Soliton growth-signal transduction in topologically quantized T cells

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A model for growth-signal transduction of the T cell and its growth factor, interleukin-2, is presented. It is obtained as a generalization of the usual rate equation and is founded on the observation that a definite number of receptor occupations must take place in order to promote transition to the S phase and subsequent DNA replication. The generalized rate equation is identified as the equation of motion of a Lagrangian field theory of Ginzburg-Landau (Goldstone) type. However it is not an *ad hoc* model but is a microscopic theory of the interaction of interleukin-2 and its receptor. The topological quantum number of the model is related to the observed definite number of receptor occupations required to elicit growth-signal transduction. Individual receptor quanta, up to this limit, are subjected to a type of Bose condensation. This collective excitation constitutes the growth signal in the form of a topological kink soliton which is then launched by the next potential receptor occupation that makes the interaction repulsive. The model provides a possible long-absent explanation of the triggering mechanism for growth-signal transduction by means of the ambivalent interaction, which switches sign after a definite number of receptor occupations. Moreover, it offers an explanation of how Nature screens out fractional signals in the growth-signal-transduction process of T cells. Although the model is derived for assumed point-like cells and certain other restrictions, the obtained dose-response curves are in striking agreement with proliferation data from studies of both the leukemic T cell line MLA-144 from gibbon ape and normal human T cells in, and without, the presence of monoclonal anti-Tac antibodies.

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I. INTRODUCTION

The phenomenon of growth-signal transduction involves several formidable interdisciplinary subproblems. Paradoxically, however, in the laboratory the whole event seems to be governed by a very limited set of parameters, namely, the reaction time and the concentrations of extracellular agonists and receptors. However, for intermediate steps such as gene regulation, DNA melting, and replication, the number of variables appears to be very large. One might therefore assume that there exists a simple envelope model of the few above-mentioned parameters which governs the entire process and accounts for intermediate dynamics inclusively.

Theoretical studies of energy transport in deformable molecular chains follow two main lines. The first approach, undertaken by Fröhlich [1] and Holstein [2], is founded on the concept of the polaron. The second line, pursued by Davydov [3], is based on solitary wave solutions (solitons) of a nonlinear Schrödinger equation (NLS). The NLS equation is a result of a coupling between longitudinal sound waves (phonons) along the chain of peptide groups and amide-I vibrational quanta (carbonyl stretching) in the three spines of α-helical proteins. Spectroscopic evidence for Davydov-like solitons in acetanilide has been reported by Careri *et al.* [4].

In recent years different nonlinear models have also been proposed to explain long-range signals in DNA; by Englander *et al.* [5], Yomosa [6], Krumhansl and Alexander [7], Muto *et al.* [8], and others. In particular these models appear to be of interest in gene regulation, DNA transcription and replication, and related base-pair opening and closing reactions, alias premeltons, which according to Sobell [9] should be observed in DNA at 310 K. Among other problems exhibited in such models are questions of lifetime, energy turnover, and the origin of these long-range signals, both for DNA and α-helical proteins [3]. From another point of view such problems may be attributed to the lack of knowledge of how hormone-receptor dynamics proceeds to growth-signal transduction and the following division of the cell.

A nonlinear model for growth signaling is constructed here in terms of the hormone-receptor system. It is obtained as a generalization of the usual rate equation, the latter complying with experiments at lower receptor densities. The model also makes use of an alternative approach to the concept of duality and rests extensively on the observation by Smith [10] that a definite number N_0 of receptor occupations must occur in order to irrevocably promote transition to the S phase with subsequent DNA replication.

The generalized (dual) rate equation is identified as equation of motion of a Lagrangian field theory which resembles that of Goldstone [11] and the Ginzburg-Landau model, familiar from superconductivity and ferromagnetism [12]. However, the proposed model is not of *ad hoc* type, but is rather a result of the microscopic theory in terms of densities of the agonists and receptors involved.

The model contains a topological quantum number, which is here related to the definite number of receptor occupations required to start DNA replication. Existence of such a number implies a nondissipative solution [13]. The growth signal is elicited as a collective

phenomenon, exerted by many receptor occupations and triggered by the switch from attractive to repulsive interaction exactly at this definite number of receptor occupations at high density.

In this work on T cells the eliciting source is interleukin-2 (IL-2) [14], with corresponding receptors IL-2R [15]. The growth signal obtained, a topological kink soliton, is remarkably consistent with binding studies of normal and leukemic human T cells [16], and typical dose-response curves of both a leukemic cell line MLA-144 from gibbon ape [17] and normal human T cells in, and without, the presence of monoclonal anti-Tac antibodies [16,18]. By virtue of these findings, from coherent cell-expansion data, it is concluded that the obtained soliton kink can be interpreted as the growth signal.

The next two sections are devoted to basic current immunological concepts which are relevant to the problem. The following two sections, IV and V, deal with the alternative approach to duality and the Lagrangian formulation of the generalized rate equation. Section VI discusses the launching mechanism and is followed by a derivation of dose-response curves in Secs. VII and VIII, and phenomenology is developed in Sec. IX. The final section summarizes the results of the entire work.

II. IMMUNOLOGICAL PRELIMINARIES

During the past decade it has become obvious that the immune system is regulated by hormones and their receptors, in a way similar to other organ systems. Main actors are the lymphocytes, differentiable leukocytes with receptors for agonists important to their growth and differentiation. In particular the T cell, which maturates in thymus, and its growth factor IL-2 have recently become the model of choice for studies of hormone-receptor systems and growth-signal transduction [10]. Besides being one of the most crucial steps of the immune response, mitotic division of the T cell is a model for cell proliferation in general.

The majority of all T lymphocytes are metabolically quiescent cells, confined in the G_1 phase of the cell cycle. Only after contact with a foreign antigen are these cells activated for DNA replication, the S phase, and subsequent proliferation. Clonal expansion of cytotoxic T cells or helper T cells depends critically on the generation of IL-2 and the expression of the corresponding receptors IL-2R at an equal order of magnitude. This requires a prolonged or repeated stimulation by the antigen, because a substantial expression of IL-2R is a markedly delayed process. The major source of IL-2 for these two cell types is the activated $CD4^+$ helper T cell. (The CD4 molecule helps the T-cell receptor to identify an antigen.) Hence, according to Cantrell and Smith [19], proliferation may be controlled by an autocrine type of pathway, i.e., self-interaction, where the helper T cell both secretes and responds to IL-2 (Fig. 1).

As clearly stated by Smith [10], it appears to be of fundamental importance that there are only three parameters which determine the rate of progression of the cell cycle; the IL-2 concentration, the IL-2R density and the interaction time. Despite the fact that binding of IL-2 to IL-2R already reaches a stationary state after 10–15 min, the irrevocable decision to initiate DNA replication only occurs 5 or more hours later, though with markedly different growth rates within a T-cell population. However, the duration of the S phase and the rest of the cell cycle is rather constant in time for most cells. The observed time variation of the full cell cycle is therefore chiefly attributable to the fact that the number of receptors varies a 1000-fold within a population of T cells. Individual T cells therefore require different times to reach an adequate starting level.

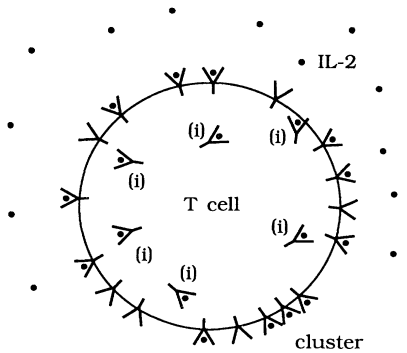

FIG. 1. T-cell blast with (i) internalized and noninternalized receptors occupied by IL-2 molecules.

Smith [10] further narrows these conclusions and suggests that the 5-h delay for DNA replication is due to the fact that a definite number N_0 of receptor occupation (of the order of 10 000) must accumulate before the irrevocable step from G_1 to S can take place. The corresponding elicited signal is further assumed to imply a sequential expression of genes, the products of which prepare the cell for division and finally signal for DNA replication. The energy of this quantum signal corresponds to the energy threshold [19] in the G_1 phase which must be surpassed. This also explains the different lengths of individual cell cycles in terms of the spread of initial receptor densities within a population.

Provided that this is interpreted such that the growth signal not only triggers but also controls the whole cell cycle, the quantum number should be related to the doubling of the cell as a whole and thus to DNA replication, which is also a quantized process. Taken seriously, these interpretations of experimental data, as outlined here, imply major restrictions on the choice of possible dynamical model.

III. BINDING OF IL-2 TO IL-2R

Until recently it has been agreed that activated T cells express two polypeptide chains that bind IL-2: one $p55$ low affinity α chain (Tac antigen) [15] and one $p75$ intermediate-affinity β chain, without which no growth signal is transduced [20–23]. Together these two transmembrane polypeptides constitute the high-affinity IL-2 receptor [16]. However, today it is known that a third subunit of the human IL-2 receptor family is present [24], the $p64$ γ chain.

Different models, based on the simple rate equation and its equilibrium form, the law of mass action, have been proposed to explain the dynamics of IL-2 and its receptors. In the preformed heterodimer [PH] model, Wang and Smith [16] proposed that the two chains $p55$ and $p75$ form the high-affinity receptor prior to association with IL-2. Saito *et al.* [25] proposed an affinity conversion (AC) model, in which IL-2 is first assumed to associate with the smaller α chain, after which this complex binds to the β chain. It was argued that this mechanism speeds up the binding rate in agreement with data. These results are obtained by a linear approximation within the rate equation model, on the assumption that the IL-2 concentration is much higher than the receptor densities.

