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Symmetry Breakdown is Inevitable in the Living Cell

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Abstract

The questions of growth signal firing dynamics, and the need for symmetry breakdown of the corresponding gross interaction, are solved here for T cell division in terms of a microscopic Ginsburg-Landau type model. A dose-response theory is derived directly from the nonstationary ligand-receptor interaction in the surface membrane boundary of the cell. The firing mechanism is thus explained as a stochastic switch of interaction from a condensating phase of attractive interaction to a scattering phase with repulsive forces. This change occurs for one extra receptor occupancy above the observed quantal number of receptor occupancies required for DNA replication. Contrary to many inanimate models of chemically stationary systems driven by temperature the interpolation between harmonic and displacive modes is here driven by the interaction of the two reactants. This concentration dependent alteration and switch of forces in the deterministic, linear and nonlinear parts of the interaction, which are direct consequences of the stochastic ligand-receptor process on the surface membrane, thus appear to be the prerequisites needed to understand the elementary life function of a cell that starts with the decision to replicate DNA. However, full compliance with all experimental evidences, also considering that each receptor occupancy should contribute an equal quantum of energy, could not be obtained until after a spontaneous symmetry breakdown of the lyotropic Ginsburg-Landau type theory. The phenomenon of life, apart from the important but computer program like DNA mapping, could thus be understood in terms of quantum fluctuations. The nonstationary response derived is in striking agreement with the experimental growth data of T cells. Also the EC50 value of the growth factor, contrary to the mass-action based Hill and Langmuir models and stationary state models such as the Ising model, is in stunning agreement with the value assessed. The slope of response, which contrary to that obtained in mass action models is a nontrivial result obtained only after summation over all orders ligand-receptor interaction, agrees almost exactly with the experimental value.

1. Introduction.

One of the most intriguing questions in biophysics, presumably closely related to the function and asymmetry of biomolecules, concerns the difference between living and inanimate condensed matter systems. For instance, it may be asked what makes the living cell different from a corresponding inanimate condensed system. One answer to this ill defined question would be that, contrary to many inanimate condensed matter systems, a living cell defines a chemically open system, however, depends on a rather constant temperature. Therefore the standard statistical and equilibrium considerations do not apply.

In fact the gross interaction that complies with the actual constraints and the overall division rate of a cell should also be the enveloping dynamics that complies with the function and asymmetry of all involved subsystems in the living cell. Recall the fact that a chemical laboratory synthesis always produces both right and left handed molecules whereas a natural production (like in a dividing cell) only yields molecules of a definite chirality state. Hence, it is likely that this natural dynamics, responsible for the chirality superselection principle, should integrate up to the same inclusive gross interaction that dictates the rate of cell cycle progression. As a matter of fact there is no other option available, although this does not automatically mean that we can give the ultimate answer to the important question of biomolecular asymmetry.

Therefore, instead of asking directly the question of asymmetry of biomolecules in three spatial dimension we will here demonstrate that breakdown of symmetry is inevitable already in the enveloping gross interaction. This modeling also exhibits a close relation between cooperativity in the molecular system and elementary life functions such as growth signal firing which is the start moment of DNA replication. (*Literature references related to the questions of asymmetry are given in the summary*).

The cell cycle of mitotic division includes a vast number of biochemical processes and morphological transitions and a description in physical terms is hence expected to be very complex. However, in studies on T cells, the main actors in the cellular immune defences, Smith et. al. [1] found that the proliferation rate (i. e. the response) depends on the concentrations of the growth factor (IL-2) and its

receptors (IL-2R) only. Hence, it could be assumed that all other variables are heavily damped and moving too fast to be observed at this level of experimental resolution. An example of such fast moving coordinates is the hard part, Q, of the exchanged momentum which must be absorbed by the blast cell in order to bind IL-2 to its receptor since the bound complex only allows for small momentum fluctuations, $q \approx 0$, to remain in a bound state.

According to Paton [2], contrary to the most common belief, this hard type prefiring interaction, which induces a number of sequentially expressed gene products [1], should result merely in the storage of a quantum of energy equal for all receptor occupations. Contributions to proliferation due to such induced gene products (other than IL-2), which are expected to yield cooperative effects, could be excluded by comparing the one-, two- and three-day data [3]. Consequently, in a first order approximation the remaining soft and slowly varying, almost nondissipative, interaction should govern the growth signal firing dynamics.

An observed minimal lag time of about five hours, between exposure to the growth factor and the first division events, was assumed by the experimentalists to indicate that the blast cell must first reach a definite quantal threshold number of receptor occupancies in order to take the irrevocable decision to fire the accumulated growth signal and replicate DNA [4]. Morover, this assumption is indicated by the fact that the initial number of vacant receptors must also first exceed a certain threshold value [1]. Obviously, such an observation could not be made precise due to possible experimental errors, however, only the exact quantal interpretation seems to comply with high fidelity in the DNA replication which does not admit fluctuations.

Practically all time variation in the cell cycle was found to reside solely in the G_1 phase, i. e., prior to the DNA replication (=S phase) the start moment of which defines the growth signal firing. The post signal firing part of the cell cycle normally proceeds at a rather constant time [1]. Therefore, the rate of cell division should be approximately equal to the rate of cells taking a decision to replicate DNA. Hence, post signal firing dynamics should not contribute to the response but merely transmit the growth signal, at least in a leading order approximation at the given experimental accuracy.

