INTERNATIONAL ATOMIC ENERGY AGENCY
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SECOND SUMMER COLLEGE IN BIOPHYSICS

30 July - 7 September 1984

The Fröhlich Model and DNA Studies.

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- Introduction
- Dissipative Structures, order and structures
- Davydov solitons
- The Fröhlich model
- Quantum field theory, collective processes, coherence and the role of water
- Raman spectroscopy of living cells and DNA
- Order and nonlinear processes
- Nonlinear properties of biological systems (electric and electromagnetic fields)
- Formation of structures by an energy flow
- Red blood cell rouleau formation
- Cytoskeleton dynamics

Biological systems
(from a physicist's point of view)

Two types of approach :

i) analysis of the properties of single subsystems of the biological system

ii) analysis of the global properties of a biological system (without a discussion about a microscopic realization)

- along the line of thought of thermodynamics and Statistical Mechanics

↳ Time : a fundamental variable in <u>life</u>

One of the most interesting aspects of the world is that it can be considered to be made up of patterns.

A pattern is essentially an arrangement. It is characterized by the order of the elements of which it is made rather than by the intrinsic nature of these elements.

Norbert Wiener

Physics knows other types of order and organization, besides spatial order. This order of motion is widely known and exists in thermal equilibrium (liquid helium II, superconducting electrons) as well as away from equilibrium (lasers, sound waves in air).

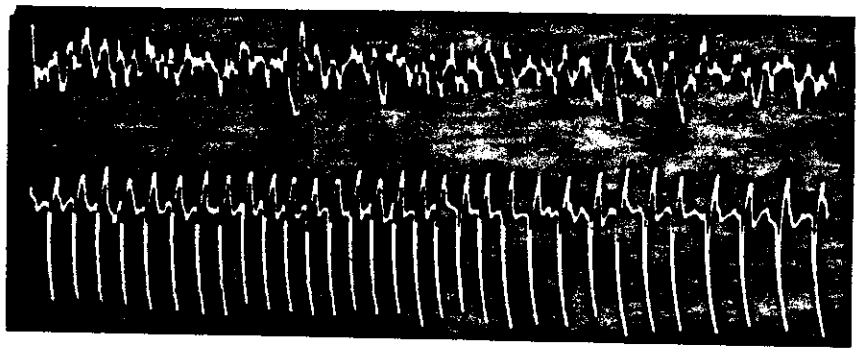
Another type of order, better termed organization, exists in a well-working machine in contrast to a broken down one.

Thus absence of spatial order need not imply randomness. Macroscopic organization, to which we alluded in the case of a machine, is, of course, uniquely correlated to details of microscopic structure. But this does not mean that knowing all microscopic details will reveal the interesting macroscopic properties. Not only is the number of microstates so enormous that it cannot be handled, but, still more important, the relevant macroscopic properties are expressed in terms of concepts that do not exist in microphysics -they are collective properties.

Herbert Fröhlich

Warning : a higher degree of order does not necessarily imply a higher content of meaning.

Normal brain activity (chaotic behaviour ?)



Brain waves in epileptic seizures (ordered structure?)

- collective modes

  many-body physics (phonons, plasmons, magnons, ...

- cooperative behaviour

  cooperative means that the overall behaviour is quite different from the superposition of the effects arising from single subsystems and it is completely unpredictable if one neglects the coupling among the subsystems induced by long-range correlations of different kinds (photons, phonons, ...)

- self-organization, pattern formation

  in many cases the individual parts working together may produce patterns, structures or functions of the whole system on macroscopic scales. Quite often the total system exhibits new qualities which are not present at the level of the individual parts. At least in some disciplines the cooperation of the individual parts appears to be meaningful or purposeful.

- coherence

  is brought about by the cooperation of subsystems

The uniqueness of living organisms distinguishing them from non-living matter is due to the special organization of complex molecular systems. The same elementary laws apply to these systems as determine the properties of atoms and molecules in nonliving matter.

— * —

Since all living organisms are made up of molecules and atoms it is only possible to explain the mechanism of biological process at the molecular level by using quantum theory which provides a successful description of the electrons and nuclei from which molecules and atoms are made.

A.S. Davydov

"I think we all agree with Newton that the real basis of science is the conviction that Nature under the same conditions will always exhibit the same regularities.

Therefore, if we are able to push the analysis of living organisms as far as that of atomic phenomena, we should scarcely expect to find any features differing from the properties of inorganic matter."

Niels Bohr 1932 Copenhagen
lecture entitled "Light and life"

All biological entities are open systems.
Their life function is only made possible by the exchange of energy and matter with the surrounding medium.
The basic processes in living organisms involve a constant expenditure of energy. This energy is provided by the break-down products of food.

A.S. Davydov

- Open systems
- Far from equilibrium processes

  Nonequilibrium may be a source of order. This observation was the starting point of the outlook pioneered by the Brussel school

- Dissipative processes
- Time-dependent structures
- Nonlinearity (control and feedback mechanisms)

Quantum Field Theory approach to investigate self-organization (Ordering processes) in dissipative systems.

The system under investigation: biomolecules and their interactions in an aqueous medium

Biomolecules + water molecules $\Longleftrightarrow$ set of electric dipoles (Fröhlich, 1968)

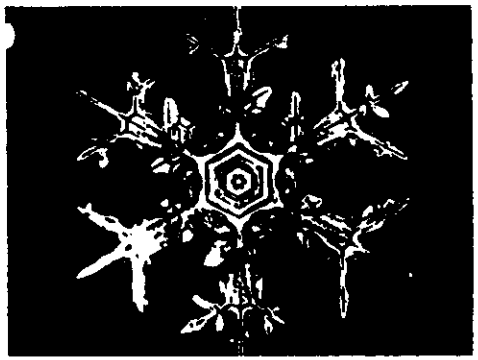
Similar systems

H. HAKEN – Synergetics

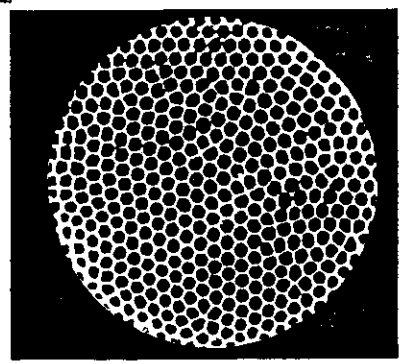
I. PRIGOGINE – Self-organization in nonequilibrium systems. From Dissipative Structures to Order through Fluctuations.

NON-LIVING MATTER $\Longleftrightarrow$ LIVING MATTER

- Atomic physics — Lasers; Optical Bistable Devices
- Fluid dynamics — Convection instabilities (Bénard cells)
- Chemistry — Belousov-Zhabotinskii reaction
- Biochemistry — The Glycolytic Cycle; Ternary systems (polymer-polymer-solvent): PVP transport in a solution of dextran
- Biology — Spontaneous pattern formation in a 3-dimensional sphere. Prepatterns in Mitosis and Cytokinetics.