However, in order to discriminate between different models, one should also permit IL-2 concentrations and receptor densities of the same order of magnitude, which is the case in the autocrine region, near the G_1 threshold. Without this coordination in time of IL-2 and IL-2R there is no growth-signal transduction and hence no proliferation. Therefore nonlinear effects cannot be neglected in the autocrine region.

Goldstein *et al.* [26] have derived an interesting model for the equilibrium case, where it is assumed that synthesis, internalization, and recycling of receptors are blocked. The model contains the PH and AC models as limit cases. They find that published IL-2 binding data, based on interpretations of Scatchard plots, are consistent with the PH model but incompatible with the AC model. The physical situation, however, is far from equilibrium and one should therefore start from the rate equation.

Here, this problem is circumvented by first studying the problem of growth signaling in the leukemic cell line MLA-144 from a gibbon ape [17]. This cell expresses only β chains [21] and should therefore be easier to handle compared to normal T cells. Let r be the density of β chains, ρ the IL-2 concentration, and ψ the density of the binary complex of IL-2 associated with the β chain. The corresponding rate equation is then defined by

$$\frac{\partial\psi}{\partial t}=k\rho r-k'\psi \ , \tag{3.1}$$

where k and k' are the association and dissociation constants, respectively. In the very early G_1 phase for small ψ values, if changes due to internalization and synthesis of receptors are small, the following initial constraints are approximately valid:

$$\rho+\psi=\rho_0 \ , \tag{3.2a}$$

$$r+\psi=r_0 \ . \tag{3.2b}$$

With these insertions the rate equation (3.1) reads as

$$\begin{aligned}\frac{\partial\psi}{\partial t}&=k(\psi^2-2A\psi+B^2)\\&=k[(A-\psi)^2-(A^2-B^2)] \ ,\end{aligned} \tag{3.3}$$

where the constants A and B are defined by

$$A=\tfrac{1}{2}(\rho_0+r_0+K) \ , \tag{3.4a}$$

$$B=\sqrt{\rho_0 r_0} \ , \quad K=k'/k \ . \tag{3.4b}$$

For a stable ligand-receptor complex, where $K=0$, the solution is given by

$$\ln\left[\frac{\rho_0-\psi}{r_0-\psi}\frac{r_0}{\rho_0}\right]\equiv\ln\left[\frac{\rho}{r}\frac{r_0}{\rho_0}\right]=k(\rho_0-r_0)t \ . \tag{3.5}$$

By replacement of the initial constants ρ_0 and r_0 by the dynamical ones

$$\rho_K=A+\sqrt{A^2-B^2} \ , \tag{3.6a}$$

$$r_K=A-\sqrt{A^2-B^2} \ , \tag{3.6b}$$

for which $\rho_K>\rho_0$ and $r_K<r_0$ the solution for $K>0$ is obtained from (3.5)

$$\begin{aligned}\ln\left[\frac{\rho_K-\psi}{r_K-\psi}\frac{r_K}{\rho_K}\right]&=\ln\left[\frac{\rho}{r}\frac{r_K}{\rho_K}\right]=k(\rho_K-r_K)t\\&=2k\sqrt{A^2-B^2}t \ .\end{aligned} \tag{3.7}$$

Hence one effect of $K>0$ is to increase the amount of dynamically accessible IL-2 and, respectively, to decrease that of IL-2R, as compared to the case $K=0$ for which $\rho_K=\rho_0$ and $r_K=r_0$. For $\rho_0\gg\psi$, $\rho_0\gg r_0$, and $K=0$ one obtains the same result as with a linear approximation [25]

$$\ln\frac{r_0}{r_0-\psi}=k\rho_0 t \ , \tag{3.8}$$

where ψ approaches r_0 for increasing t

$$\psi=r_0(1-e^{-k\rho_0 t}) \ . \tag{3.9}$$

The same derivation also applies to PH models for almost stable ternary or tertiary complexes, by including two $(\alpha\beta)$ or three $(\alpha\beta\gamma)$ chains, respectively, bound to IL-2 in a preformed high-affinity receptor, provided that contributions from intermediate-affinity receptors are negligible in comparison to those from high-affinity receptors. This appears to be the limit of predictive power of rate-equation models.

However, careful inspection of (3.7) reveals a dependence on the logarithmic densities of IL-2 and IL-2R, which are absent in (3.8). Without explicit dependence on these two parameters it seems impossible to study proliferation of T cells, for which the dose-response curve exhibits a characteristic nonlinear dependence of the actual logarithm of the IL-2 concentration. This indicates the importance of nonlinear effects in both ligand-receptor dynamics as well as for the intrinsic growth signal.

It is not known if internalization as such is at all required for growth-signal transduction. In the present study internalization is included only in the sense that the total number of accumulated ligand-receptor occupations is counted irrespective of internalization. Thus no distinction is made between occupied receptors and their internalized conjugates. The rationale for this is that eli-

cited energy quanta accumulate for approximately 5 h prior to the irrevocable launch of the signal for DNA replication, whereas internalization already occurs with 15 min of receptor occupation [10].

IV. A NONLINEAR GENERALIZATION

Until now, the rate equation has been used without restrictions for macroscopic densities of agonists and receptors. At a molecular level, however, for increasing densities, a realistic model should also include correlations which are not present in the simple form of the rate equation (3.1). Nevertheless, PH models appear to comply well with experiments in the early G_1 phase at lower concentrations of IL-2 receptors. Moreover, since coherent cell proliferation is controlled by the same variables, it is tempting to anticipate that the simple rate-equation dynamics not only triggers the cell expansion but also constitutes the low-density limit of the full growth-signal-transduction amplitude.

In order to generalize the model one first implements the simple rate equation in a Lagrangian field-theory. However, the pure exponential result (3.9) does not exhibit the correct high-density behavior of the ligand-receptor dynamics. Without ruining its correct low-density behavior, one thus rearranges (3.1) into a formally identical equation

$$\frac{\partial\psi}{\partial t}=k[A^2(1-\psi/A)^2-(A^2-B^2)]$$
$$=k(1-\psi/A)^2\left[A^2-(A^2-B^2)\frac{1}{(1-\psi/A)^2}\right], \quad (4.1)$$

which permits the introduction of a dual field,

$$\varphi=\frac{1}{1-\psi/A}=\sum_{n=0}^{\infty}\frac{1}{A^n}\psi^n, \quad (4.2)$$

with the differential

$$\partial\varphi=\frac{\varphi^2}{A}\partial\psi. \quad (4.3)$$

By means of these substitutions an alternative generalized (dual) rate equation is obtained,

$$\frac{\partial\varphi}{\partial t}=\frac{k}{A}[A^2-(A^2-B^2)\varphi^2], \quad (4.4)$$

which comfortably implements the ligand-receptor interaction (3.1) in intact form. Through (4.2) it now also contains a nontrivial higher-order structure, which is readily exploited due to integrability.

For the simple rate equation (3.1) fully uncorrelated IL-2 receptors have been assumed. However, a more realistic model should also include correlations of corresponding orders in ψ:

$$\sum_{\nu=0}^{n}\frac{C_\nu}{\nu!}\sum_{\substack{\text{symm}\\(i)}}\prod_{j=1}^{\nu}\psi_{ij}=\sum_{\nu=0}^{n}C_\nu\psi^\nu. \quad (4.5)$$

Here ψ_{ij} denotes the probability density for the jth receptor to be occupied by the ith IL-2 molecule. The factorized form (4.5) is valid for a pointlike cell and the simple power form ψ^ν is obtained by assuming that all receptors and IL-2 molecules are identical. The assumption of a pointlike cell surface makes sense only for very soft interaction, the infared (IR) limit, between occupied receptors. This is the classical limit with slowly varying field. The weight factors C_ν are then given by the expansion (4.2) with factorizable and summable correlations. Thereby the usual simple rate equation (3.1) is implemented in intact form as required by experiments at lower densities of occupied receptors.

Experimental data indicate that about 10^4 receptor occupations per cell are needed to start DNA replication [10], which does not mean that all 10^4 receptors must be simultaneously occupied to induce a growth signal. However, by virtue of convergence, summation of (4.5) to an infinite order creates a negligible difference. With a more rapid convergence of (4.5) and a lower threshold for DNA replication, compared to the previous case, the same generalized rate equation (4.4) is also obtained if only the order of 10^3 occupied but not yet internalized receptors are included in the sum (4.5). Hence, from this point of view, internalization is not an indispensable prerequisite for signal transduction.

The reason why the simple rate equation (3.1) also seems to work for unexpectedly high ψ values is that in fact T cells are not pointlike objects. Within an extracellular hemisphere of a certain radius, individual surface receptors may therefore be treated as mutually independent, as long as ψ, and therefore also correlations, are small. Beyond such a limit near the G_1 threshold, as the receptors come closer to each other, correlations are of crucial importance.

V. LAGRANGIAN FORMULATION

In order to study growth signaling, the T cell with a pointlike surface is then generalized to an object with depth in one spatial dimension ($d=1$) along the x axis. It is then demonstrated that the generalized rate equation obtained (4.4) can be derived from a Lagrangian density

$$\mathcal{L}(\varphi)=\frac{1}{2}\left[\frac{\partial\varphi}{\partial t}\right]^2-\frac{1}{2}\left[\frac{\partial\varphi}{\partial x}\right]^2-U(\varphi). \quad (5.1)$$

The potential U, defined by

$$U(\varphi)=\frac{1}{2(A^2-B^2)}[A^2-(A^2-B^2)\varphi^2]^2, \quad (5.2)$$

is symmetric under $\varphi(x)\rightarrow-\varphi(x)$ (Fig. 2).