Although the actual data were extracted from a set of well constrained laboratory assessments employing synchronized startpopulations exposed to constant levels of a purified growth factor, and maintained at constant temperature, these results should be treated with all precautionary measures. However, in earlier experimental studies,

which have formed the basis for many theoretical models in current literature, cells were often expanded in serum and without a proper classification of receptors. Nevertheless, it seems embarrassing that essentially no adequatly working response theory for living systems, beyond the level of mass action type models such as the Hill [5] and Langmuir [6] equations, has been provided during the entire century [7]. However, without these recent experimental results it is somehow excused.

The derivation of Hill's equation starts out from the stationary state limit of the rate equation for binding of oxygen (O_2) to haemoglobin (Hb); $nO_2+(Hb)_n=(HbO_2)_n$:

$$\frac{\partial \psi}{\partial t} = k\rho^n r - k'\psi \qquad (1)$$

where ρ is the concentration (partial pressure) of oxygen, and r is the concentration of Hb. Hill thus obtained the binding equation

$$R(\rho) = R_{max}\frac{\rho^n}{K_d+\rho^n} \qquad (2)$$

where the response (R) is assumed to be linearly proportional to the fraction of Hb that has reacted (ψ) to the total density of receptors (r_0), $\psi/r_0=\psi/(r+\psi)$, and $K=k'/k$ denotes the dissociation/association constant. The Hill coefficient, n=number of binding sites per haemoglobin molecule, is thus associated with cooperativity and related to the slope of the obtained response curve.

However, as pointed out by Bevan and coworkers [8], the so obtained response with a ρ scale set by $K^{1/n}$, assessed by separate binding studies, is often displaced from the experimental ρ_{50} value by up to three orders of magnitude in the ligand concentration. They suggest that part of this mismatch could be explained by a variable affinity which could also be related to coupling proteins as explained by Mackay [9]. However, such effects cannot compensate for the neglected nonstationary conditions in mass-action models and the fact that response is induced long before the development of equilibrium or a stationary state.

Moreover, also the n=1 case involves cooperative effects without which the response would not be sigmoidal, although such a cooperativity is beyond the level of a nearest neighbour approximation. Therefore also the Ising type model fails to explain this mismatch since, in the limit of vanishing cooperativity, it yields the Langmuir isotherm which also scales in K [10].

It was also realized that the response need not always be linearly proportional to ψ/r_0 (see further references in [7]) and that the maximum could occur for less

than 100% occupancy. Contrary to (2), the response should also depend on the concentration of unoccupied (=spare) receptors, r, which may vary drastically from one system to another. The standard "pharmacological" recipe to cure these failures is to simply let the experimentally assessed parameter ρ_{50}^{n} replace K. Thus (2) becomes a logistic type equation which, according to Barlow and Blake [11], fits data better but lacks a molecular physical explanation.

A simplified but sufficiently comprehensive picture of the experimental development is given previously [3,12] (see further references in [1]). Taking advantage of these results a solution to the growth signal firing problem is provided and a dose-response curve at nonstationary boundary conditions is derived, both of which results comply with all actual observanda. In section 2 an alternative derivation [12] of the macroscopic binding rate of ligands to the entire cell is given. Section 3 explains the growth signal firing mechanism in terms of the so obtained alternating dynamics which changes sign exactly for one extra receptor occupancy at the quantal threshold defined by the observed definite number of receptor occupancies. In section 4 the results are summarized.

II. Rate of binding to the entire cell derived from a molecular level.

In order to better understand the nature of cooperative effects associated with the Hill coefficient n=1 the previously proposed model [3,12] is here limited to the monomeric (single valued) receptor system of the leukemic gibbon ape cell line MLA-144 [13] which is assumed to lack cooperative effects, the latter of which are usually associated with a Hill coefficient $n\neq1$.

Since the mean value definition of concentration breaks down, due to correlations at large numbers of vacant receptors, it appears useful to consider the ligand-receptor association and dissociation as a scattering process, and to interprete the concentration ψ of bound ligand-receptor complexes as a "forward scattering" amplitude where both constituents are at rest relative to each other in the center of mass system, i. e., that of the blast cell (Fig. 1). The justification for this is that a ligand-receptor collision in which the large part, Q, of an exchanged total momentum, Q+q, is not absorbed by the blast cell does not lead to a bound complex ψ but rather leads to a rescattering of the ligand. Consequently, each binding only allows for a small momentum exchange, $q\approx0$, between the two bound constituents. The typical wavelength of the associated soft quanta exchanged, $\lambda=2\pi/q$, is thus large compared to the cell which could, hence, be

treated as a pointlike particle ("localization").

The total probability φ of bound ligand-receptor complexes for an entire pointlike blast cell, although with unknown number of occupied receptors, is thus given by a Bethe-Salpeter type ladder expansion of factorizable probability amplitudes (Fig.2) summed to infinite order

$$\varphi = \sum_{n=0}^{\infty} \frac{1}{a^n}\psi^n = \frac{1}{1-\psi/a} \tag{3}$$

Truncation of the series (3) at a finite order would not guarantee the observed definite number of receptor occupations required for a transition to the S phase, because of the probability interpretation. Consequently, the time variation of (3) should yield the rate of receptor binding to the entire cell and, hence, also the growth signal solution.