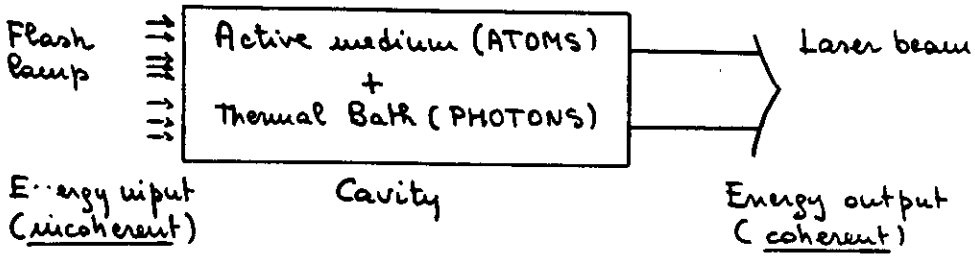


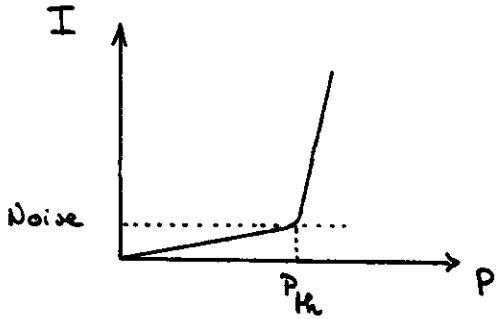
Snow crystal



Beehive structure

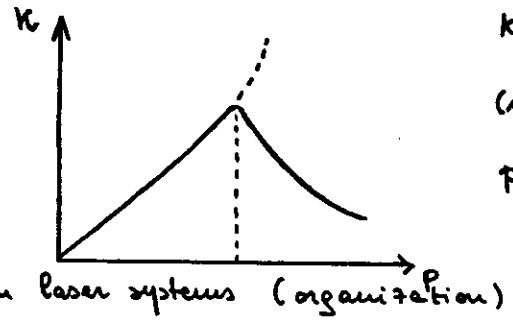
The LASER – a dissipative system showing self-organization





I : power output

P : pump power



K : intensity (I) fluctuations (normalized to I)

P : pump power

Order in laser systems (organization)

Order parameter : I

Analogy with a SECOND-ORDER PHASE TRANSITION for a physical system in thermal equilibrium.

Critical phenomena : order-disorder transitions induced by external parameters (e.g. power input) for systems far from thermal equilibrium.

- Long-range order created by the appearance of a discontinuity (discontinuity of the second derivative of the free-energy)
- changes in the symmetry of the system
- order parameter ϕ ($\phi = 0$ in the disordered state, $\phi \neq 0$ in the ordered state)
- time-dependent properties of the order-disorder transition :

  when the transition take place a fluctuation appear which covers the whole system and is characterized by a long relaxation time

Experimental evidence in these transitions

CRITICAL SLOWING DOWN

(order parameters change more and more slowly in time as the system approaches the critical point)

To give a phenomenological picture of the dynamics of the system it is necenary to identify the "SLOW MODES"

(characteristic times $\tau \to \infty$ in the neighbourhood of the critical point)

Physical systems in the equilibrium	"Synergetic" systems
ORDER PARAMETER	ORDER PARAMETER
TEMPERATURE	EXTERNAL PARAMETER (power input)
ENTROPY	ACTION (power output

ORDER $\Longleftrightarrow$ (SPONTANEOUS) SYMMETRY BREAKDOWN

a new situation arises: the state of the system exhibits no longer all the symmetry properties which in principle would be allowed by its interactions.

Therefore a reduced number of configurations are available for the system.

The changes in the symmetry creates two phases of the systems characterized by different types of order. These changes satisfy some general theorems

$\Downarrow$

When a continuous group of symmetry is broken an excitation appear (Goldstone excitation) in the phase with lower symmetry with a frequency going to zero for the longest wavelength

It is possible to connect in a dynamical way the order parameter and the symmetry properties of the system.

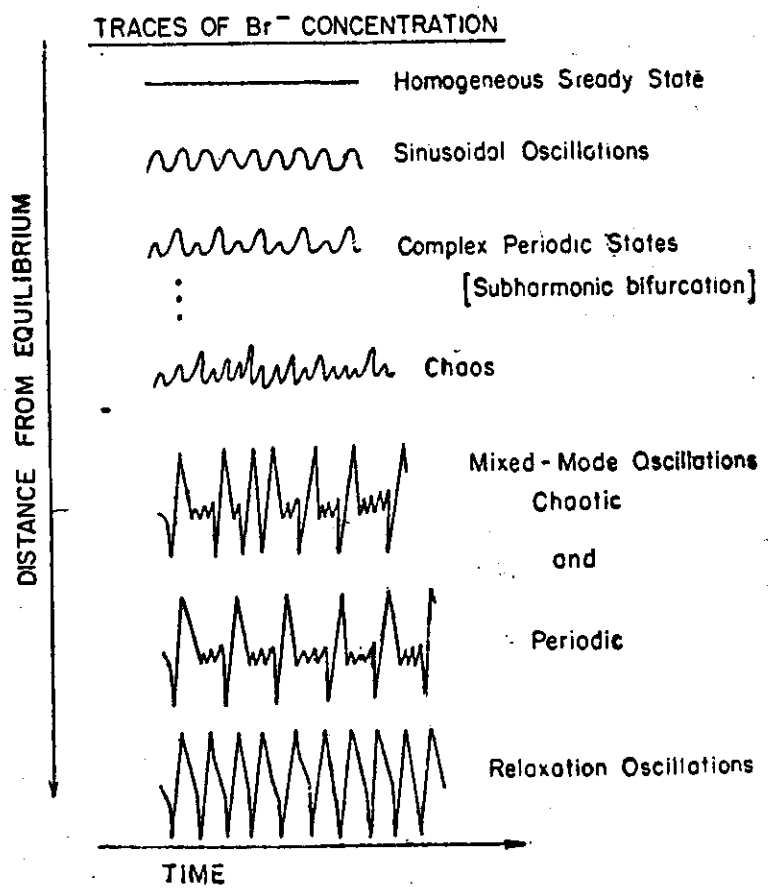


Fig. 4

Sequence of different types of oscillatory behaviour in the Belousov-Zhabotinskii system as it is driven away from equilibrium.