Formally, this potential resembles the one of Goldstone [11] and the Ginzburg-Landau models for superconductors and ferromagnets [12]. However, it should be emphasized that the proposed model is not of such an *ad hoc* type. As will be demonstrated, the Lagrangian (5.1) is a microscopic theory of the hormone-receptor-system, for which the generalized rate equation (4.4) is the equation of motion. Thus A and B of (5.2) are explicit functions of the parameters of the microscopic system, i.e., the densities of IL-2 and IL-2R and the affinity constants. An excellent layout of the corresponding *ad hoc* type of

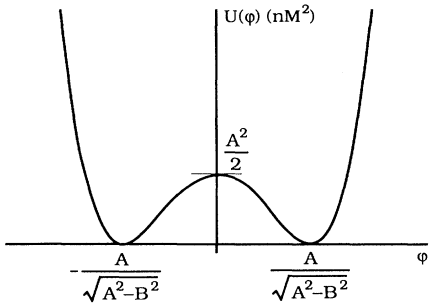

FIG. 2. The symmetric quartic potential of the proposed model.

model has been given by Jackiw [27]. However, since this is a microscopic theory and the physical interpretation is different, the derivations are carried through here in some detail.

The equation of motion of (5.1) is given by

$$\frac{\partial^2\varphi}{\partial t^2}-\frac{\partial^2\varphi}{\partial x^2}=-\frac{\partial U}{\partial\varphi}\ . \tag{5.3}$$

For time and position independent φ (5.3) reduces to

$$\frac{\partial U}{\partial\varphi}=0\ , \tag{5.4}$$

which has three solutions; $\varphi=0,\ \pm A/\sqrt{A^2-B^2}$. The requirement that the solution should also minimize the potential, leaves one with

$$\varphi=\pm\frac{A}{\sqrt{A^2-B^2}}\ . \tag{5.5}$$

For a T cell in one spatial dimension x, which represents its depth, it is now possible to look for nondissipative space-dependent but time-independent solutions. This is of particular interest here because of the requirement for high fidelity of the growth-signal-transduction process. Multiplication of (5.3) by $\partial\varphi/\partial x$ and integration yields

$$\frac{\partial\varphi}{\partial x}=\pm\sqrt{2U(\varphi)}=\pm\frac{1}{\sqrt{A^2-B^2}}[A^2-(A^2-B^2)\varphi^2] \tag{5.6}$$

with the solution

$$\left[\operatorname{arctanh}\frac{\sqrt{A^2-B^2}}{A}\varphi\right]_{\varphi_0}^{\varphi}=\pm A(x-x_0)\ . \tag{5.7}$$

Apart from the constant term, these are the familiar kink (+) and antikink (−) solutions,

$$\varphi(x)=\pm\frac{A}{\sqrt{A^2-B^2}}\tanh(Ax)\ , \tag{5.8}$$

which interpolate between the two constant solutions $\varphi=\pm A/\sqrt{A^2-B^2}$ for which the potential (5.2) is zero (Fig. 3).

Since the model is Lorenz invariant and involves only a scalar field, the corresponding boosted solution is obtained from (5.8) through a simple coordinate transformation

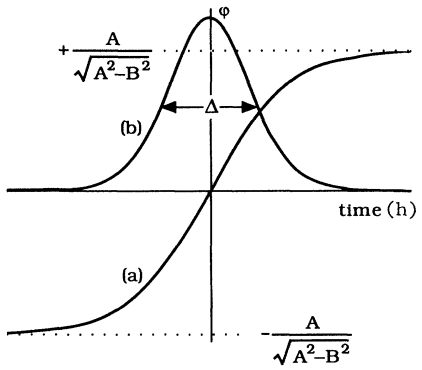

FIG. 3. (a) The kink soliton. (b) The corresponding energy density peak of width $\Delta=1/(\sqrt{2}A)$.

$$x\to\xi=\frac{x-vt}{\sqrt{1-v^2}} \tag{5.9}$$

for an arbitrary velocity v such that $v<s=1$, where s is the velocity of sound. It should be noted that the model is relativistic and the role of the velocity of light is played here by that of sound.

Observed from a point on the T-cell membrane ($x=0$) the antikink equation (5.6), boosted to the constant velocity

$$\frac{v}{\sqrt{1-v^2}}=k\frac{\sqrt{A^2-B^2}}{A} \tag{5.10}$$

coincides with the generalized rate equation (4.4). Hence, for the constant velocity (5.10) with known parameters A and B in terms of the IL-2 and IL-2R densities (3.4), the model (5.1) represents the desired Lagrangian formulation of the generalized (dual) rate equation.

By the use of (3.6), (3.7), (5.8), and (5.10), for $x=0$ (on the cell surface) and with $\varphi_0=1$, the boosted antikink solution appears in the form

$$\tau\equiv\frac{\rho_K-r_K}{\rho_K+r_K}\varphi=\tanh\left[\frac{1}{2}\ln\frac{1+\dfrac{\rho_K-r_K}{\rho_K+r_K}\varphi}{1-\dfrac{\rho_K-r_K}{\rho_K+r_K}\varphi}\right]\equiv\tanh\theta\ . \tag{5.11}$$

In this relation, which is dual in the sense of Kramers and Wannier [28], the time parameter is expressed as a function (3.7) of the density of occupied receptors or equivalently by the IL-2 concentration.

Duality here relates dynamical observables at low densities to their dual counterparts at high densities. Through a duality transformation one can thus find new parameters τ^* and θ^* for which

$$\tau=\tanh\theta=\exp(-2\theta^*)=\frac{1-\tau^*}{1+\tau^*} \tag{5.12}$$

such that $\tau^*=\tanh\theta^*$. One readily finds that $\theta^{**}=\theta$, $\tau^{**}=\tau$, and

$$\sinh(2\theta)\sinh(2\theta^*)=1 , \tag{5.13}$$

which shows the involutory nature of (5.11). The fixed point of the transformation (5.12), which satisfies $\theta_f=\theta=\theta^*$, where θ_f and the corresponding φ_f are given by

$$\theta_f=\tfrac{1}{2}\ln(1+\sqrt{2}) , \tag{5.14a}$$

$$\varphi_f=\frac{1}{1+\sqrt{2}}\frac{\rho_K+r_K}{\rho_K-r_K} , \tag{5.14b}$$

separates a disordered low-density phase $\psi<\psi_f$ from an ordered phase at a higher density $\psi>\psi_f$. However, if IL-2 is removed at $\varphi\le\varphi_f$ and $\varphi_f<\varphi_{N_0}$, where N_0 is the number of receptor occupations required for growth signalling in one single cell, this would imply a premature abortion and the cell would return to the quiescent state due to internalization and catalysis. Thus φ_f is not a critical fixed point in the usual sense.

On the other hand, it is known from experiments that only the densities of IL-2 and IL-2R and the time of reaction determine the rate of T-cell cycle progression [10]. Hence, since time is eliminated, as will soon be demonstrated, one can now obtain a dose-response curve that allows for a physical interpretation of the kink soliton (5.8) as the growth signal.

The kink energy density is defined by the Hamiltonian

$$\mathcal{H}(\varphi)=\frac{1}{2}\left[\frac{\partial\varphi}{\partial t}\right]^2+\frac{1}{2}\left[\frac{\partial\varphi}{\partial x}\right]^2+U(\varphi) . \tag{5.15}$$

By the use of (5.6) and (5.8) one obtains

$$\mathcal{H}(\varphi)=\left[\frac{\partial\varphi}{\partial x}\right]^2=\frac{A^4}{A^2-B^2}\frac{1}{\cosh^4(Ax)} \tag{5.16}$$

which is localized around $x=0$ with a spatial width characterized by $\Delta=1/(\sqrt{2}A)$ (Fig. 3). For the moving kink the width is Lorentz contracted as for a classical particle

$$\Delta_v=\sqrt{1-v^2}/(\sqrt{2}A) . \tag{5.17}$$

The total static energy defines the classical rest mass of the kink

$$M=\int_{-\infty}^{\infty}dx\left[\frac{d\varphi}{dx}\right]^2=\frac{4}{3}\frac{A^3}{A^2-B^2}$$
$$=\frac{2}{3}\frac{(\rho_K+r_K)^3}{(\rho_K-r_K)^2} , \tag{5.18}$$

which for a moving kink is divided by a factor of $\sqrt{1-v^2}$.

In the present model of one scalar field the theorem by Derrick [29] states that one can obtain classically stable, time-independent solutions only in one dimension. Such a solitary nondissipative wave resembles very closely an extended classical particle (of nonzero size) and is termed a soliton. In this particular case that of + sign is termed a kink (soliton) and that of a − sign an antikink (antisoliton).

VI. INSTABILITY TRIGGERS GROWTH SIGNALING

Finiteness of the energy (5.18) ensures the existence of the limits [13]

$$\lim_{x\to\pm\infty}\varphi(x,t)\equiv\varphi(\pm\infty,t)=\pm\frac{A}{\sqrt{A^2-B^2}} \tag{6.1}$$

and that these two must be zeros of the potential (5.2). From this follows the interesting conservation law

$$\partial_0\varphi(\pm\infty,t)=0 , \tag{6.2}$$

which is not a consequence of symmetry, as is usually the case, but a result of a topological property of the space of solutions. The kink is therefore termed a topological soliton. This becomes more obvious in matter physics, where it is also termed a domain wall [7], since its passage changes the conformational (physical) character of the system. If the two limits are equal, it is termed a nontopological soliton since its passage through the system does not leave behind any conformational change.