Neglecting the spread, within a cell population, of the initial number of vacant receptors and the expression of new receptors, the uncorrelated binding of ligands to receptors at concentrations ρ and r, respectively, is given by the second order rate equation

$$\begin{aligned}\frac{\partial\psi}{\partial t} &= k\rho r - k'\psi = k[(a-\psi)^2-(a^2-b^2)] \\ &= k(1-\psi/a)^2[a^2-(a^2-b^2)/(1-\psi/a)^2]\end{aligned} \tag{4}$$

where the parameters $a=1/2(\rho_0+r_0+K)$ and $b=\sqrt{\rho_0\, r_0}$ are given by insertion of the initial constraints, $r+\psi = r_0$ and $\rho+\psi = \rho_0$.

Straightforward integration yields

$$\ln\left(\frac{\rho_K-\psi}{r_K-\psi}\frac{r_K}{\rho_K}\right) \equiv \ln\left(\frac{\rho'}{r'}\frac{r_K}{\rho_K}\right) = k(\rho_K-r_K)t = 2k\sqrt{a^2-b^2}\; t \tag{5}$$

where the dynamical variables, $\rho_K=a+\sqrt{a^2-b^2}$, $r_K=a-\sqrt{a^2-b^2}$, ρ' and r', play the role of renormalized concentrations such that $r'+\psi = r_K$, $\rho'+\psi = \rho_K$. Henceforth, no distinction will be made between primed and unprimed variables unless required.

Insertion of (3) into (4) gives the rate of ligand binding to the entire blast cell

$$\frac{\partial\varphi}{\partial t} = \frac{k}{a}[a^2-(a^2-b^2)\varphi^2] \tag{6}$$

which by integration yields

$$\varphi = \frac{a}{\sqrt{a^2-b^2}}\left(1+\tanh\left(k\sqrt{a^2-b^2}\; t\right)\right) \tag{7}$$

Combining (5) with (7) the probability for ligand binding to the entire blast cell is given

by the logistic type equation

$$\varphi = \frac{\rho_K+r_K}{\rho_K-r_K}\left[1+\tanh\left(\frac{1}{2}\ln\left(\frac{\rho}{\rho_{50}}\right)\right)\right] = 2\frac{\rho_K+r_K}{\rho_K-r_K}\frac{\rho/\rho_{50}}{1+\rho/\rho_{50}} \qquad (8)$$

where $\rho_{50}=r\rho_K/(Er_K)$ and E is an integration constant that could be related to efficacy. Contrary to (2), (8) does not enforce $\rho_{50}=K^{1/n}$, but rather expresses this entity in the initial reactant concentrations and the density of spare receptors.

At the observed definite number of receptor occupancies the probability density (8) should thus yield the dose-response curve (Fig.3):

$$R(\rho) = C_P\frac{N}{2}\left[1+\tanh\left(\frac{1}{2}\ln\left(\frac{\rho}{\rho_{S50}}\right)\right)\right] = C_PN\left(\frac{\rho/\rho_{S50}}{1+\rho/\rho_{S50}}\right) \qquad (9)$$

where $\rho_{S50}=r_S\rho_K/(Er_K)$, ρ_S and r_S are the stationarized values of ρ_{50}, ρ and r, respectively, and C_P is a constant proportional to the number of cells in the start population and C_PN is the maximal response. As expected (9) is thus proportional to the observed tritiated thymidine incorporation. Before proving that $(\rho_K+r_K)/(\rho_K-r_K)$ is proportional to N, the dose-response curve (9) is compared to assessed growth data.

Form and slope of the logistic type response (9) (Fig.3a), which now depends on the two reactant concentrations only, are in striking agreement with growth data (dots) of the cell line MLA-144 from a leukemic gibbon ape [13]. (Corrections due to expression of new receptors, expected in the upper parts of (7), (8) and (9) are discussed in section IV.) Despite the fact that the ligand-receptor reaction is not limited to the lowest order the derived growth signal (8) has a slope n=1. However, contrary to mass-action type theories, this is here a nontrivial result [3, 12] since it is obtained only after summation over all orders perturbation expansion (3).

Hence, slope and cooperativity are not directly related to the order of reaction as in mass-action based models (2). In equilibrium type models, cooperativity is associated with a harder, short-range, or contact type of interaction such as that related to affinity conversion, due to hetero- or homo oligomerization of monomeric chains, or induced conformational changes in the individual receptor proteins.

These data could not easily be explained by a mass-action based response curve (Fig. 3b), mainly because the assessed value of the dissociation constant, K=1.0±0.5 nM, displaces the response-curve by almost two orders of magnitude in the ligand concentration away from the experimental growth data. In the actual nonstationary approach these drawbacks are not interfering. All parameters of $\rho_{50}=r_s\rho_K/Er_K$ in (9) can now be given realistic values. One should recall, however, that both r and ρ should be

renormalized (primed) variables here.

