Appendix A1

Cellular response theory for nonstationary ligand-receptor interaction. Talk given at the 2nd Symposium on Biological Physics at the Technical University, Munich, 30 July - 1 August, 1995. (Published as an extended abstract in the abstract booklet).

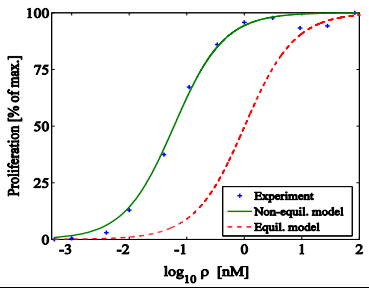
Growth data from laboratory T cell models (K. A. Smith, *Annu. Rev. Cell Biol.* **5**, 397-425, 1989) shows that the rate of cell cycle progression depends on the concentrations of growth factor and it's receptor only, and that a quantal number of receptor occupations is needed for the blast cell to transit to the S phase. Normally, the rest follows automatically at a rather constant time. All time variation was found to be due to the stochastic dynamics of the G_1 phase, and the Gaussian spread in the number of vacant receptors in the population. At the actual level of resolution the leading order of the blast cell, throughout the entire cell cycle, thus appears to be enslaved under the interaction of the two reactants, at a rather constant physiological temperature. This experimental picture of the living cell does not seem to comply with a dynamics primarily driven by thermal variations, as often anticipated for inanimate *ad hoc* type systems, or with models in which the hormone-receptor interaction merely ignites the subsequent myriad of biochemical processes.

The leading order gross dynamics (response dynamics) should rather be described by a blast cell, modelled as an open non-stationary system of hormones and receptors, with the conjugated complexes of occupied receptor compartments floating in a liquid background phase with relatively low viscosity. Over the actual time scale of (1-3) days. Components in the cell compartments described by heavily damped variables seem to be glued together with the receptor complexes. Moreover, one of the major functions of the surface membrane is to imply correlations amongst the receptors. By summing over such receptor correlations in the stochastic hormone-receptor interaction, employing perturbation techniques, and implementing the initial constraints from the start, a deterministic, microscopic Ginsburg-Landau (GL) type model in one time and one space (1+1) dimensions is obtained (L. Matsson, *Phys. Rev.* E **48**, 2217-31, 1993). The so obtained result provides answers to four major questions which could be raised for the standard mass-action based response theory; the lack of equilibrium, the presence of receptor correlations, the lack of linearity between response and occupancy (percentage of activated receptors), and the unknown number of receptors per cell which would lead to a hierarchy of rate equations of indefinite order.

Implementation of the initial constraints thus leads to the microscopic GL type model, the coefficients of which become functions of the concentrations of hormones and receptors. The so obtained dynamics interpolates between harmonic and displacive interaction modes, as a function of the hormone-receptor interaction, rather than thermal variations. This might contribute an explanation to the large range variation of the phenomenological coefficients of *ad hoc* type models for living matter systems, and the proteins involved. The concomitantly alternating dynamics of the model proposed also explains the growth signal firing mechanism in terms of a switch of sign of interaction at the observed definite number of receptor occupations.

Form and slope of the dose-response curve derived (Fig. A), which is a logistic type function of the ligand concentration (ρ), is in striking agreement with assessed growth data (dots) of the leukemic cell line MLA-144 from a Gibbon ape. These data could not easily be explained by the mass-action based response curve, mainly because of the assessed value of the dissociation constant $K = 1.0 \pm 0.5$ nM. This number should be compared with $\rho_{50} = 0.024$ nM in the microscopic model in which ρ_{50} is expressed in terms of other parameters. Noteworthy is also that in the microscopic model the slope of the curve is obtained only after summation over all perturbation orders and, hence, not directly related to the lowest order

action principle. It is the hope that this 1+1 dimensional model with neutral particles could work as an experimentally connected platform for generalizations to 1+3 dimensional models designated for living cells of charged and polarized matter.

A (green): Non-stationary response: $R=R_{max}\ \rho/(\rho+\rho_{50})$		B (red): Mass-action based response: $R=R_{max}\ \rho/(\rho+K)$