As is well known there exists a corresponding conserved vector current

$$J^\mu=\sum_{\nu=0}^{1}\epsilon^{\mu\nu}\partial_\nu\varphi , \tag{6.3}$$

where $\epsilon_{\mu\nu}$ is the antisymmetric tensor

$$\epsilon_{\mu\nu}=\begin{bmatrix}0 & 1\\ -1 & 0\end{bmatrix} . \tag{6.4}$$

Although the current (6.3) is trivially conserved,

$$\sum_{\mu=0}^{1}\partial^\mu J_\mu=0 , \tag{6.5}$$

it has a nonzero charge, which is termed the topological quantum number

$$\int_{-\infty}^{\infty}dx\,J^0(x,t)=\int_{-\infty}^{\infty}dx\,\partial_1\varphi=\varphi(+\infty,t)-\varphi(-\infty,t)$$
$$=\frac{2A}{\sqrt{A^2-B^2}} . \tag{6.6}$$

It can be proven that the existence of such a nonzero charge ensures stability of the corresponding solution [13]. The use of (3.6) for $K>0$ yields

$$\frac{2A}{\sqrt{A^2-B^2}}=2\frac{\rho_K+r_K}{\rho_K-r_K} \tag{6.7}$$

which diverges for $r_K=\rho_K$ and thereby violates the stability of the solution. Such a solution does not exist in reality since it would require infinite energy (5.18) and hence the kink would dissipate.

T cells activated by antigen primarily produce IL-2 but very few receptors, IL-2R. In order to surpass the G_1 threshold the kink must then acquire sufficient but finite energy (5.18), i.e., the coupling constant in the model (5.2)

$$\sqrt{A^2-B^2}=\tfrac{1}{2}(\rho_K-r_K) \tag{6.8}$$

must become sufficiently small but remain nonzero.

Hence r_K must come close enough to ρ_K, which further explains the requirement for a sustained stimulation by antigen, to start the cell cycle progression. Correspondingly, the kink amplitude (6.1) becomes large enough to make proliferation a predominant phenomenon in the T-cell population.

As concluded from experiments [10] a definite number of receptor occupations N_0 must occur before the cell acquires sufficient energy to take the irrevocable decision to replicate DNA. Moreover in this weak-coupling theory the elicited scalar quanta can be considered as loosely bound. As will be indicated in the next section the theory describes scalar particles with rest mass $2A$. Hence with N_c coherent cells in the population the total kink energy is given approximately by

$$\frac{4}{3}\frac{A^3}{A^2-B^2}=2AN_0N_C\equiv 2AN \ , \tag{6.9}$$

which for a coherent expansion relates the topological quantum number (6.6) to the total number N of receptor occupations

$$\frac{2A}{\sqrt{A^2-B^2}}=\sqrt{6N} \ . \tag{6.10}$$

By means of (3.6), the kink amplitude in (5.8) is given by

$$\frac{A}{\sqrt{A^2-B^2}}=\frac{\rho_K+r_K}{\rho_K-r_K}=\sqrt{3N/2} \ . \tag{6.11}$$

Thus according to (5.14b) for $N_c=1$ one finds that $\varphi_f<\varphi_{N_0}$. Hence removal of IL-2 at $\varphi\leq\varphi_f$ does imply premature abortion since in that case the cell would return to the quiescent state in absence of antigen, due to internalization and catalysis of receptors.

In the presence of IL-2 (and in real life, of antigen also) the system chooses one of the two possible minima (5.5) as the ground state, with absolute value φ_N, and undergoes spontaneous symmetry breakdown. Irrevocability of growth-signal transduction can now be attributed to the ambivalent interaction governed by the potential (5.2). For a single cell the force (5.3) changes sign at a value equal to the kink amplitude (6.11). In the presence of IL-2 for less than or equal to N_0 receptor occupations, all quanta are mutually attracted by a "long-range" force and subjected to a type of Bose condensation. This long-range attraction can then promote clustering (Fig. 1) and different forms of receptor aggregation, provided there is little or no repulsion or internalization of isolated occupied receptors. It may also be partly responsible for internalization as such.

One extra receptor occupation, above the critical value, makes the interaction repulsive and turns the condensate and the extra quantum into a scattering state. Hence the localized object of N_0 accumulated quanta, i.e., the condensate, is thereby irrevocably repelled by the next and subsequent potential receptor occupations. The launching of the growth-signal kink into the cell could thus be viewed as a result of an extracellular pressure exerted by excess IL-2.

VII. GROWTH SIGNAL AND DOSE-RESPONSE CURVE

In a perturbative approach to this type of symmetric models, where the static solutions (5.5) minimize the potential, the field is shifted to one of these minima. The idea is to extract the major part of the solution, inversely proportional to the small coupling constant (6.8), and then calculate the small next-order correction in the displaced field theory with broken symmetry before comparison with physical data.

The φ space is here shifted to the left minimum of the potential (Fig. 2),

$$\varphi=-\frac{A}{\sqrt{A^2-B^2}}+\phi \ , \tag{7.1}$$

which, if the classical kink solution (5.8) is present, does not extract the entire major part but makes the kink nonnegative for all x values. The correspondingly displaced potential (Fig. 4) with broken symmetry is given by

$$U(\phi)=\frac{A^2-B^2}{2}\phi^2\left[\phi-\frac{2A}{\sqrt{A^2-B^2}}\right]^2 \tag{7.2}$$

which reveals that the rest mass of the elementary scalar particle is $2A$. The corresponding boosted solution reads as

$$\phi\left[\frac{x-vt}{\sqrt{1-v^2}}\right]=\frac{A}{\sqrt{A^2-B^2}}\left[1\pm\tanh\left[A\frac{x-vt}{\sqrt{1-v^2}}\right]\right] \tag{7.3}$$

and the displaced force now changes sign at $\phi_N=0$ and $\phi_N=2A/\sqrt{A^2-B^2}$. For a single cell the latter value is related to $N=N_0$ through (6.10). Hence the kink, which interpolates between these two points, is now positive definite and can be interpreted as a probability amplitude.

Observed from a point on the T-cell membrane ($x=0$), the launched solitary wave is identified as the antikink ($-$ sign) part of (7.3). Combining (3.7), (5.10), and (7.3) for $K>0$, the growth signal is given by

$$\phi(\rho)=\frac{\rho_K+r_K}{\rho_K-r_K}\left\{1+\tanh\left[\frac{1}{2}\ln\left[C\frac{\rho}{r}+\delta\right]\right]\right\} \ , \tag{7.4}$$

where the r_K/ρ_K dependence in (3.7) is canceled by the constant term of (5.7) at $\varphi_0=1$. The constant C is a crude modification of the density r of spare (unoccupied) receptors due to synthesis and internalization. The shift δ compensates for competition from agonists not considered here. The corresponding translation mode is also due to perturbations from potential extra receptor occupations, a degeneracy which is removed by matching δ to experimental data. Perturbations will be considered in a forthcoming study.

Somewhat unexpectedly, the formula obtained predicts a constant tangential slope factor $\frac{1}{2}$, independent of the association constant k (3.7). This intrinsic property of the model is obtained by means of the duality relation (5.11), which links the solution of the simple rate equation (3.1) to that of the generalized rate equation (4.4). Duality thereby relates the low-density amplitude to that

of a high density of occupied receptors, which is clearly exhibited here thanks to integrability.

It is further noted that instead of $\ln\rho$, as expected from experimental growth data, the signal depends on $\ln(\rho/r)$, where r is the density of spare receptors. Since the occurrence of such spare receptors depends on the synthesis and dissociation of receptors, the density r must stationarize at some low nonzero value. Henceforth it is thus assumed that r attends one and the same lowest possible limit $r=r_{\min}>0$ for iterated experiments with aliquot samples of cells expanded at successively increased IL-2 concentrations. Interpreting the growth-signal (7.4) as a probability amplitude, the dose-response curve is then obtained as ϕ^2 times a factor C_N,

$$D(\rho)=C_N\left[\frac{\rho_K+r_K}{\rho_K-r_K}\right]^2\left\{1+\tanh\left[\frac{1}{2}\ln\left[C\frac{\rho}{r_{\min}}+\delta\right]\right]\right\}^2, \tag{7.5}$$

which permits a direct interpretation in counts per minute. This is required because cell proliferation is assessed as an activity due to tritiated thymidin [^{3}H] TdR incorporation. For a coherent cell expansion, the form of the amplitude of (7.5) remains the same also for $N_C\neq 1$ which follows from (6.11). The form (7.5) proves to match data on cell expansion better than corresponding trials with an unsquared amplitude (7.4) do. Moreover this makes the dose-response curve (7.5) linearly proportional to N (6.11), which is in fact the observed rate of incorporation of tritiated thymidin.