III. Symmetry breakdown, quantal threshold and firing mechanism.

The explanation of the firing mechanism first requires some steps of theoretical formalisation. As demonstrated previously [3,12] the rate equation for binding to the entire blast cell (6) could be interpreted as a once integrated traveling wave equation:

$$\frac{1}{v}\frac{\partial\varphi}{\partial t}=\frac{\partial\varphi}{\partial x} = \pm\sqrt{2V(\varphi)} = \pm\frac{k}{va}[a^2-(a^2-b^2)\varphi^2] \qquad (10)$$

where x=vt is perpendicular to the cell membrane and the kink velocity v, given here in units of the association constant k, is a function f(a, b) of the initial concentrations through a and b. The spatial rate equation (10) could thus be generated by a nonlinear potential (Fig.4):

$$V(\varphi^2) = \frac{1}{2a^2f^2(a,b)}[a^2-(a^2-b^2)\varphi^2]^2 \qquad (11)$$

with f(a, b)=v(a, b)/k. The corresponding superconduction like wave equation

$$\Box\varphi \equiv \frac{\partial^2\varphi}{\partial t^2} - \frac{\partial^2\varphi}{\partial x^2} = -\frac{\partial V}{\partial\varphi} = F(\varphi) \qquad (12)$$

could also be associated with the dynamics of some periodic biological structure such as DNA molecules or helical receptor proteins. Equation (12) is thus the equation of motion of a Ginsburg-Landau (GL)type model in one time and one space (1+1) dimensions, with energy (Hamiltonian) density:

$$H(\varphi) = \frac{1}{2}\left(\frac{\partial\varphi}{\partial t}\right)^2+\frac{1}{2}\left(\frac{\partial\varphi}{\partial x}\right)^2 + V(\varphi) \qquad (13)$$

Due to dependences of the "mass" term a^2 and the nonlinear coupling constant $g^2=a^2-b^2$ of $V(\varphi)$ on the reactant concentrations the model (13) is a so called "microscopic" theory. This results directly from the implementation of the initial constraints which accounts for the nonstationary boundary conditions of the blast cell [3].

The displacive (anharmonic) part of this microscopic interaction is, hence, primarily driven by the two reactants (concentrations) rather than temperature variations. Accordingly, the obtained model is also a lyotropic type model rather than thermotropic. This appears to be a fundamental difference between living and inanimate condensed matter systems and should, hence, be an important prerequisite for the understanding of life phenomena at the lowest level of organization.

As always in nature, the system chooses one of the lowest energy states (Fig.4), for instance:

$$\varphi \rightarrow \frac{a}{\sqrt{a^2-b^2}}+\varphi = -\frac{\rho_K+r_K}{\rho_K-r_K}+\varphi \tag{14}$$

and thereby undergoes so called spontaneous symmetry breakdown since the reflection symmetry of $V(\varphi)$ (Fig. 4) is lost. The field displacement (14) also explains the constant term in (7) which makes the growth signal (8) positive definite.

With the correspondingly displaced potential (Fig.5),

$$V(\varphi) = \frac{(a^2-b^2)^2}{2f^2a^2}\,\varphi^2\left[\varphi-\frac{2a}{\sqrt{a^2-b^2}}\right]^2 \tag{15}$$

the equation of motion (12) reads

$$\Box\varphi = -\frac{\partial V}{\partial\varphi} = F(\varphi) \equiv -2\frac{(a^2-b^2)^2}{f^2a^2}\left(\varphi-\frac{a}{\sqrt{a^2-b^2}}\right)\left(\varphi-\frac{2a}{\sqrt{a^2-b^2}}\right)\varphi \tag{16}$$

where $F(\varphi)$ is the mutual (classical) force between occupied receptor quanta.

Equation (16) could also be written on the form

$$\left(\Box+4\frac{a^2-b^2}{f^2}\right)\varphi = 6\frac{a(a^2-b^2)\sqrt{a^2-b^2}}{f^2a^2}\,\varphi^2 - 2\frac{(a^2-b^2)^2}{f^2a^2}\,\varphi^3 \tag{17}$$

A comparison of (17) with the Klein-Gordon equation [14] shows that φ has now acquired a real and finite "rest-mass", $m=2\sqrt{a^2-b^2}/f(a,b)$, which could thus be associated with the energy triggered per receptor occupancy. According to Paton [2] this energy is equal for all receptor occupancies. For more than one rung in a ladder of definite order (Fig.2), however, the total energy elicited is not proportional to the number of rungs, because as stated previously, in a probabilistic interpretation each rung in the ladder expansion (3) need not always represent a receptor occupancy.

By insertion of the solitary wave solution of (10), the growth signal kink $\varphi(x)=a/\sqrt{a^2-b^2}\tanh(x\sqrt{a^2-b^2}/f(a,b))$ (Fig.6a), the energy density (13) becomes (Fig.6b)

$$\left(\frac{\partial\varphi}{\partial x}\right)^2 = \frac{a^2}{f^2}\,\frac{1}{\cosh^4\left(x\sqrt{a^2-b^2}/f\right)} \tag{18}$$

and the total static kink energy is given by

$$M = \int_{-\infty}^{\infty} \left(\frac{\partial \varphi}{\partial x}\right)^2 dx = \frac{4}{3} \frac{a^2}{\sqrt{a^2-b^2}\, f} \tag{19}$$

The integration is here extended approximately to the full x-space perpendicular to a flat surface membrane, which should anyhow be treated as pointlike. Namely, in this long wavelength limit only the number of occupancies is counted but not their sites as previously discussed. Accordingly, in the leading order approximation the two surface coordinates could be dropped.