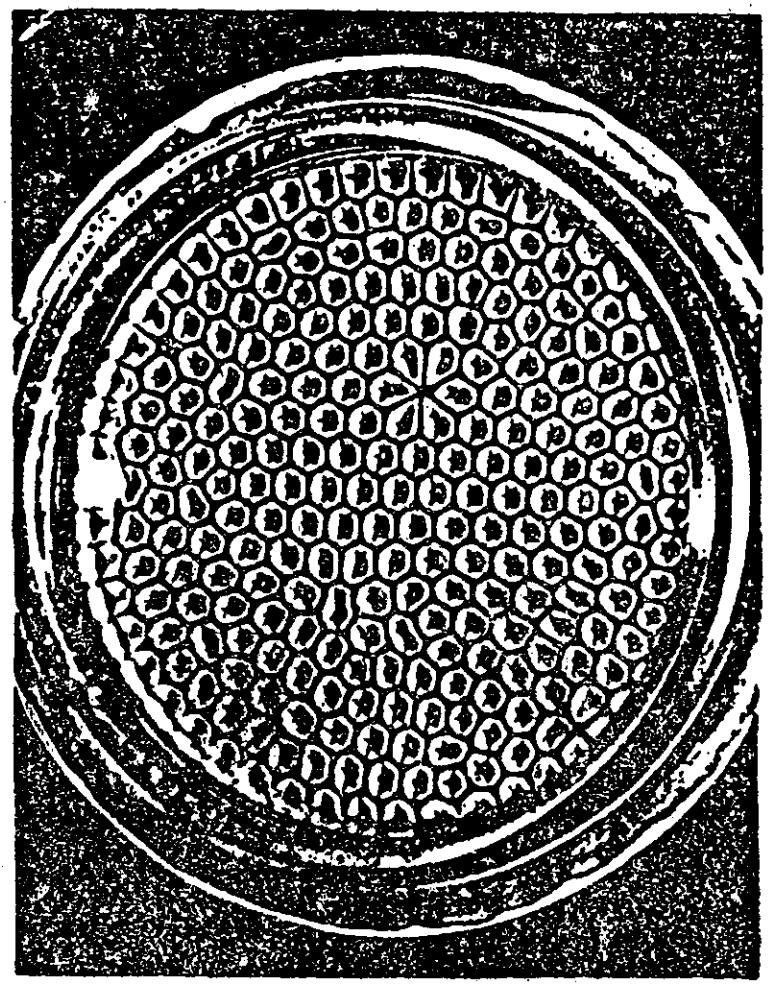
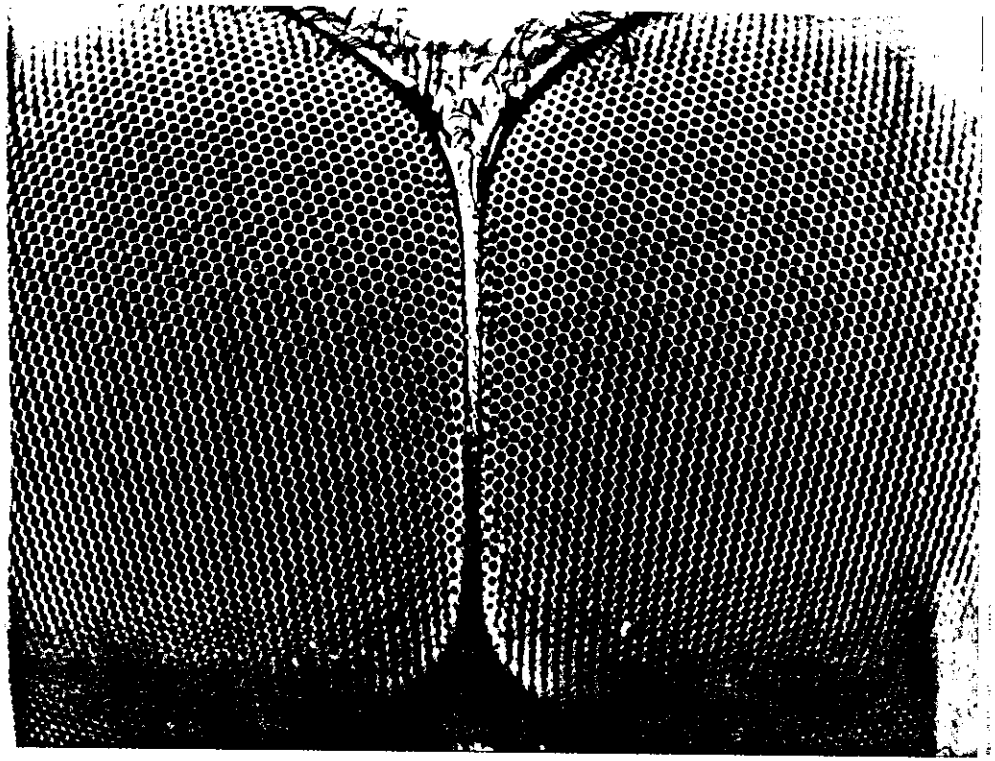


Fig. 8

Benard convection pattern. When a liquid is heated from below, beyond a certain critical temperature, patterns such as this spontaneously form.



Magnification of dragonfly eyes

TOOLS: | Classical Physics

Quantum Physics

Quantum Field Theory
(Nonperturbative Methods - quantum optics)

Long-range order → long-range propagation wave
→ massless quantum particles

Small amount of energy
Boson condensation of a large number of quantum particles
↓
Creation of macroscopic structures
(creation and annihilation of particles ⟺ fields)

Q F T scheme proposed by Umezawa and coworkers

Postulate: a connection ("dynamical map") between microscopic and macroscopic levels

This approach explicitly stresses the connection between laws of symmetry and creation of order.

(It is suitable for getting informations about qualitative properties and not for numerical computations)

PHENOMENOLOGICAL MODEL

System : • (open) set of electrical dipoles (biomolecules)

+

• energy input (metabolic reaction
ATP → ADP + 0.54 eV)

Properties :

far from equilibrium
nonlinear (control and feedback mechanisms)
dissipative

+

• thermal bath (to ensure dissipation of energy)
=
set of electrical dipoles
(water surrounding biomolecules and/or other biomolecules)

+

• investigation of elementary collective excitations in large protein molecules

(Davydov theory of excitations of the collective type on biomolecules : excitons and solitons)

the general requirement of DISSIPATIVITY must be articulated in two regimes

a) the "energy uptake" (or "charge" regime)
(it takes place at definite times and sites)

DAVYDOV regime

conservative process – energy storage (10^{-1}–10^{-2} s) on biomolecules via soliton mechanism

b) the "energy release" (or "discharge" regime)
(the energy previously stored on biomolecules is released over quite large regions)

FRÖHLICH regime

dissipative process – energy exchange with other parts of the biological system (acting as a heat bath) – coherent electric polarization waves

this energy flow can act as energy input for other processes at a higher level of organization and in principle can control the metabolic reaction thus realizing a feedback mechanism.

* — * — *

A cyclic structure and consequent timing of biological processes could be then understood

DAVYDOV Solitons

Davydov and coworkers have investigated different excitations of the collective type on quasi-periodic molecular systems consisting of weakly interacting identical molecules (group of atoms) (one-dimensional molecular systems)

excitons and solitons

SOLITONS: slowly moving local intramolecular excitations accompanied by chain deformations

They are excited by chemical reactions and by other local actions

ex α-helical proteins: valence vibration C=O in peptide groups of protein molecules (amide I)

The solitons are described by a nonlinear Schrödinger equation

$$\left\{ i\hbar \frac{\partial}{\partial t} - \Lambda + J \frac{\partial^2}{\partial \xi^2} + G \left| a(\xi,t) \right|^2 \right\} a(\xi,t) = 0$$

Their bell-like form

$$\left| a(\xi,t) \right|^2 = 2\mu \operatorname{sech}^2 \left| \mu(\xi - \xi_0 - vt) \right|$$

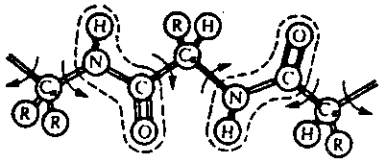
is independent of the manner of excitation

Davydov proposed that solitons could be the tool to overcome the "crisis" of modern bioenergetics and used this concept to explain the contraction mechanism of animal muscles at the molecular level.