VIII. CONTRIBUTIONS FROM TWO KINDS OF RECEPTORS

The dose-response curve obtained is valid for cells expressing only one type of receptor with one and the same affinity, such as the leukemic cell line MLA-144 from a gibbon ape [17]. If two receptor systems with densities r_1 and r_2, of different affinities $K_1=k_1'/k_1$ and $K_2=k_2'/k_2$ ($K_2>K_1$), are expressed on the same T-cell membrane, and both contribute to the growth signal, mutual interaction will render dynamics more complex. However, in a phenomenological description, if affinity conversion effects are neglected by assuming fully preformed receptor systems, the rate equations of the two corresponding densities ψ_1 and ψ_2 of occupied receptors,

$$\frac{\partial\psi_1}{\partial_t}=k_1\rho r_1-k_1'\psi_1\,, \tag{8.1a}$$

$$\frac{\partial\psi_2}{\partial t}=k_2\rho r_2-k_2'\psi_2\,, \tag{8.1b}$$

are coupled only by the initial boundary conditions

$$r_1+\psi_1=r_{10}\,, \tag{8.2a}$$

$$r_2+\psi_2=r_{20}\,, \tag{8.2b}$$

$$\rho+\psi_1+\psi_2=\rho_0\,. \tag{8.2c}$$

It is known from experiments that the intermediate-affinity receptors need a higher IL-2 concentration to promote growth-signal transduction, compared to the receptor system of high affinity. Hence in this case the dose-response curve will contain two corresponding kinks separated by a stationary region. Under these conditions the event for each receptor system can be separately solved, but for different boundary conditions. Thus for ($i,j=1,2$; $i\neq j$) the equations of motion for the two decoupled systems are given by

$$\frac{\partial\psi_i}{\partial t}=k_i\rho r_i-k_i'\psi_i\,, \tag{8.3}$$

$$\rho+\psi_i=\rho_{i0}=\rho_0-\psi_{cj}\,, \tag{8.4}$$

where ψ_{cj} is an approximately constant contribution from the alternate stationary receptor system. The two separate kink solutions are then readily given by

$$\phi_i(\rho)=\frac{\rho_{iK}+r_{iK}}{\rho_{iK}-r_{iK}}\left\{1+\tanh\left[\frac{1}{2}e_i\ln\left[C_i\frac{\rho}{r_i}+\delta_i\right]\right]\right\}, \tag{8.5}$$

where the dynamical densities are defined according to (3.6)

$$\rho_{iK}=A_i+\sqrt{A_i^2-B_i^2}\,, \tag{8.6a}$$

$$r_{iK}=A_i-\sqrt{A_i^2-B_i^2}\,. \tag{8.6b}$$

The constants A_i and B_i are, as in (3.4), defined by

$$A_i=\tfrac{1}{2}(\rho_{i0}+r_{i0}+K_i)\,, \tag{8.7a}$$

$$B_i=\sqrt{\rho_{i0}r_{i0}}\,,\quad K_i=k_i'/k_i\,. \tag{8.7b}$$

In the present case with two kinks, the exact slope factor of $\frac{1}{2}$ is replaced by

$$\frac{1}{2}\to\frac{1}{2}\frac{A_i}{\sqrt{A_i^2-B_i^2}}\frac{v_i}{\sqrt{1-v_i^2}}\frac{1}{k_i}\equiv\frac{1}{2}e_i\,. \tag{8.8}$$

According to (5.10) the association constants k_i correspond to the velocities of two noninteracting, hence ψ_{cj} independent monoreceptor systems.

$$k_i=\frac{A_{0i}}{\sqrt{A_{0i}^2-B_{0i}^2}}\frac{v_{0i}}{\sqrt{1-v_{0i}^2}}\,. \tag{8.9}$$

By using (8.8), (8.9), momentum conservation

$$\frac{M_iv_i}{\sqrt{1-v_i^2}}=\frac{M_{0i}v_{0i}}{\sqrt{1-v_{0i}^2}}\,, \tag{8.10}$$

and the kink rest mass formula (5.18), the form factors e_i can be written in the more explicit form

$$e_i=\frac{M_{0i}}{M_i}\frac{A_i}{A_{0i}}\frac{\sqrt{A_{0i}^2-B_{0i}^2}}{\sqrt{A_i^2-B_i^2}}$$

$$=\frac{A_{0i}^2}{A_i^2}\frac{\sqrt{A_i^2-B_i^2}}{\sqrt{A_{0i}^2-B_{0i}^2}}\,, \tag{8.11}$$

where A_{0i}, A_i, B_{0i}, and B_i are defined by (8.7) and

$$A_{0i}=\tfrac{1}{2}(\rho_0+r_{i0}+K_i)\ , \tag{8.12a}$$

$$B_{0i}=\sqrt{\rho_0 r_{i0}}\ ,\quad K_i=k_i'/k_i\ . \tag{8.12b}$$

The dose-response curve from the two different receptor systems is then defined by the sum of the two contributions,

$$D_2(\rho)=C_N\left[\left[\frac{\rho_{1K}+r_{1K}}{\rho_{1K}-r_{1K}}\right]^2\left\{1+\tanh\left[\frac{1}{2}e_1\ln\left[C_1\frac{\rho}{r_{1\min}}+\delta_1\right]\right]\right\}^2 + \left[\frac{\rho_{2K}+r_{2K}}{\rho_{2K}-r_{2K}}\right]^2\left\{1+\tanh\left[\frac{1}{2}e_2\ln\left[C_2\frac{\rho}{r_{2\min}}+\delta_2\right]\right]\right\}^2\right]\ . \tag{8.13}$$

A comparison with available data tends to support this form compared to that obtained by summation before squaring. Moreover the form of (8.13) is motivated by the fact that the two receptor systems are different.

In this case C_1 and C_2, apart from competition, synthesis and internalization, also compensate to some extent for affinity conversion effects. It should be recalled, however, that no attachments of IL-2 to $p55$ alone are counted before binding to $p75$, since occupied $p55$ chains alone do not contribute to the growth signal.

IX. PHENOMENOLOGY

The threshold effect, as observed by Smith [10], that an order of 10 000 receptor occupations must occur to trigger growth signaling is clearly exhibited only by a coherent proliferation of T cells. Experimental data from Gillis *et al.* [14], Smith [17], Robb, Munck, and Smith [15], and Wang and Smith [16] show these characteristics and match very well the dose-response curves, (7.5) and (8.13), of the proposed model. A coherent expansion of T cells is accomplished by 3-day activation by antigen at 4 °C in the presence of glucocorticoids, i.e., dexamethasone (DEX), prior to a 3-day culture at 37 °C in exogenously supplied IL-2 at different fixed concentrations. Glucocorticoids thereby regulate cell growth by suppressing endogenous IL-2 production [17].

The simplest case studied is the cell line MLA-144 from a gibbon ape suffering from a spontaneous lymphoma. As pointed out by Tsudo *et al.* [21], this cell line expresses solely $p75$ chains, with an order of about 6800 such binding sites per cell. The corresponding kinetic affinity constant, $K_d=1.0\pm0.5$ nM, was assessed by Smith [30]. The presence of fluctuations in proliferation data (Fig. 4) below and about 10^2 nM enforces a higher start concentration in order to fully saturate the dose-response curve. As will be shown, this also follows from the fact that r_0 approaches ρ_0 from below, hence $r_0<\rho_0$.

In order to relate the volume density of IL-2 to the surface density of receptors, one now considers the spatial extension of the cell. The rate equation is assumed to apply within an extracellular hemisphere of radius $L/2$ and volume $V=(L/2)^3(2\pi/3)$ around each separate receptor. Thus abut 6800 such hemispheres cover the MLA-144 surface, except for a fraction $(L^2-\pi L^2/4)/L^2=0.215\%$ of the cell surface which is located between the hemispheres. With a cell surface of 5×10^{-6} cm^2, the average separation of the 6800 receptors is thus about $L=(5\times0.785/68)^{1/2}\times10^{-4}$. This corresponds to a density $r_0=1/V=275.59\times10^{12}$ receptors/ml, which equals $r_0=457.55$ nM. (Decimals are given here to the extent known.)

The model predicts a dose-response curve (7.5) with an exact tangential slope factor of $\frac{1}{2}$, which for an anticipated saturation at $\rho_0=500$ nM and constants $C_N=0.099$, $r_{\min}/C=0.024$, and $\delta=0$ matches experimental data (Fig. 5) obtained by Smith [17] excellently.

If the cell volume increases to the double before growth signaling, then the cell area and thereby L increases such that also the hemisphere volume V doubles and hence the value of $r_0=1/V$ is halved. Obviously this scaling law also applies to the density of spare receptors r

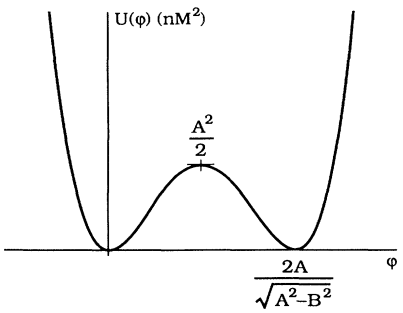

FIG. 4. The asymmetric (displaced) quartic potential.

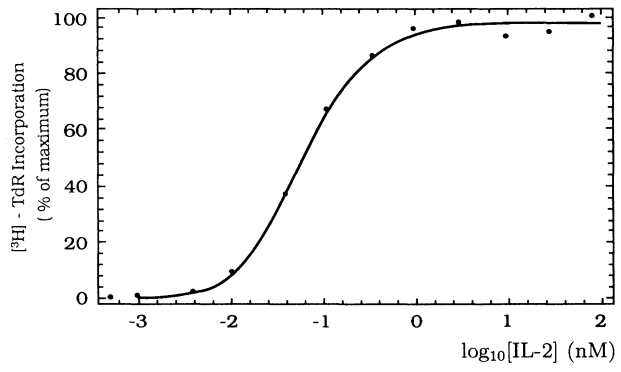

FIG. 5. Dose-response curve of the proposed model (solid line) compared with proliferation data of the cell line MLA-144 (dots) from a gibbon ape suffering from a spontaneous lymphoma. (Data from Smith [17] with permission.)

in (7.4) and (7.5). With $r_0=457.55/2=228.78$ one can then choose the saturation level at 300 nM and again obtain an excellent fit. The uncertainty surrounding these parameter values, in particular that of ρ_0, here partly compensated for by the choice of C_N, can be resolved by collecting data of higher resolution. As will be understood from the following example, one can also use more exactly assessed numbers of the different receptors as input in the search for a more consistent set of values.