Momentum conservation then yields

$$Mv = Nmv_r \tag{20}$$

where $v_r = ck$ is the mean velocity for a ligand-receptor association and c is a constant. Assuming further that

$$f(a,b) = \sqrt{a^2-b^2}/a = (\rho_K - r_K)/(\rho_K + r_K) \tag{21}$$

by the use of (20) and with $v = kf(a,b)$, the quantal occupancy number, N, becomes a function of the two reactant concentrations:

$$\frac{a}{\sqrt{a^2-b^2}} = \frac{\rho_K + r_K}{\rho_K - r_K} = cN/2 \tag{22}$$

where a factor 3 has been absorbed in an overall renormalization constant. This proves the amplitude of the response (9).

In order to reach the quantal threshold, N which is a topological quantum number [17], according to (22) the cell must first express an adequate number of vacant receptors, r_0 (related to r_K as shown previously). This explains the need for a prolonged antigen exposure before growth signal firing occurs [1]. Such a property could not easily be described in ad hoc type models because then the coupling and the rest-mass were not defined as functions of the ligand-receptor concentrations, but rather as temperature dependent coefficients.

In order to demonstrate the firing mechanism, by insertion of (22) in (8), it is first noted that the growth signal (8) interpolates between zero and $\varphi_N = cN$, the two minima of the displaced classical potential (15) (Fig.5), for zero and N receptor occupancies, respectively. The (classical) force in (16) which then reads as

$$F(\varphi) \equiv -1/2\ (\rho_K - r_K)^2 (\varphi - cN/2)(\varphi - cN)\varphi \tag{23}$$

vanishes for N receptor occupancies, at $\varphi = \varphi_N \equiv cN$. Thus the growth signal kink is a bound state of N loosely bound receptor quanta at negligible perturbations (e. g. small thermal fluctuations in the water like surrounding).

Adding a small time dependent excitations to the classical kink $\varphi_c(x)$ solution (the translation (14) has no impact on this part)

$$\varphi(x,t) = \varphi_C(x) + e^{i\omega_q t}\,\psi_q(x) \tag{24}$$

and keeping only linear terms a Schrödinger like equation is obtained

$$\left(-\frac{d^2}{dx^2}+V''(\varphi_C)\right) \equiv \left(-\frac{d^2}{dx^2}+4a^2-\frac{6a^2}{\cosh^2(ax)}\right)\psi_n(x) = \omega_n^2\,\psi_n(x) \tag{25}$$

This equation is exactly soluble [18] and has two discrete eigenmodes $\omega_n^2 = a^2n(4-n)$; n = 0,1 and a continuum starting at $4a^2$ (n≥2): $\omega_q^2 = 4a^2+q^2$.

Hence, for one extra receptor occupancy with energy $2a$ (at q=0), above the quantal threshold (22) the system switches into a scattering state. The growth signal kink (8), in the form of a bound state condensate of N occupied receptor quanta, is then repelled into the blast cell by the subsequent occupancies as advocated previously [3,12]. Growth signalling may thus be seen as a result of an extracellular pressure of the growth factor IL-2.

Comparing equation (24) with a linear expansion of the kink, $\varphi_c(x+\Delta x)\approx\varphi_c(x)+\Delta x d\varphi_c(x)/dx$, and observing that $d\varphi_c(x)/dx$ is proportional to ψ_0, the bound state at $\omega_0=0$ is recognized as a translation mode of the growth signal kink $\varphi_c(x)$, and $\omega_1^2=3a^2$ is a stable eigenvibration of the same bound state condensate.

IV. Summary and outlook.

A solution to the long standing problem of growth signal firing is obtained under assumption that all vacant receptors of the blast cell are expressed prior to the exposure to IL-2. The dose-response curve derived [3,12] that depends on the concentrations of the growth factor and its receptor only [1], agrees strikingly well with growth data from MLA-144 and the predicted slope, n=1, is almost exactly equal to that observed [13] (Fig. 3). **However, unlike the situation in equilibrium type models such as in the Hill equation, the slope is here a nontrivial result obtained only after summation of all orders ligand-receptor interaction** [3].

The response theory obtained, contrary to mass-action type models, does not enforce a scale in the ligand concentration set by K, but rather defines a scale ρ_{50} in terms of the initial reactant concentrations and the density of spare receptors which can now all be given realistic values. Unlike "inanimate" *ad hoc* type model

systems, which are usually driven by temperature variations and are in chemical equilibrium with the boundaries, the actual nonstationary, lyotropic type model of the living blast cell, which is a reflection symmetric, microscopic Ginsburg-Landau type theory, depends on a rather constant temperature. The interpolation between harmonic and displacive (anharmonic) interaction modes is here predominantly driven by the two reactants. The problem is that in such a model the "mass"-parameter is nonsensical since it is imaginary (mass squared is negative).