Solitons corresponds to stationary states described by the Hamiltonian

$$H = H_{ex} + H_{ph} + H_{int}$$

this hamiltonian is associated to a biopolymer that can be represented as a soft one-dimensional molecular lattice consisting of N monomers at the position $z_n = a \cdot n$ $(n = 1, 2, \ldots, N)$

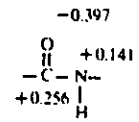


A polypeptide chain with two peptide groups (possible rotations about the single bond are shown by arrows).

The four atoms HNCO forming part of the protein molecule in the form of a repeating structure

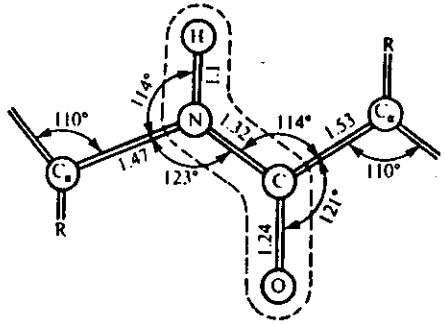
are called the peptide (or amide) groups

A quantum mechanical calculation shows the following electrical charge density distribution around the atoms of the peptide group:

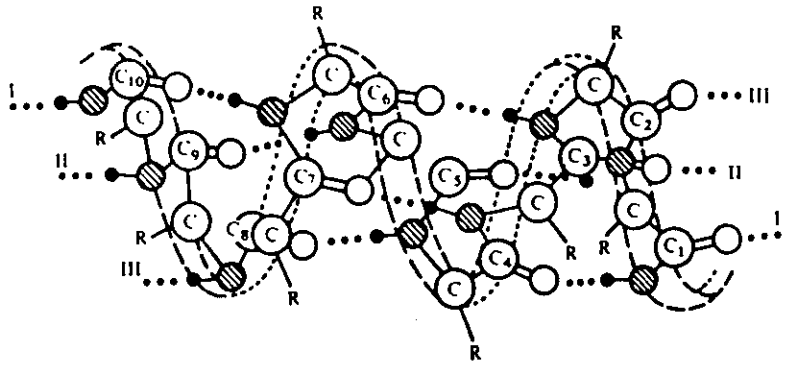


Thus the peptide group possesses an electrical dipole moment.

(from A.S. Davydov)



The peptide group in the protein chain. The peptide group is made up of the atoms H, N, C, O enclosed by the dotted line. They all lie in one plane.



Three hydrogen bond chains in the α-spiral protein molecule.

FRÖHLICH Vibrational Model

Biological system → z electrical dipoles coupled and oscillating dipoles far from equilibrium (external energy supply $S = S(s_k, \omega_k)$) dissipation

$$\dot{n}_{k,1} = -\phi \left\{ n_k e^{\beta\hbar\omega_k} - (n_k + 1) \right\}$$

$$\dot{n}_{k,2} = -\chi \Sigma_i' \left\{ n_k (1 + n_i) \exp \beta\hbar\omega_k + - n_i (1 + n_k) \exp \beta\hbar\omega_i \right\}$$

$\phi \simeq \phi(T)$ $\chi \simeq \chi(T)$ $\qquad$ $\phi = \phi(T, \omega_k)$ $\chi = \chi(T, \omega_k)$

Stationary regime

$$n_k = \left\{ 1 + \frac{\phi}{\chi} \frac{s_k}{S} (1 - e^{-\beta\mu}) \right\} \frac{1}{\exp[\beta(\omega_k - \mu)] - 1}$$

$$\exp(-\beta\mu) = \frac{\phi + \chi \Sigma_j' (1 + n_j)}{\phi + \chi \Sigma_j' n_j [\exp \beta\omega_j]}$$

$\beta = \hbar/kT$ $\qquad S = \Sigma_k' s_k$

$\mu \equiv \mu(s_j)$ chemical potential on the thermodynamic branch

$N \equiv \Sigma_k' n_k \propto S \Rightarrow 0 \leq \mu < \omega_1$

N must increase with growing supply S Once N(S) has surpassed a critical value $N_0(S_0)$, this is possible only if μ closely approaches ω_1 in which case n_1 will become very large

This is exactly the situation met in Einstein condensation of a Bose gas that arises in equilibrium below a certain critical temperature.

$$\phi = \phi(T, \omega_k) \qquad \chi = \chi(T, \omega_k)$$

$$n_j = \left\{ 1 + \frac{s_j}{S} (1 - e^{-\beta\mu_j}) \frac{\Sigma_\ell \phi_\ell n_\ell (e^{\beta\omega_\ell} - 1)}{\Sigma_\ell' \chi_{j\ell} n_\ell (e^{\beta\omega_\ell} - 1)} \right\} \cdot \frac{1}{\exp[\beta(\omega_j - \mu_j)] - 1}$$

$$\exp(-\beta\mu_j) \cong \frac{\phi_j + \Sigma_\ell' \chi_{j\ell} (1 + n_\ell)}{\phi_j + \Sigma_\ell' \chi_{j\ell} n_\ell \exp \beta\omega_\ell}$$

$$\boxed{0 \leq \mu_j < \omega_j}$$

QFT Framework

Dynamical level	Phenomenological level
ψ : Heisenberg field	ϕ : quasiparticle physics
$\Lambda(\partial)\psi = J(\psi)$	$K(\partial)\phi = 0$
$\langle a \mid \psi \mid b \rangle$	$\langle a \mid \Psi[\phi] \mid b \rangle$

dynamical map

$|a\rangle, |b\rangle$ belong to the Hilbert space of physical (observable) states

Original symmetry	Observable symmetry
$\psi \to g\psi = \psi'$	$\phi \to h\phi = \phi'$
$\Lambda(\partial)\psi' = J(\psi')$	$K(\partial)\phi' = 0$
$g \in G$	$h \in H$

$G \neq H$ in spontaneous breakdown of symmetry = = dynamical rearrangement of symmetries

In general : H is a group contraction of G

Example : $G = SU(2)$ $\quad [D_i, D_j] = i\,\varepsilon_{ijk} D_k$

$H = E(2)$ $\quad [D_1^\phi, D_2^\phi] = 0$

$[D_2^\phi, D_3^\phi] = \mp i D_2^\phi$

SET of QUASI-FREE FIELDS

ϕ : dipole quasi-polaron

B, B^+ : polarons (polarization waves)

Dynamical map :

$$\langle a \mid \psi \mid b \rangle = \langle a \mid \Psi[\phi, B] \mid b \rangle$$

Dynamical Rearrangement of Symmetry

$SU(2)$: $\psi \to e^{i\vec{\alpha}\cdot\vec{\tau}}\psi$ $\qquad \vec{\alpha} \equiv (\alpha_1, \alpha_2, \alpha_3)$