Normal human T cells thus express three different peptide chains, α, β, and γ, which can fuse to several different IL-2 receptors. By performing binding studies on human leukemic T-cell lines, which express only $p75$ or $p55$ chains, and comparing these results with studies from cells expressing both these chains, Wang and Smith [16] assessed the corresponding kinetic and equilibrium affinity constants. The kinetic intermediate-affinity constant $K=2.5/3.8=0.7$ nM was assessed on YT cells from a child with acute lymphoblastic leukemia, the cell line that expresses solely $p75$ (β) chains. This result was then compared with results of studies where YT cells were induced to also express $p55(\alpha)$ chains, by the use of adult T leukemia (ATL) cell lines, The kinetic high-affinity constant assessed in this model was $K=(2.3/3.1)\times10^{-2}=0.7\times10^{-2}$ nM. A similar result could also be obtained by transfection of the gene coding for the $p75$ chain into a Jurkat transformed clone, which expresses $p55$ chains [31] only. The corresponding kinetic low-affinity constant, $(4.0/1.4)\times10=29$ nM, was assessed on the latter type of cell line [16].

Apparently the γ chain has been present throughout the years of these assessments and is therefore not assumed to essentially change the observed values of the constants. However, its presence is still assumed to have an impact on the relative strength of affinity of a receptor compared to that without a γ. Obviously, it can also give rise to a number of alternative receptor conformations.

Caligiuri *et al.* [32] have shown that upon CD3 activation a majority of all $p75$ chains on normal human peripheral blood monocytes (PBMC) bind noncovalently to excess $p55$ chains and form about 1099 ± 135 high-affinity IL-2 receptors. (The CD3 molecule helps to transmit the activation signal by antigen recognition of the T-cell receptor.) This is concluded from the fact that there is no statistical difference with respect to the number of intermediate-affinity receptors, 1452 ± 373, detected in the presence of anti-$p55$ antibodies (mAb), which indicates a total number of about 1500 IL-2 receptors. This could be compared to anti-CD3 activated T cells with 2100 detected intermediate-affinity receptors in the presence of anti-$p55$ mAb and 1900 detectable high-affinity receptors in the absence of the same mAb, as observed by Wang and Smith [16]. It is shown that removal of IL-2 after 3 h abrogates any G_1 progression if the number of high-affinity receptors is less than or equal to 1500 per cell. Only after 5 h exposure is this number of receptors adequate for some cells to enter the S phase [10]. Henceforth it is therefore assumed that there is a total of around 2100 IL-2 receptors per T cell.

In the equilibrium model, Goldstein *et al.* [26] show that only 95% of the $p75$ chains form heterodimers (trimers with γchains), whereas the above data, from Caligiuri *et al.* [32] are not inconsistent with the order of 32% unbound $p75$ chains, if γ chains are not considered. The physical situation, however, is not one of equilibrium and therefore more than 5%, and up to an order of 32%, intermediate-affinity IL-2 receptors may be expected. Moreover, it is recalled that modifications due to affinity conversion are not completely excluded.

As before, it is assumed here that the rate equation applies within an extracellular hemisphere of volume $V=(L/2)^3 2\pi/3$ cm^3 located around each receptor, where $L=[5\times0.785/21]^{1/2}\times10^{-4}$ cm denotes the estimated average distance between any two of the 2100 receptors on the cell surface $A=5\times10^{-6}$ cm^2. This corresponds to a density of $r_0=1/V=47.296\times10^{12}$ receptors/ml which is $r_0=78.525$ nM.

The dose-response curve (8.13) of the model proposed is consistent with data on normal human T cells for the order of 10% intermediate-affinity receptors if $\delta_1=\delta_2=0$, and a corresponding form factor $e_2=2.11$ for the second kink (Fig. 6). This form factor is multiplied by the bare tangential slope factor of $\frac{1}{2}$ (8.8), in good agreement with dose-response data obtained by Wang and Smith [16]. It should be remarked that the existence of an interpolating field value, $\psi_1=81.94$, is crucial in the sense that it should correspond to suitable values for both the form factor e_2 and the amplitude of the second kink. Obviously, this result also depends on the choice of ρ_0 and the degree of accuracy of r_0, K, and C_N for both kinks.

A more conclusive approach therefore requires better assessed numbers of receptors with particular emphasis on the number of signal contributors of intermediate affinity. Further information on the role of natural killer (NK) cells in this respect and on the impact of γ chains on different affinities is also required. The numbers thus obtained can then be used as input in trials, to examine the dependence on a nonpointlike cell surface, internalization and synthesis of receptors, affinity conversion, competion, temperature, pH, etc.

The choice of interpolating field value $\psi_2=48.76$ for the first kink of the curve appears to be less crucial, as it should only match the form factor $e_1=1.30$ of the first kink, whereas the size of the kink amplitude in this case

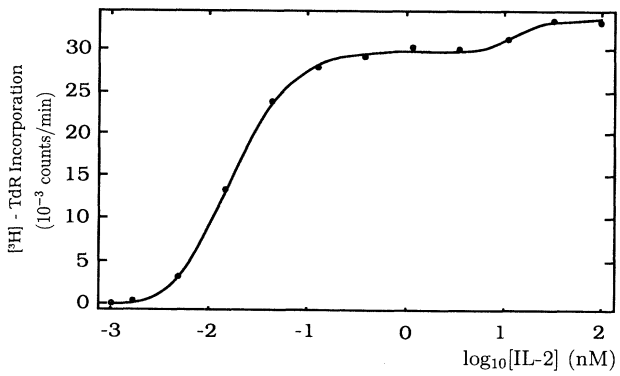

FIG. 6. Dose-response curve of the proposed model (solid line) compared with proliferation data of normal human anti-CD3 activated T cells (dots). (Data from Wang and Smith [16] with permission.)

is easily adjusted by the choice of C_N. It thus also accounts for a contribution from natural killer cells [32], which express high-affinity IL-2R constitutively and are therefore assumed to expand together with the first. The dose-response curve as a whole is in remarkable good agreement with experimental data for the choice $r_{1\min}/C_1 = 8.86 \times 10^{-3}$, $r_{2\min}/C_2 = 9.0$, and $C_N = 0.19$ (Fig. 6). The two ratios $r_{1\min}/C_1$ and $r_{2\min}/C_2$ express the shift of the second kink relative to the first. This is obviously related to the different affinities of the two receptor systems but is also due to a more complicated dynamics including internalization, synthesis, competition, and affinity conversion with all three chains involved.

The match is still good for 12% receptors of intermediate affinity, which gives a form factor $e_2 = 1.83$ for the second kink. For less than 10% intermediate-affinity receptors, and with the same restrictions, a corresponding increase in e_2 is observed. The larger the number of different receptors the smaller will be the corresponding form factor. For $\delta_1 = 0$, $\delta_2 = 0.5$, and $r_{2\min}/C_2 = 13.0$, the second kink becomes flatter and therefore requires a corresponding increase in the form factor, $e_2 = 2.56$, which is obtained for 8% receptors of intermediate affinity.

In a third example the proposed model (8.13) is confronted with dose-response data from human T cells in the presence of a monoclonal anti-Tac (anti-$p55$) mAb. The corresponding 3-day-growth data from Wang and Smith [16], include an end-point spectrum at 100-nM IL-2 which clearly deviates from the otherwise smoothly saturating curve. The corresponding 1-day data also contain fluctuations of the same order of magnitude at 10-nM IL-2, which, however, are already absent by the second day, except for the end-point jump which persists for all 3 days (Fig. 7). One could therefore assume that this deviation in the end-point spectrum, which from these data appears to be unsaturated, may also constitute a second kink due to isolated occupied $p75$ chains. The intermediate kinetic affinity of the bulk of receptors, $K_1 = 0.36$ nM, is assessed by Wang and Smith [16]. For the possible second kink the corresponding $p75$ chains, as for the YT cells, are assumed to exert an intermediate kinetic affinity $K_2 = 2.5/3.8$ nM. However, the shift in the dose-response curve is not only a result of different affinity, synthesis, internalization, and conversion effects, but is also due to competition with the anti-$p55$ mAb. As in the previous case the shift will also depend on the translation mode, which is left for a future study.

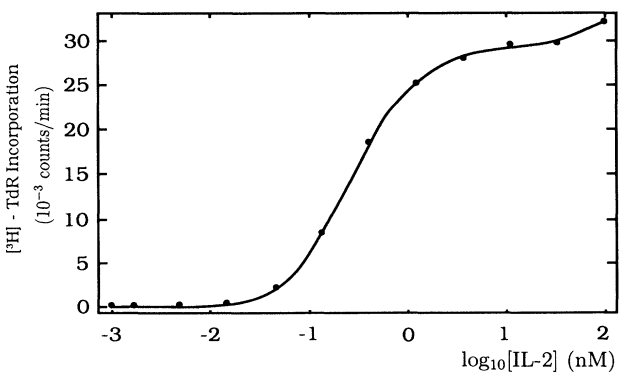

FIG. 7. Dose-response curve of the proposed model (solid line) compared with proliferation data of normal human anti-CD3 activated T cells (dots) in the presence of anti-Tac antibodies. (Data from Wang and Smith [16] with permission.)

In the present calculations, as in the preceding cases, suitable r/C ratios are therefore chosen here merely to locate and match the shifts, whereas the shape of the dose response curve, its bare tangential slope $\frac{1}{2}$ and the relative magnitude of the amplitudes are taken more seriously in the present study of the proposed model. For 10% different receptors of intermediate kinetic affinity $K_2 = 2.5/3.8$, $\delta_1 = \delta_2 = 0$, and a total number of 2100 receptors, one obtains a good match with $\psi_1 = 82.12$ and $\psi_2 = 45.04$. The corresponding form factor of the second kink is $e_2 = 2.11$ with the same rate of dependence on the number of different receptors as in the absence of anti-Tac mAb. The form factor of the first kink, $e_1 = 1.08$, shows little or no dependence on this type of variation. Correspondingly $r_{1\min}/C_1 = 0.12$, $r_{2\min}/C_2 = 40.0$, and $C_N = 0.16$ give an excellent match with the dose-response curve of normal human T cells in the presence of anti-Tac mAb (Fig. 7). For $\delta_1 = 0, \delta_2 = 0.5$ an increased form factor, $e_2 = 2.56$, is required for the second kink, which also here is obtained by 8% different receptors with intermediate kinetic affinity $K_2 = 2.5/3.8$. However, in this case, as in the previous ones, the result depends very little on the values of affinity constants, and one may therefore drop these parameters. Moreover it is not excluded that the extra kinks may also be due to other receptor conformations involving γ chains, pair aggregation, and higher-order cluster effects.

