrome manifests what appears to be a post-bifurcational state associated with a typical, but not inevitable, pattern of failure in response habituation relatable to other statistical properties of state. In Bellak's first exhaustive review of multidisciplinary studies of the schizophrenic syndrome, he concluded that in all measures the most consistent deviations from normal were found in the qualities of the population's variance[36]. Ergodic theory suggests that statistical descriptions of the variational characteristics of a population may be isomorphic with the behavior of a typical member sampled repeatedly over time[674]. Examining time-dependent data,

we have concluded that, indeed, there is statistical evidence that behaviors within individual schizophrenic patients manifest the sort of deformations in distribution functions that have been observed in the population studies; that is, stochastic independence (i.e. normal distribution of values) is lost through what appear to be pathological ordering processes.

High variability in sensory-motor responding characterizes the schizophrenic patient[610] as do irregularity and failure in habituation of both psychophysiological[680] and neurophysiological behaviors[673]. Power spectral profiles of the EEG of such patients, stable over many years[320] show a decrease in the amount of alpha rhythm and its bifurcation into high frequency patterns (40 Hz) as well as an increase in power in the range of 1 to 2 Hz[413, 587] or theta[359]. This bifurcated state, perhaps statistically analogous to the condition following anticholinergic drugs, is concordant with the characteristic response irregularity and habituation failure as well as the low amplitude of the emergent state-sensitive intermediate waves of somatosensory, auditory, and evoked potentials[330, 396, 586, 607, 608]. As might be predicted by the increased recurrence time anticipated in systems constituted by a heterogeneity of ensembles, the amplitude recovery time was prolonged following somatosensory evoked potentials from peripheral nerves[606], as well as evoked potentials following auditory[108] and visual stimuli[316]. The attentional defect of the syndrome, one of its most experimentally verifiable features[82, 314], fits well with loss of the potential for emergent order reflected in the low amplitude of the middle waves of the evoked responses. A low coefficient of variation, fast frequency flatness, is characteristic of the EEG of many schizophrenic patients[236], especially those with severe thought disorder[587]. The loss of the unimodal, Gaussian condition appears consonant with the characteristically abnormal, flat stimulus-generalization gradients[461] as well as what has been called "response set instability"[610]. Thus the missing normal randomness may be replaced by either the pre-Gaussian or post-bifurcational distributions.

The high variance of the distribution functions seen in studies of the schizophrenic population appear consistent with the spectral heterogeneity observed in time-dependent measures in individual subjects in data from EEG, in evoked potentials, in eye-movement tracking, in attentional set, in stimulus generalization, in response times, and in autonomic, electrophysiological, and behavioral habituation tasks[37]. These distributional properties, high variance and spectral heterogeneity, in the brain's putative population of dissipative, nonlinear oscillators may mirror the loss of the functionally integrative harmonic limit cycle characteristic of Gaussian distribution. Resistance to normal self-ordering processes may also result from a low threshold for the induction of bifurcations into subpopulations—for example, intense and/or rapid evoked potentials discriminate best the schizophrenic patient from the normal subject[73]. In addition, temporal mechanisms can be observed in the spatial domain; for example, the division of a single average limit cycle in the Gaussian population of elements into two or more rhythms might separately entrain the brain's largest system of coupled oscillators, functionally dividing the hemispheres. In fact, a good deal of evidence is accruing that hemispheric asymmetries[274] are increased in schizophrenia[260].

Listed in Table 2 are representative studies of schizophrenic patients suggesting: a decrease in the amount of alpha rhythm which is considered by some to be the limit cycle of the EEG[711] and its replacement by the high frequency bursting rhythms of coherent subpopulations; the inability of the attention-sensitive N_1-P_2 complex (intermediate) to manifest nonvariable emergent order; high variability in the contingent negative variation (CNV); loss of the limit cycle in eye tracking rhythms; and defects in subjective and objective indicators of regularity in the marking of time. Spectral heterogeneity is characteristic of the statistical population, and, along with this increase in the number of quasi-

Table 2. Temporal-spatial asymmetries in the schizophrenic syndrome.

Time		
EEG spectra	Beta. High frequency bursts (20–50 Hz)	Lifshitz and Gradijan[412]
	Less alpha, more delta	Flor-Henry *et al.*[201]
EP (intermediate)	Small. low signal/noise ratio	Buchsbaum and Coppola[74]
EP (late)	High variability	Roth *et al.*[578]
Eye tracking	Loss of sinusoidal pattern	Holzman *et al.*[297]
Time estimation	Greater error, more variability	Orme[507]
Musical rhythm	Irregular	Feder and Feder[185]
Space		
Handedness	Increased left	Lishman and McMeekan[418]
Footedness	Increased left	Gur[262]
Eye/hand dominance	Crossed	Oddy and Lobstein[502]
EEG	High beta density, left	Flor-Henry *et al.*[201]
	High frontal coherence, left	Flor-Henry and Koles[200]
	Focal abnormalities, left	Taylor[663]
Time-space		
EEG, left/right energy oscillations	Slow	Flor-Henry and Koles[200]

stable configurations of state, reports of slowing in the remaining amount of alpha rhythm[73] are consistent with an increase in recurrence time—relaxation through all available ensembles before a cycle begins again[674].