$\Updownarrow$

$E(2)$

$$\begin{cases} \phi \to \phi \\ B \to B + \text{const} \\ B^+ \to B^+ + \text{const} \end{cases} \qquad \alpha_1 \neq 0 \quad \alpha_2 = \alpha_3 = 0$$

$$\begin{cases} \phi \to \phi \\ B \to B + \text{const} \\ B^+ \to B^+ + \text{const} \end{cases} \qquad \alpha_2 \neq 0 \quad \alpha_1 = \alpha_3 = 0$$

$$\begin{aligned} \phi &\to e^{i\alpha_3 \tau_3}\phi \\ B &\to e^{i\alpha_3} B \\ B^+ &\to e^{-i\alpha_3} B^+ \end{aligned} \qquad \alpha_3 \neq 0 \quad \alpha_1 = \alpha_2 = 0$$

DAVYDOV Regime

Ψ = molecular dipole field

1 + 1 dimensions
dipole degrees of freedom are FROZEN

ψ : complex scalar field

$\Lambda(\partial)\psi = J(\psi)$ Nonlinear Schrödinger Equation

(Davydov's model)

ϕ : exciton field = molecular dipole quasiparticle field

$K(\partial)\phi = 0$

$$\langle a|\psi|b\rangle = \langle a|\Psi[\phi]|b\rangle$$

$\phi \longrightarrow \phi + f(x)$ $\qquad K(\partial) f(x) = 0$

$\langle a|\psi'|b\rangle = \langle a|\Psi[\phi + f(x)]|b\rangle$

$\langle 0|\psi'|0\rangle_{t\to 0}$ => Davydov's soliton

↳ localized condensation of excitons

FRÖHLICH Regime

ψ : molecular dipole field

3+1 dimensions : $\psi = \begin{pmatrix}\psi^+\\ \psi^-\end{pmatrix}$

$\Lambda(\partial)\psi = J(\psi)$

Assume SU(2) invariance

$$\psi \to \psi' = e^{i\vec{\alpha}\cdot\vec{\tau}}\psi$$

$\Lambda(\partial)\psi' = J(\psi')$

Electret state $\Rightarrow \langle 0|P(x)|0\rangle = P \neq 0$

POLARIZATION

P is directed along the third direction

Spontaneous Breakdown of SU(2)

⇓ GOLDSTONE theorem in QFT

Massless modes ⟺ long range correlations

⇕

polarons (polarization waves)

Homogeneous coherent condensation

Role of water ⇒ changes in the dimensionality of the system

Fröhlich wave ⇒ the field can be taken as the order parameter
($10^{11} - 10^{13}$ Hz)

- Low energy theorems : stability under external perturbations exciting "soft" (low momentum) dipole wave quanta
- Finite volume effect : dipole wave quanta acquire effective mass
  mass $\neq 0$ ⇒ THRESHOLD

Experimental data

- **Spectroscopy of active cells:**

  MICROWAVE : Deviatkov (1974)
  Webb MPI - STUTTGART
  Geuzel " "
  Geiindler " - MÜNCHEN

  INFRARED : Webb, Drissler

  VISIBLE : Letokhov

  - Stability of the system against small perturbation
  - Selective response of the system to peculiar frequency (with narrow bandwith)
  - Highly nonlinear response : the effects induced in the system are not proportional to the intensity of the applied field

- **Measurements of relaxation times on bioelectrets** (> soliton lifetime)

  S. MASCARENHAS - S. Paolo (BRASIL)

- **Water electret state creation energy ≃ soliton creation energy**

  S. MASCARENHAS

Recently it has been shown that bound water in proteins and other biopolymers may store large amounts of electrical polarization via the electret state.

Charge and polarization storage via the electret state has now been found in many biomaterials.

(see S. Mascarenhas
J. Hasted)

The electret state

The electric state of inorganic and organic materials has been investigated in detail by several authors. Essentially it is a metastable state in which polarization can be stored in an insulator with a long relaxation time.

For insulators such as teflon, the electret polarization is virtually constant at room temperature for periods as long as decades.

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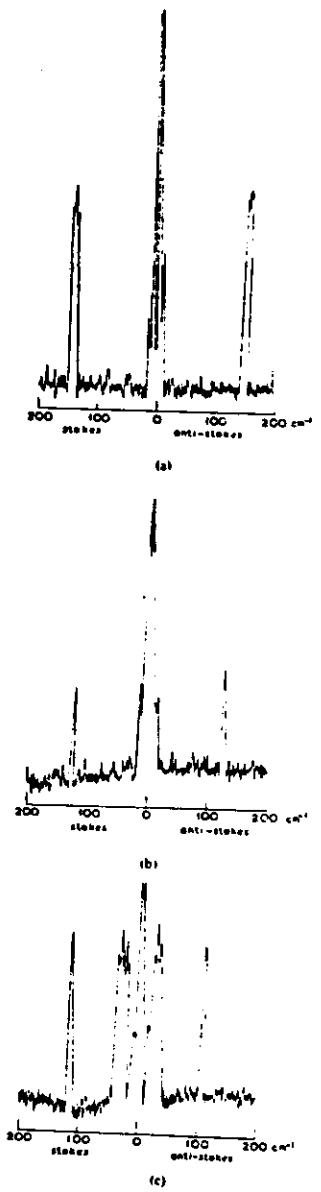
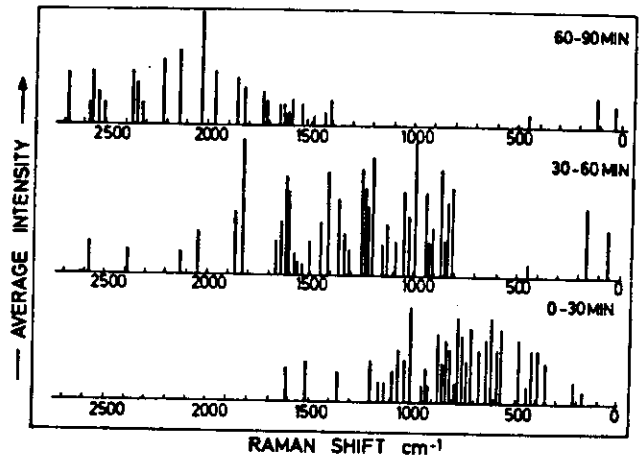
A substance is said to be an electret if the decay time of its stored polarization is long in relation to the characteristic time of experiments performed on the material.

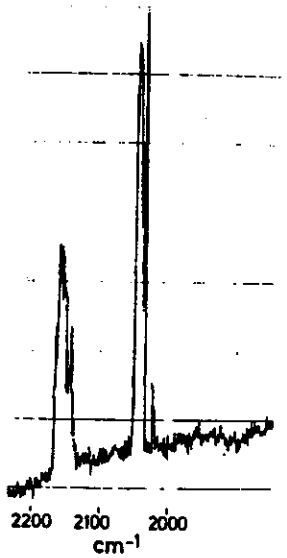


An example of Stokes and anti-Stokes low frequency spectra of Escherichia Coli cells obtained at 40, 50 and 60 minutes after resuspension. From S.J. Webb et al.



The timed appearance of Raman lines seen in the spectra of synchronized populations of Escherichia Coli during a 90 minutes cell cycle. The times shown represent the time after the cells were placed in a minimal medium and, at which, their Raman shift spectrum was determined. The average intensity of each line is that calculated from two, or more, spectra in which the line appeared and is presented merely to demonstrate the relative intensities of the lines and change in them with time

(From S.J. Webb, Phys. Rep. 60 (1980) 201)



The strong Raman lines which appeared in the spectrum of *Escherichia coli* just before cell divisions began.