X. DISCUSSION

The usual rate equation is consistent with ligand-receptor binding at lower densities of occupied receptors, whereas its exponential high-density behavior (3.9) is not. It lacks the characteristic signs of dose-response curves for cell proliferation, such as a point of inflexion. This indicates the gap in our knowledge of how ligand-receptor interaction can elicit the intrinsic growth signal and the following DNA replication.

In the present report a model for growth-signal transduction in T cells is proposed. The model is based on an alternative approach to the duality concept, obtained by a rearrangement of the usual rate equation (4.1) which permits the introduction of a dual field (4.2). If equilibrium or soft interaction with the boundary regions is assumed, as in the lattice-gas model [28,33], one could obtain a duality relation that relates observables at low temperatures to their dual counterparts at high temperatures.

In the proposed model duality relates conditions at low densities of occupied receptors to those at high densities. It is of importance here since the actual phase transition, which is an essential event of the immune response, occurs approximately at one and the same physiological temperature of around 310 K. This does not exclude the possibility that a slight fever could stimulate the receptor

expression and thereby facilitate the immune response. However, the present model reveals that the major driving factor is IL-2 and not heat. The formation of a highly nonlinear interpolating domain wall, apart from a high consumption of energy, in this case elicited by IL-2, thereby also implies vast conformational changes in the receptor densities which also change through synthesis and internalization.

In contrast to the usual statistical-physics approach, equilibrium therefore could not be assumed, because the phase transition in this case is a collective phenomenon which involves drastic changes in the transition region. These changes, in terms of the constraints (3.2), are implemented in the generalized (dual) rate equation (4.4), which appears to be the equation of motion of a Lagrangian field theory of the Ginzburg-Landau (Goldstone) type. However, as previously emphasized, the proposed model is not of an *ad hoc* type, but is a microscopic theory, in the sense that the parameters A and B in (5.2) and the coupling constant (6.8) are known functions of the densities of IL-2 and IL-2R. The model, which has not previously been used in the context of hormone-receptor interaction, describes the intrinsic growth-signal dynamics and thereby also provides an elicitor mechanism.

The solution of the generalized rate equation is a topological kink soliton (7.4) with predicted bare tangential slope $\frac{1}{2}$, which agrees well with growth data from the cell line MLA-144 and normal human T cells, in and without the presence of anti-Tac mAb (Figs. 5–7). It is therefore concluded that the solution can be interpreted as the growth signal. What makes identification of the soliton in dose-response curves possible here is the use of the relation between the time and the IL-2 density (3.7) for low densities of occupied receptors, in combination with the dual rate equation (4.4). This relates the low-density behavior to that of high densities (7.4).

The model and its physical interpretation thereby also rest extensively on the observation by Smith [10] that the process is controlled only by the densities of agonist and receptors and the reaction time, and by the fact that a definite number of receptor occupations are required to irrevocably promote transition to the S phase of the cell cycle, with subsequent DNA replication and cell division. This cumulate number of receptor occupations is related to the topological quantum number of the proposed model. The mere existence of such a quantum number ensures stability of the growth signal [13], which is not only crucial for the event as such, but is also in compliance with the requirement for high fidelity of DNA replication. This indicates that Nature does not accept fractional messages.

In the idealized case, where dissipative forces are absent, such a localized nondissipative wave can travel unattenuated from its source throughout the cell to the recipient DNA system. This should follow, irrespective of the hierarchy of intervening carriers, whose dynamics is thereby implemented inclusively. Hence, the result obtained is that of an inclusive spectrum, exhibited as if all intervening subprocesses of importance were integrated.

Apart from a normalization factor in the overall amplitude, this appears to be the case here. The form of the experimentally observed dose-response curve does agree with that of the signal induced by the hormone-receptor system. However, it thus allows for a linear amplification by an extra "inflow" of metabolically created energy, triggered and controlled by the same signal. This could also balance a possible energy loss due to dissipative forces not included in the present model. Nor does this interpretation exclude possible dependencies on other gross variables such as start densities of $p55$, $p64$, and anti-$p55$ mAb; pH and temperature. However, if a dependence on the $p55$ density is included, one should recall that this parameter is augmented by IL-2 occupations of the high-affinity receptor [10]. In or without the presence of γ chains [24], conversion effects could also modify the results obtained.

As usual it is assumed that DNA melting is an inevitable precursor to transcription and replication of DNA. Hence the same signal, amplified by ATP or similar factors, must also have passed through and thereby temporarily melted (denaturated) the DNA duplex. Accordingly, it then also represented the interpolating domain wall between the state of intact DNA and that of melted and subsequently replicated DNA. The domain wall thus propagates a disruption of one long-range order and precedes the reestablishment of another long-range order, i.e., the replication of DNA. Hence the growth signal displays a phase transition of the DNA system, although many questions remain to be solved.

Similarly, prior to the signal transduction, the receptor system is subjected to a transition from a state of low or no order at low density $\psi < \psi_f$ to one of long-range order at high density $\psi > \psi_f$. Since it may create some confusion to speak here of long-range order of a cell with a pointlike surface, it should again be remembered that the surface of the real T cell is nonzero. However, unlike the (two-dimensional) Ising model for ferromagnets [28] at low temperatures $T < T_c$, where magnetization also persists for a vanishing external magnetic field, abortion of the actual process, by removal of IL-2 at a value $\varphi \leq \varphi_f$, would in this case return the T cell to its quiescent state, due to internalization and catalysis because $\varphi_f < \varphi_{N_0}$ according to (5.14b), (6.10), and (6.11).

Thus the growth signal is a collective excitation of many "long-range" ordered occupied-receptor quanta, which in an attractive "long-range" interaction are subjected to a type of Bose condensation. This ordering proceeds up to the definite number of receptor occupations, $N_0 = 10\,000$, after which the ambivalent interaction becomes repulsive. The growth signal, i.e., the quantized condensate, is thereby launched as a kink soliton by the next approaching IL-2 molecules, which makes the force repulsive. The topological quantization described appears to be Nature's perfectly controlled switch and filter, which screens out all fractional signals in life with energy below the threshold and releases the ones above. This "all or nothing" behavior digitalizes the information as ones and zeros.

Had one assumed equilibrium, as by derivation of Peierls instability [34], some of this information, such as

the indispensable nonlinear dependences on the densities of IL-2 and IL-2R, would have been lost. That would have made the identification of the growth signal impossible and the model would have been more of an *ad hoc* type.

Apart from the question of elicitor mechanism, a formally identical type of interaction model for the recipient DNA system was found by Krumhansl and Alexander [7] who observed that puckering of sugar in the DNA backbones (spines) couples to the base twist angle via the glycosidic torsion angle. Apart from an extra term due to the relative humidity, a formally identical type of Lagrangian for the DNA double helix was also obtained by Khan, Bhaumik, and Dutta-Roy [35], who argued heuristically for this type of model on the basis of the two right-handed A and B states of DNA.

As a function of time, the displacement field solution of these models, as well as that from the nonlinear Schrödinger model by Davydov [3], irrespective of the meaning of the different parameters involved, formally coincides with that of the proposed model. It is also noted that the partial time derivative of the proposed solution coincides with that of the Boussinesq equation, obtained by assuming that the DNA duplex is modeled as a homogeneous cylindrical rod with nonlinear elasticity [8]. A similar type of kink also appears in the sine-Gordon model [5,6].

Despite questions of the origin, and lifetime of the corresponding soliton solutions, these models are no doubt of great interest. However, as functions of time they are not easily compared with experiments.

The proposed model provides the missing launching mechanism for these long-range signals, thereby also the explicit dependence on the growth factor, which is necessary for the derivation of proliferation spectra.

From the model one can thus derive dose-response curves which are in striking agreement with experimental studies. The bare tangential slope factor $\frac{1}{2}$ obtained agrees well with typical dose-response curves for T cells from normal humans and a leukemic gibbon ape. The model also provides a possible explanation why no fractional growth signals are accepted and why a sustained antigen exposure is required to promote growth-signal transduction.

Unlike the previous models the one proposed here can only be obtained for a definite velocity given by (5.10). With $s_{0i} \neq 1$ reintroduced in (8.9) the two contributing receptor systems of different affinities thus provide an interesting relation between the receptor association constants k_i and the two corresponding velocities of sound s_i. One could speculate that this is then somehow linked to the two conformations of DNA of dry (A form) and wet (B form) fibers, respectively [36,37].

To obtain a stable solution in higher dimensions, to account for effects due to cell geometry, requires the introduction of more scalar fields [29] and of the electromagnetic gauge vector field, in order to eliminate unphysical Goldstone bosons [38]. Internalization and synthesis of receptors, affinity conversions involving $p55$ and $p64$ chains, anti-$p55$ mAb, pH, temperature, and, as in real life, the presence of foreign antigens are further potential correction factors.

It also remains to be shown whether the growth signal is conducted through the helical transmembrane $p75$ polypeptide chains by means of a Davydov type of mechanism [3], via internalization or something else. In relation to the above questions, a better understanding of the intermediating processes leading to DNA melting [39,40] and subsequent replication is also required.

A semiquantitative understanding of the DNA melting process by means of the Ising model has been available for more than 20 years [41], but in this case the energy source and intervening carriers, respectively, are apparently not heat. As a precursor to replication, disruption of the duplex appears to be a more controlled process than DNA melting by a type of random thermalization. However, thermal melting can no doubt reveal important information on DNA denaturation [42].