In the absence of the time invariance and reversibility associated with Gaussian processes, spatial asymmetries emerge[269]. Bifurcations into coherent autorhythmic subpopulations are neither temporally nor spatially symmetrical, and Table 2 includes a representative sample of hemispheric asymmetries in a number of measures, including left frontal coherence and spike foci, which suggest persistent autonomous rhythmicity. See Buchsbaum[73], Flor-Henry[199], and Gruzelier and Flor-Henry[260] for many more. Anterior-posterior asymmetries have been observed in studies of schizophrenic patients by means of modern tomographic methods [Sokoloff, Cancro, personal communications]. Functional disconnection of brain systems was suggested by Geschwind[223] to account for the division between affective and cognitive function in schizophrenic symptomatology[53] and, taken with an increase in the number of stable states in the system, is consonant with the slow interhemispheric EEG energy oscillations (recurrence time) reported by Flor-Henry and Koles[200].

As is the case with multicausality in the creation of defects in solid substances[21], if this general and distributed property of statistical incoherence were characteristic of the schizophrenic brain, quests for a single etiology for the syndrome would be less productive than efforts to describe and repair the defect. Such a model would also fit the multifactorial patterns of inheritance that attend the schizophrenic syndrome[85] and, in fact, has already been proposed as the genetic mechanism for inheritance of the condition reflected in high densities of beta activity in the EEG[425, 684]. Clinical strategies dictated by these views have been developed elsewhere[447].

Recently, propranolol, a drug that orders into regular periodicity the fluctuations of denervated fibrillating cardiac atrium[468] and of rat brain tyrosine hydroxylase[449, 450] and tryptophan hydroxylase[367, 368] activities regardless of whether the *d-* or *l-*isomer is used, has been found to bring into harmony the affect and cognition of some schizophrenic patients[734; Jonathan Cole, personal communication]; moreover, it normalizes the habituation defect in schizophrenic patients[259]. A return to more Gaussian randomness via a dose-responsive phenothiazine-induced shift in the EEG spectrum of schizo-

phrenic patients from beta to alpha dominance[321, 586] may be consonant with reports of the therapeutic effect of cholinergic agonists in schizophrenia[532, 576]. The repair of the periodic order in time through the return to normal function of the average limit cycle of a Gaussian distribution may reconnect disaggregated islands of brain function through more coherent oscillations in space.

It was Pavlov who first saw the deep relationships among the post-habituated state of "internal inhibition," the chronic "inhibitory condition" of schizophrenic patients, the functional cortical hemispheric splitting involved in dissociative phenomena, and the schizophrenic syndrome as resulting from "the destruction of the normal unification of the activity of the whole cortex"[518]. It may be that a statistical re-examination of the large body of already available observations of the functions of the schizophrenic brain will make these generalities more specific.

8. SUMMARY

Data from studies of habituation and its analogy at molecular scale, desensitization, are re-analyzed using statistical reflections of temporal-spatial order in a population of similar dissipative, nonlinear oscillators at several concentric levels of nervous system function including protein receptor-conductance molecules, ionic membrane conductances, synaptic dynamics, electromagnetic fields, animal behavior, and psychopathological states in man. Perturbation by periodic stimulation or ligand concentration fluctuations leads to systematic changes at several scales in transformational representations of variational behavior including probability density, spectral density, and autocorrelation functions as well as characteristic exponents indicating successive transitions from equiprobable, through Gaussian, to multimodal random states.

Desensitization and habituation are seen generally to involve a breakdown of symmetrical order in time and space following a critical phase transition, bifurcation, creating new, nonfunctional, nonequilibrium steady states at several levels of function in the brain as an open system. More specifically, the frequency and amplitude of deviations from mean function, second-order variations, change predictably over the course of periodic perturbation. Simultaneous consideration of the distributional and frequency dimensions of these systems in transition is exemplified by the use of the characteristic exponent D representing both the quality of roughness of the surface of the time-dependent random function (stochastic frequency) and, as $e^{-x^{-D}}$, the roll-off of the tail (boundedness) of the probability density function. This combination of probabilistic and wave-mechanical approaches to entropic description derives from the view that the representative sensitive and stable dissipative structure in brain function manifesting hysteresis and other nonlinearities including quasi-periodicity and phase transitions is not a single physical entity, but a distribution of constituitive elements in variably coherent statistical motion at a level below that of the mean measurement.

Increased coherence engendered by periodic perturbation leads from a more equiprobable to a more Gaussian distribution of parameter values and the emergence of a limit cycle whose frequency is inversely related to the number of coupled elements. Further synchronization leads to increased slowing and more tightening of the distribution around the mean, tending to separate the main probability mass away from subpopulations, bifurcation associated with the loss of integrated macrofunction, and the emergence of autonomous bursting of the satellite densities. Without impairing the functional capacity of individual elementary units or altering the potential energy of the aggregate such as the membrane resting or reversal potential, the inactivation-desensitization-habituation process prevents normal cooperative actions, such as membrane depolarization, evoked field electrical phenomena, and behavioral responses by disaggregating the spontaneous

quasi-periodic activity of the constitutive microparticipants in time and space into a non-functional ordered state.

Cholinergic drugs as brain field influences on behavior and the psychophysiological correlates of the schizophrenic syndrome as a statistical state are used to exemplify this systems approach to habituation and desensitization at largest scale.

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