From S.J. Webb, Phys. Rep. 60 (1980) 201

Examples of spectra obtained with washed B. Megaterium cells in Davis NH_4^+ salts medium.

A without glucose at any incubation time

B, C, D with glucose at 30, 60, 90 minutes of incubation.

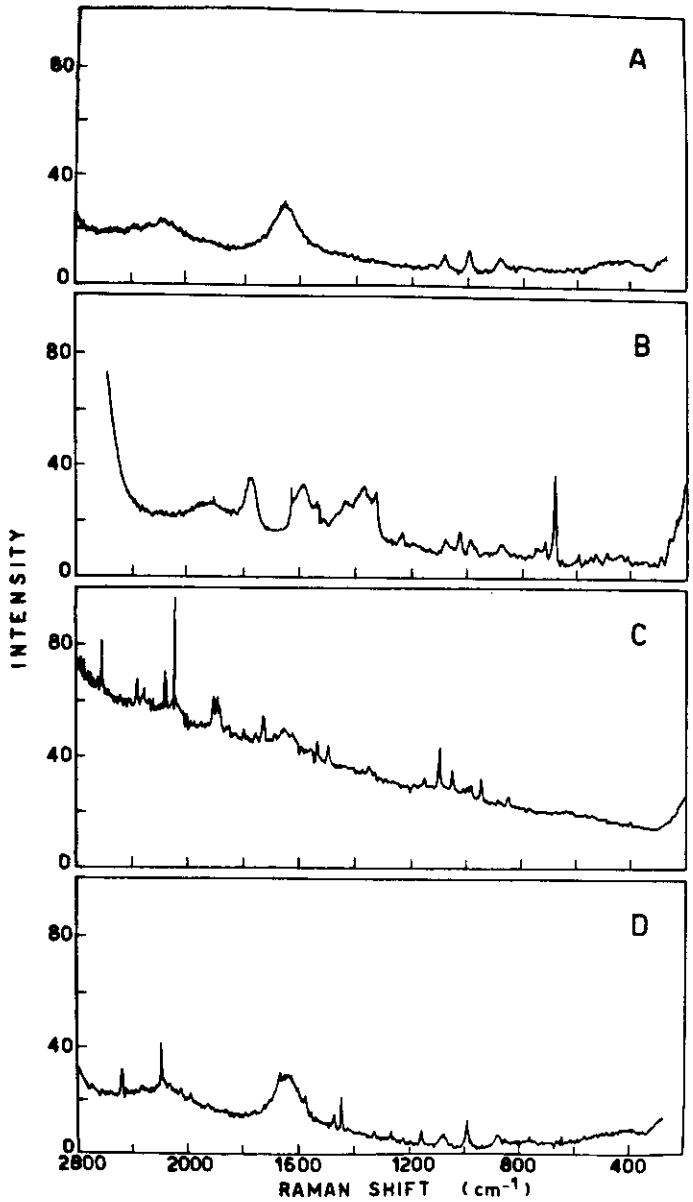
— x —

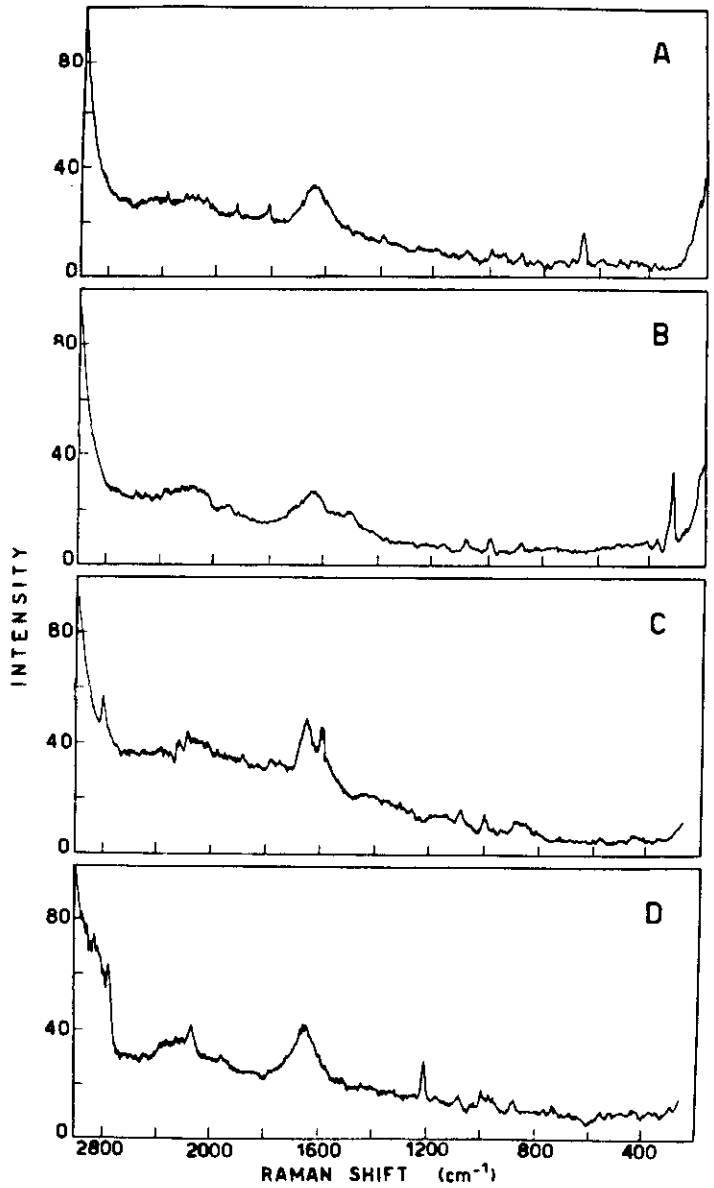
Examples of spectra obtained with synchronized E. Coli cells in Davis NH_4^+ salts.

Spectrum	Minutes of incubation
A	3
B	20
C	25
D	65
E	104
F	126
G	147

(From S.J. Webb)