Further improved high-resolution data are required for the dose-response curves. In particular this is important near the end-point spectra, in order to better resolve details of the shifted second kink and possible fluctuations. One also needs to better assess the numbers of different receptors in cases where two or more different receptor systems contribute to the signal.

In studies of drug interaction with a cell system one normally expects a certain proportionality (linear response) between the concentration of the agonist and the effect. In the present model this is reversed such that the effect increases with a decrease in the coupling constant (6.8) of the interaction (5.2). This may serve to explain the effects of various humoral factors on differentiation and maturation of T cells and their precursors, thymocytes, in particular in immune-deficient states. Besides an increased release of interferons and IL-2 [43], it is observed that factors such as thymic peptides modulate the expression of CD3, CD4, CD8 antigens [43], and IL-2R [44,45]. Hence one may speculate that a direct or indirect stimulation of the expression of IL-2R makes the coupling constant (6.8) weaker, which may increase the immune capacity in contrast to the result of linear response models. The effect of thymic peptides on differentiation of prothymocytes to thymocytes is also linked to a transduction mechanism involving elevation of the intracellular levels of cyclic GMP and cyclic AMP [43,46,47]. These may well be indications of solitons.

The interpretations and the results obtained by Smith [10] taken seriously, as exemplified by the proposed model, apparently turn this type of immunological phenomena into basic nonlinear problems of theoretical physics. Similar techniques should also apply to related types of neuroendocrine ligand-receptor systems and cell function in a more general sense. After all, this should not come as a surprise, since these processes involve molecules, protons, and electrons which are subjected to collective excitation phenomena.

Apart from a more detailed knowledge of the growth signal and the immune response, it is hoped that this model will give relevant information about cell division in general. By means of a similar mechanism one may also learn about the maturation and development of self-tolerance of T cells [48,49] and thereby begin to under-

stand the dynamics of small networks of the immune system. As already outlined one can also gain further information on the observed differences between normal and leukemic cell lines, in children and adults and in animals, as well as uncontrolled and scarcely understood proliferation of other malignant cells. According to the form of IL-2R it could be anticipated that expansion of YT cells from a child with acute lymphoblastic leukemia is governed by the same rules as MLA-144.

Interesting information is also expected from further experiments on NK cells [32] and ATL cell lines by infection with HTLV-I [50], both of which appear to express IL-2R constitutively. Hence NK cells are able to express IL-2R without prior exposure to foreign antigens and could thus serve as model systems in comparison with normal human cell lines.

In order to understand intercalation of drugs with DNA [9], long-range effects of carcinogen binding to DNA, and the principles of activation of oncogenes, this type of nonlinear model appears to be of great interest. The possibility of long-range forces between different cells should also be considered within the proposed type of model interaction. As also highlighted by many authors, the T cell and its growth factor IL-2 as a model system in general is anticipated to go far beyond the scope of the immune defenses.

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[1] H. Fröhlich, Proc. R. Soc. London, Ser. A **215**, 291 (1952); Adv. Phys. **3**, 325 (1954).
[2] T. Holstein, Ann. Phys. (N.Y.) **8**, 325 (1959); **8**, 343 (1959).
[3] A. S. Davydov, J. Theor. Biol. **66**, 379 (1977).
[4] G. Careri, U. Buontempo, F. Galluzzi, A. C. Scott, E. Gratton, and E. Shyamsunder, Phys. Rev. B **30**, 4689 (1984).
[5] S. W. Englander, N. R. Kallenbach, A. J. Heeger, J. A. Krumhansl, and S. Litwin, Proc. Natl. Acad. Sci. USA **77**, 7222 (1980).
[6] S. Yomosa, Phys. Rev. A **27**, 2120 (1983).
[7] J. A. Krumhansl and W. M. Alexander, in *Structure and Dynamics: Nucleic Acids and Proteins,* edited by E. Clementi and R. H. Sarma (Adenine Press, New York, 1983), p. 61.
[8] V. Muto, J. Halding, P. L. Christiansen, and A. C. Scott, J. Biomol. Struct. Dyn. **5**, 873 (1988).
[9] H. M. Sobell, Proc. Natl. Acad. Sci. USA **82**, 5328 (1985).
[10] K. A. Smith, Annu, Rev. Cell. Biol. **5**, 397 (1989).
[11] J. Goldstone, Nuovo Cimento **19**, 154 (1961).
[12] V. L. Ginsburg and L. D. Landau, J. Exp. Theor. Phys. (USSR) **20**, 1064 (1950).
[13] S. Coleman, in *Aspects of Symmetry, Selected Erice Lectures* (Cambridge Univ. Press, Cambridge, 1985), p. 185.
[14] S. Gillis, M. M. Ferm, W. Ou, and K. A. Smith, J. Immunol. **120**, 2027 (1978).
[15] R. J. Robb, A. Munck, and K. A. Smith, J. Exp. Med. **154**, 1455 (1981).
[16] H.-M. Wang and K. A. Smith, J. Exp. Med. **166**, 1055 (1987).
[17] K. A. Smith, Immunobiology **161**, 157 (1982).
[18] S. Gillis, G. R. Crabtree, and K. A. Smith, J. Immunol. **123**, 1624 (1979).
[19] D. A. Cantrell and K. A. Smith, Science **224**, 1312 (1984).
[20] K. A. Smith and D. A. Cantrell, Proc. Natl. Acad. Sci. USA **82**, 864 (1985).
[21] M. Tsudo, R. W. Kozak, C. K. Goldman, and T. A. Waldmann, Proc. Natl. Acad. Sci. USA **83**, 9694 (1986).
[22] K. Teshigawara, H.-M. Wang, K. Kato, and K. A. Smith, J. Exp. Med. **165**, 223 (1987).
[23] R. J. Robb, C. M. Rusk, J. Yodoi, and W. C. Greene, Proc. Natl. Acad. Sci. USA **84**, 2002 (1987).
[24] T. Takeshita, H. Asao, K. Ohtani, N. Ishii, S. Kumaki, N. Tanaka, H. Munakata, M. Nakamura, and K. Sugamura, Science **257**, 379 (1992).
[25] Y. Saito, H. Sabe, N. Suzuki, S. Kondo, T. Ogura, A. Shimizu, and T. Honjo, J. Exp. Med. **168**, 1563 (1988).
[26] B. Goldstein, D. Jones, I. G. Kevrekidis, and A. S. Perelson, Int. Immunol. **4**, 23 (1992).
[27] R. Jackiw, Rev. Mod. Phys. **49**, 681 (1977).
[28] H. A. Kramers and G. H. Wannier, Phys. Rev. **60**, 252 (1941); **60**, 263 (1941).
[29] G. H. Derrick, J. Math. Phys. **5**, 1252 (1964).
[30] K. A. Smith (private communication).
[31] M. Hatakeymaa, M. Tsudo, S. Minamoto, T. Kono, T. Doi, T. Miyata, M. Miyasaka, and T. Taniguchi, Science **244**, 551 (1989).
[32] M. A. Caligiuri, A. Zmuidzinas, T. J. Manley, H. Levine, K. A. Smith, and J. Ritz, J. Exp. Med. **171**, 1509 (1990).
[33] L. Onsager, Phys. Rev. **65**, 117 (1944).
[34] R. Peierls, Proc. Cambridge Philos. Soc. **32**, 471 (1936); **32**, 477 (1936).
[35] A. Khan, D. Bhaumik, and B. Dutta-Roy, Bull. Math. Biol. **47**, 783 (1985).
[36] M. B. Hakim, S. M. Lindsay, and J. Powell, Biopolymers **23**, 1185 (1984).
[37] W. N. Mei, M. Kohli, E. W. Prohofsky, and L. L. van Zandt, Biopolymers **20**, 833 (1981).
[38] P. W. Higgs, Phys. Rev. Lett. **13**, 508 (1964).
[39] M. Peyrard and A. R. Bishop, Phys. Rev. Lett. **62**, 2755

(1989).
[40] M. Techera, L. L. Daemen, and E. W. Prohofsky, Phys. Rev. A **41**, 4543 (1990); **42**, 5033 (1990).
[41] R. M. Wartell and A. S. Benight, Phys. Rep. **126**, 67 (1985).
[42] J. F. Currie, J. A. Krumhansl, A. R. Bishop, and S. E. Trullinger, Phys. Rev. B **22**, 477 (1980).
[43] M. Dardenne and J. F. Bach, Prog. Clin. Biol. Res. **288**, 363 (1989).
[44] M. Sztein, S. A. Serrate, and A. L. Goldstein, Proc. Natl. Acad. Sci. USA **83**, 6107 (1986).
[45] W. Barcellini, P. L. Meroni, M. O. Borghi, D. Frasca, R. Perego, G. Doria, and C. Zanussi, Clin. Immunol. Immunopathol. **48**, 140 (1988).
[46] G. Goldstein, M. P. Sheid, E. A. Boyse, A. Brand, and D. G. Gilmour, in *Origins of Lymphocyte Diversity* (Cold Spring Harbor Symposia, New York, 1977), Vol. 41, p. 5.
[47] G. H. Sunshine, R. S. Basch, R. G. Coffey, K. W. Cohen, G. Goldstein, and J. W. Hadden, J. Immunol. **120**, 1594 (1978).
[48] P. Kisielow and H. von Boehmer, Sem. Immunol. **2**, 35 (1990).
[49] P. Marrack and J. Kappler, Sem. Immunol. **2**, 45 (1990).
[50] J. Yodoi, Y. Tagaya, and M. Maeda, in *Interleukin 2,* edited by K. A. Smith (Academic, San Diego, 1988), p. 197.