A lowest finite energy state, associated with the energy quantum stored per receptor occupation [2], **could be identified only after a spontaneous breakdown of the reflection symmetry of** [11].

Unlike the neuron firing model [16], which fires at a mean-field potential threshold, the model proposed fires at a definite quantal number (22) of receptor occupancies in compliance with the experimental observations [1]. **The microscopic model obtained** [3,12] **thus explains the growth signal firing mechanism in terms of a switch of interaction, for one receptor occupancy above the observed quantal number of receptor occupancies (22), from a condensating phase with attractive interaction to a scattering state with repulsive forces.** This might also provide a clue to understand the large range of variation of the coefficients in phenomenological models, observed by Frauenfelder *et al.* [17], and why inanimate condensed model systems, with temperature dependent coefficients and in chemical equilibrium, do not easily comply with living matter.

If one quantum (ligand-receptor complex) tries to escape it is immediately attracted back. Conversely, if one extra surface-bound receptor is occupied the growth signal condensate is repelled into the cell and so decouples from the background due to a vanishing force (23). Hence, the model not only yields a dynamics in approximate compliance with experimental observanda, it also explains an elementary life function: **The blast cell first collects the required pieces of information (receptor triggered quanta) and then self takes the decision to replicate its DNA and divide.**

It may thus be asked what makes the living blast cell different from a machine or the *ad hoc* version of the same model for inanimate matter [18] where the addition of one extra particle similarly turns the system into a scattering state? The discrepancy is that in the latter case, with chemical equilibrium and constant

coefficients, someone outside the system must take a decision to add one extra particle whereas in the microscopic model proposed the living blast cell itself collects the quanta of information (=receptor occupancies), so becomes "concious" and then decides on it's own to fire when it reaches the quantal threshold at which the interaction changes sign. **The alternation of the interaction between stochastic and deterministic dynamics, in combination with the concentration dependent switch from attraction to repulsion appear to be the two crucial prerequisites needed in order to understand the decision of the blast cell to start DNA replication.** Our model so also explains an elementary cell function crucial for life.

Despite the fact that we started out from an open system with a stochastic interaction, the growth signal condensate of N receptor induced quanta defines a closed system with a deterministic type post firing dynamics that proceeds at a rather constant time. Although expected to be very complex and to require a generalization to three spatial dimensions, such a post firing dynamics should thus yield a mere transmission of one and the same growth signal. From an immense number of degrees of freedom and taxonomic substructures [19], excited in the deep inelastic (=large Q) part of the ligand-receptor induced process which merely yields a stored quantum of energy equal for each receptor (2), the transmitted gross interaction should, hence, reduce approximately to the "Lorentz" invariant 1+1 dimensional type dynamics proposed (12), at least according to the observanda acquired at the actual level of experimental accuracy. The nonlinear premelton type DNA dynamics suggested by Krumhansl and Alexander [20] may examplify how part of such a reduction could occur, however, many questions are as of yet open.

The striking agreement of (9) with MLA-144 below 1 nM (Fig.3) could somehow be expected since the expression of new receptors should then be small compared to the initial ones 6.800 [13]. However, the almost perfect interpolation between the saturated three-day data at 1-100 nM (Fig.3) is puzzling. This could, nevertheless, be understood by observing first that the contribution from dissociation is small compared to internalization, hence, $k'\approx K\approx 0$, $\rho_K\approx\rho_0$ and $r_K\approx r_0$. The expression of new receptors then leads to a time dependent "initial" constraint $r(t)=r_0-\psi+\alpha t$, where the presence of a nonzero α merely results in the replacement of k by $(1+\alpha t/(r_0-\psi))k$.

A direct combination of (4) and (6) then shows that both the growth signal (8) and the dose-response (9) are approximately independent of this factor, thus admitting only minor corrections to the dynamics obtained (Fig. 3).

One experimental evidence which places severe constraints on the choice of theoretical model is the sensitivity of the system, with a growth signal firing already for one extra receptor occupancy, enforced by the high fidelity requirement in the reproduction process [1]. This is perhaps the strongest support for the type of model proposed and, moreover, since heavily damped variables should be enslaved under the two reactant concentrations only minor dissipative corrections are expected. Hence, a corresponding linear time derivative term, of dissipative corrections from the aqueous background phase, could be assumed to be negligible in a leading order approximation (12).

The reason for not expecting a diffusive type gross interaction (12), with a first order time derivative term and a corresponding Gaussian type solution such as employed in a Feynman path integral [21], is the lack of continuity relation, $\partial c/\partial t+\partial j/\partial x=0$, due to the reaction between hormones and receptors on the surface membrane of the living cell. This continuity relation, which anticipates conservation of particles (no reaction), inserted into Ficks first law of diffusion $j=-D\partial c/\partial x$, would otherwise have given Ficks second law of diffusion: $\partial c/\partial t=D\partial^2 c/\partial x^2$ [22]. Hence, D is the diffusion coefficient, c and j are the particle concentration and current density, respectively. In fact the growth signal derived (8) has the same form as the total probability for firing of an action potential in a neuron [16]. However, that firing mechanism with launch of the signal at a mean field potential threshold would not be sufficiently exact here where firing is observed for a definite quantal number of receptor occupancies. On the other hand the neuron firng model is integrated from a Gaussian probability density which is not applicable here.