Raman spectra of E. Coli and B. Megaterium





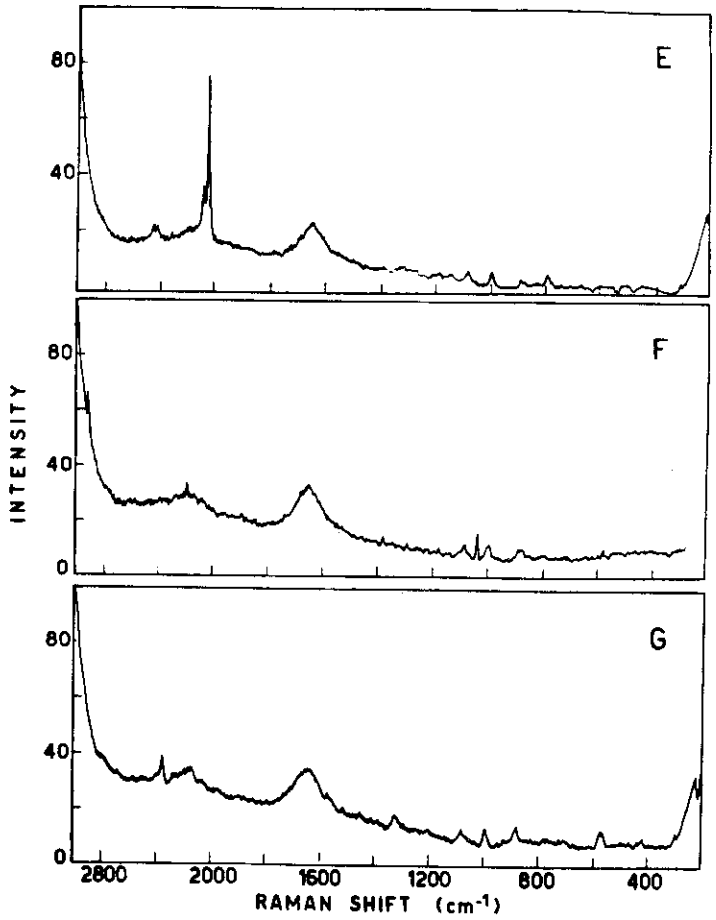


Table 1
Structure of the original Raman spectral traces of *B. megaterium*. F: fundamental frequencies, Δ: deviation of the calculated ν values from the measured ones.

	ν	Process	Δ
spectrum A (mar-time 5)	305	A1 = 2*(A4 − A3)	−5
	357	A2: F	
	450	A3: F	
	600	A4: F	
	829	A5: F	
	934	A6: F	
	1025	A7: F	
	1400	A8: F	
	1640	A9: F	
	2095	A10 = A9 + A3	−5
	2735	A11 = 3*A4 + A6	−1
spectrum B (mar-time 39)	229	A5 − A4	0
	238	A9 − A8	+2
	268	3*(A7 − A6)	+5
	300	2*(A4 − A3)	0
	418	A7 − A4	+7
	445	A3	+5
	490	A6 − A3	−6
	535	A7 − A6 + A3	+6
	550	A10 + A3 − A9 − A2	−2
	592	3*(A7 − A5)	−4
	656	A1 + A2	−4
	680	3*(A5 − A4)	+7
	715	2*A2	−1
	736	3*(A4 − A2)	−7
	740	A9 − 6*(A4 − A3)	0
	746	2*(A8 − A7)	+4
	802	A2 + A3	+5
	825	A5	+4
	964	A2 + A4	−7
	975	2*(A6 − A3)	−7
	1025	A7	0
	1132	A5 + A2	+2
	1229	2*(A9 − A7)	+1
	1270	A10 − A5	−4
	1322	2*(A2 + A1)	−8
	1365	3*(A10 − A9)	0
	1430	A5 + A4	−1
	1514	4*(A5 − A3)	+2
	1538	A6 + A4	−4
	1620	A7 + A4	+5
	1935	A*(A6 − A3)	+1
	1960	A7 + A6	−1
spectrum C (mar-time 69.5)	843	2*(A7 − A4)	+7
	942	2*(A5 − A2)	+2
	980	2*(A6 + A4) − A9 − A3	−2
	1047	A4 + A3	+3
	1091	3*A4 + A6 − A9	+3
	1143	2*(A8 − A5)	−1
	1325	A7 + A4 − A3	0
	1347	3*A3	+3
	1493	A9 + A3 − A4	−3
	1532	A6 + A4	+2
	1729	3*(A6 − A2)	+2
	1758	A8 + A2	−1
	1885	4*(A5 − A2)	+3
	1893	2*(A8 − A3)	+7
	1908	3*A4 + A6 − A5	−3
	2107	A4 + A3	−7
	2155	A5 + A7 − 2*(A4 − A3)	−1
	2167	2*(A9 + A8 − A7 − A6)	−5
	2249	5*A3	+1
	2316	2*(A9 + A3 − A6)	−4
	2369	2*(A2 + A5)	+3
	2627	5*(A8 − A6)	+3
	2802	3*A6	0
spectrum D (mar-time 86)	564	A8 − A5	+7
	646	3*A4 + A6 + A9 − A3	−2
	762	2*(A5 − A3)	−4
	849	2*(A7 − A4)	+1
	855	2*A5 − A3 − A2	−4
	935	2*(A8 − A6)	−3
	992	2*(A7 − A5) + A4	0
	1028	A7	−3
	1158	A9 + A3 − A6	−2
	1223	A8 + A7 − 2*A4	+2
	1238	A6 + 2*(A4 − A3)	−4
	1265	A9 + A3 − A5	−5
	1328	A7 + 2*(A4 − A3)	−3
	1447	2*(A6 − A3)	+5
	1473	A7 + A3	+2
	1486	2*(A4 − A3) + A5 + A2	0
	1540	A6 − A4	−6
	1555	2*A4 + A2	+2
	1576	2*A4 − A3 + A5	+3
	1602	2*(A8 − A4)	−2
	1627	A7 + A4	−2
	1640	A10 − A3	+5
	1652	2*A5	+6
	1670	A4 + A9 − A6 − A2	−7
	1726	3*(A7 − A4)	−1
	1760	A8 + A2	−3
	1795	A9 − 2*A4 + 3*A3	−5
	1862	2*A6	+6
	1930	4*(A6 − A3)	+6
	1990	A9 + A2	+7
	2050	2*A7	0
	2123	3*(A9 − A6)	−5
	2195	A10 − A5 + A6	+5
	2478	A9 + A6 − A3 − A2	+3
	2623	2*(A6 + A5 − A3)	+3
	2960	A9 + A3 + A4	0

From E. Del Giudice, S. Doglia, M. Milani and S. J. Webb
Phys. Lett. 91A (1982) 257