As demonstrated previously [3,12] the model obtained is self-dual in the sense of Kramers and Wannier [23], however, instead of relating low and high temperature dynamics the repesent model is self-dual in a lyotropic sense as it relates dynamics at high and low concentrations of activated receptors. This selebrated involutory property of the model obtained, which complies with all empirical observanda, is a clear evidence that the biological response and function of a living cell is indeed a collective phenomena as already anticipated by Chela-Flores [24]. This lyotropic type theory also complies with the general aspects on organization as a function of bulk concentrations rather than temperature as exhibited at this meeting by Easwaran [25].

A full study of the fluctuations at 1-100 nM of the growth curve (Fig. 3) and, correspondingly, of the collective coordinate $\rho_{S50}=r_{SPK}/(E_{rK})$, thus requires a consideration of expression of vacant receptors, the spread in number of initial receptors and the dissipative corrections such as due to hydration. It also requires a generalization to three spatial dimensions which also requires the introduction of a gauge field, i. e., the electromagnetic field. Hopefully this will bring the theory proposed closer to a realistic cell model with respect to geometry, polarisation, chirality etc. However, much work is required until we know the answers of the questions raised by other contributors to this minisymposium, i. e. by Keszthelyi [26], such as the selection mechanism at work in natural synthesis and leading to production of molecules of a definite chirality state.

Finally I would like to thank the organizers for the invitation.

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Figure Captions

Fig. 1 The association-dissociation process exhibits two distinct cases; (a): scattering with a large unabsorbed momentum Q, and (b): formation of a bound complex ψ, where the large momentum is absorbed by the blast cell and the remaing part is small, $q \approx 0$.

Fig. 2 Ladder diagram of forward scattering amplitudes.

Fig. 3 (a) Dose-response curve predicted by the non stationary model (solid line) compared with proliferation data of the cell line MLA-144 (dots) from Gibbon ape suffering from a spontaneous lymphoma (Courtesy K.A.Smith). (b) Dose-response curve predicted by mass-action based model with an assessed dissociation constant $K=1.0\pm0.5$ nM.

Fig. 4 The symmetric double-well potential.

Fig. 5 The asymmetric double-well potential.

Fig. 6 (a) The symmetric kink-solution. (b) The corresponding energy density peak $H=a^2 \cosh^{-4}(x\sqrt{a^2-b^2}/f(a,b))/f^2(a,b)$ of width $\Delta=f(a,b))/\sqrt{a^2-b^2}$.

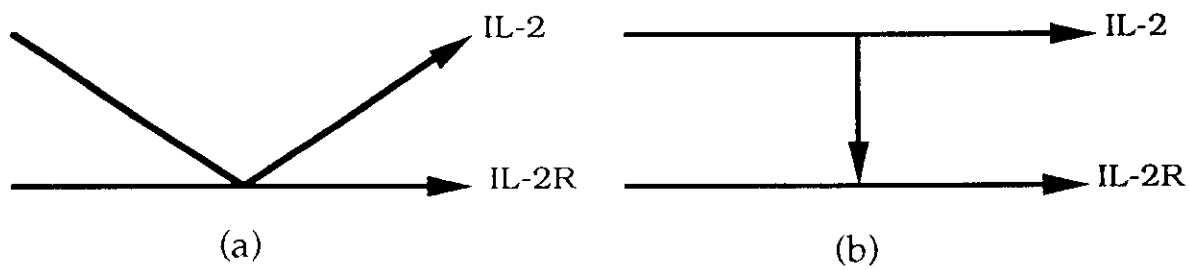

Fig. 1

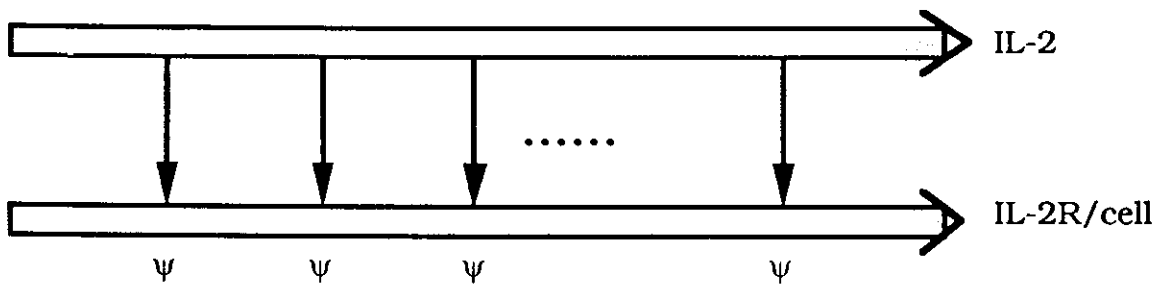

Fig. 2

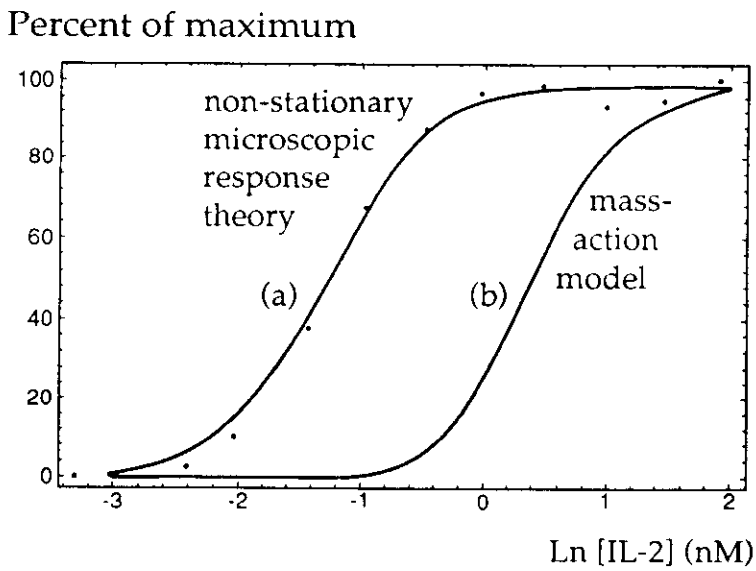
Percent of maximum
100
80
60
40
20
0
-3
-2
-1
0
1
2
non-stationary
microscopic
response
theory
(a)
(b)
mass-
action
model
Ln [IL-2] (nM)

Fig. 3

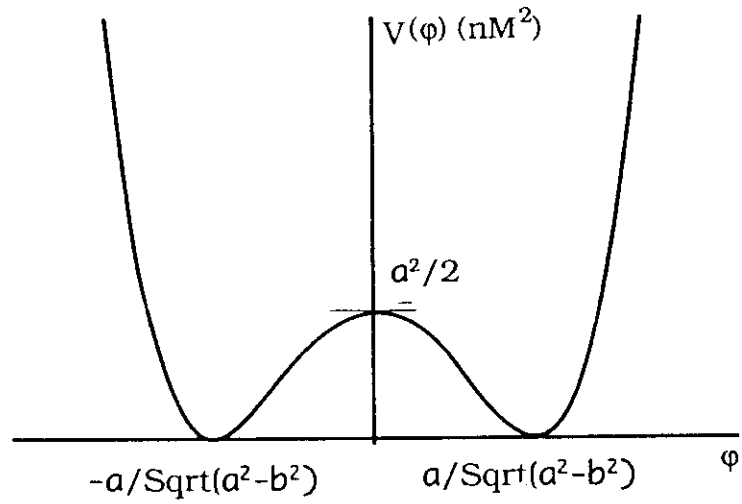

Fig. 4

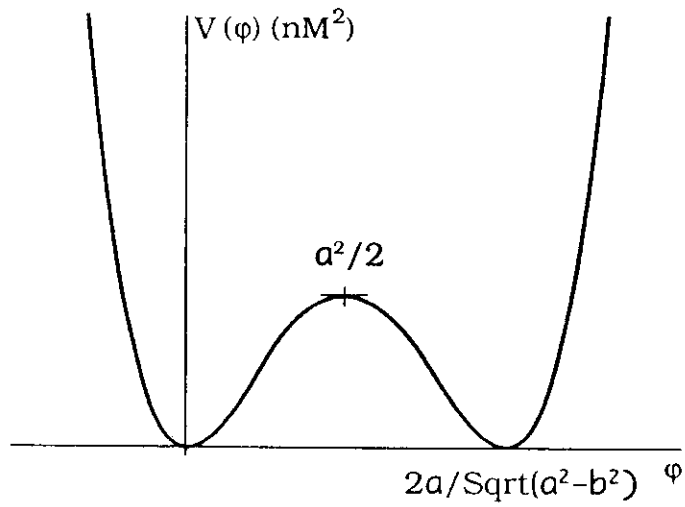

Fig. 5

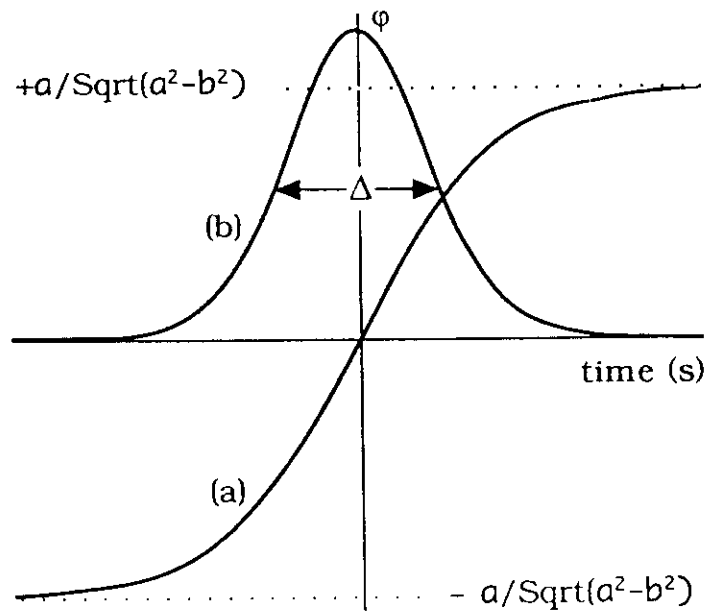

Fig. 6