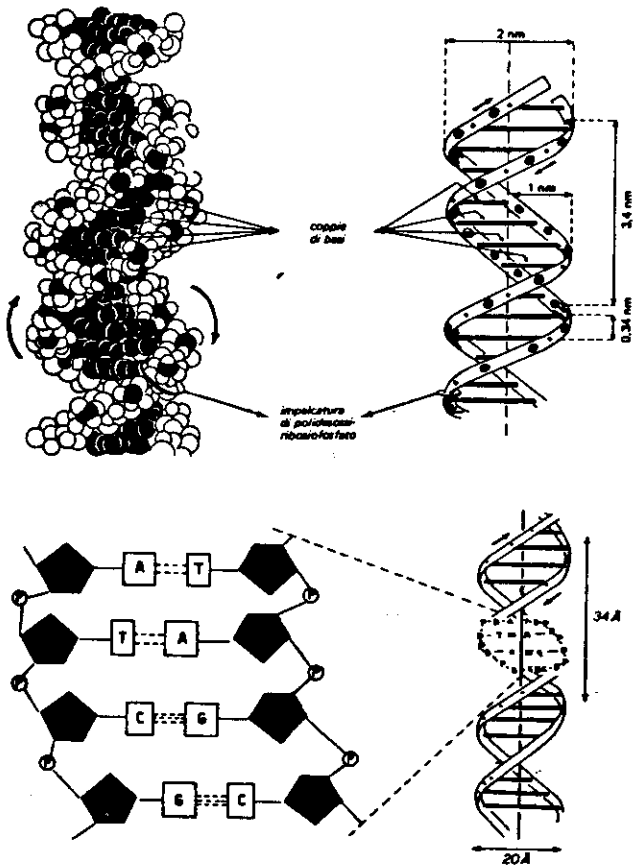


Fig. 2.16 - Modello di Watson e Crick della struttura secondaria del DNA: In *alto a sinistra*, modello molecolare a doppia elica (da M. Durand e P. Favard: *La cellula: struttura*. Mondadori, Milano, 1970). In *basso a sinistra* è rappresentato l'appaiamento complementare delle basi puriniche e pirimidiniche. P, acido fosforico; D, desossiribosio; A, adenina; T, timina; C, citosina; G, guanina. In *alto a destra* e in *basso a destra*, rappresentazione semplificata del DNA. I gruppi fosforici e saccaridici alternati formano i due assi laterali della molecola, rappresentati nella figura da due nastri avvolti a spirale, mentre le basi appaiate, rappresentate come sbarre trasversali, sono disposte trasversalmente nella parte centrale della molecola. Il DNA ha un diametro di 20 Å (2 nm); un giro completo della doppia elica ha la lunghezza di 34 Å (3,4 nm) e la distanza tra le basi contigue lungo la catena è di 3,4 Å. Le frecce indicano che le due catene affrontate sono antiparallele, cioè decorrono in direzione opposta (da E.D.P. De Robertis, W.W. Nowinski e F.A. Saez: *Biologia della cellula*. Zanichelli, Bologna, 1972).

TABLE 1 - Comparison of conformation angles in Watson-Crick base-paired DNA duplexes.

Conformation angles		ω	φ	φ'	θ	ζ	α	χ
Secondary Structure	*B*-DNA	153	-96	-46	-147	36	157	143
	B'-DNA	145	-87	-52	-136	39	157	145
	C-DNA	161	-106	-39	-160	37	157	143
	D-DNA	141	-107	-62	-152	69	157	144
	A''-DNA	-156	-74	-46	174	39	83	86
		-161	-68	-66	180	55	83	91
	A'-DNA	-155	-70	-61	176	51	83	83
		-151	-72	-82	173	72	83	84
	A-DNA	178	-47	-85	-152	45	83	86

The conformation-angles (in degrees) are defined as in Arnott and Hukins [6] and illustrated in Fig. 1. The values of σ correspond to those of fixed, standard furanose conformations (C3-*exo* in the *B* and C3-*endo* in the *A* genus). The conformation angles of *A''*- and *A'*-DNA are from the triple-stranded complexes poly d(C)·poly d(I)·poly d(C) and poly d(T)·poly d(A)·poly d(T) respectively in which there is no diad axis relating the antiparallel chains. The angles of the polypurine nucleotide strands of these are given first.

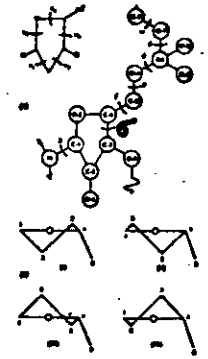


FIG. 1 - (a) The conformation angles of a nucleotide residue. All angles except σ have a wide range of values. The discrete values of σ are determined by the sugar ring shapes in (b): (I) C2-*endo*; (II) C3-*endo*; (III) C2-*exo*; (IV) C3-*exo*. In the *A* genus of polynucleotides the rings are puckered C3-*endo*, in the *B* genus C3-*exo* (or perhaps C2-*endo* which is rather similar).

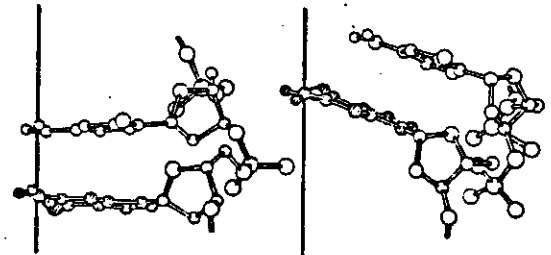


FIGURE 4-10 (a) Projection of two nucleotides in the B conformation of DNA showing bases horizontal and perpendicular to the helix axis. (b) Projection of two nucleotides in the A conformation of DNA showing bases inclined at 20°. [From L. D. Hamilton, *Nature*, 218, 635 (1968). Reprinted with permission.]

POLARIZATION can be taken as an

ORDER PARAMETER

$$\vec{P} = \vec{P}(\vec{E})$$

Role of nonlinearities in the dynamics of biological systems

Experimental evidence

- Raman spectroscopy on metabolically active cells
- Presence of high electric field: (up to 10^7-10^8 V/m inside biological systems
- Raman spectroscopy of poly-L-glutamic acid (harmonic generation)
- Electrical properties of aqueous solutions of DNA in presence of electrical fields of low frequency and intensity

Nonlinear optics (multiphoton processes)

A first group of phenomena connected with the propagation of a signal in a nonlinear medium

- Appearance of frequencies other than the one of the input signal : harmonic generation
  subharmonic generation
  optical mixing
  parametric generation
- no threshold

We will investigate the simplest model system which describes a nonlinear dielectric (cytosol, blood plasma)

Nonlinear cubic isotropic medium
Scalar approximation

$$P = \alpha E + \vartheta E^3$$

the properties of the medium can be described by its index of refraction and its dependence on the electric field

$$n = n(E)$$

Lorentz-Lorentz relation and Clausius-Mossotti equation

$$\frac{n^2-1}{n^2+2} = \frac{4}{3}\pi\rho\sigma$$

RADIATION - MATTER interaction gives rise to anisotropy and inhomogeneities inside the dielectric in presence of an electric field

- Nonlinear optics - electrooptics

KERR effect (ac and dc) gives informations on $n = n(E, \omega)$

- Measurements exists (1966 - 1975) on Kerr activity of aqueous solutions of ACTIN (the main component of cytosol) and of other molecules of biological interest (FIBRINOGEN, ALBUMIN)

Different mechanisms (characterized by different characteristic times) may be at work and give rise to changes in the index of refraction depending on the frequency and the intensity of the incident electric field

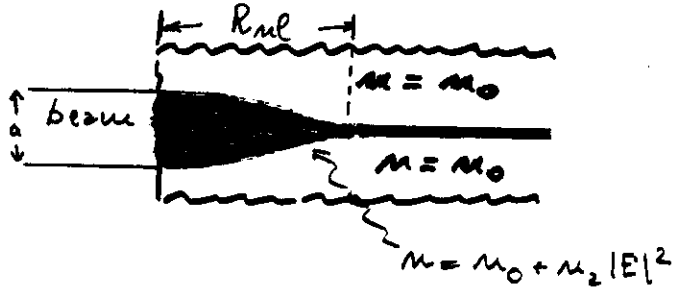
- Changes in the POLARIZABILITY
  - Optical Kerr effect
  - Molecular distribution (libration)
  - Nonlinear electronic distortion
- Changes in the MOLECULAR DENSITY
  - Changes in pressure (electrostriction)
  - Changes in temperature (heat)
- INTENSITY DEPENDENT ANOMALOUS DISPERSION :
  - Changes in the index of refraction of a medium when traversed by a wave whose frequency is near an absorption line of the material

A second group of phenomena in nonlinear optics characterized by
- only one frequency
- a threshold

SELF-EFFECTS : SELF-FOCUSING and SELF-TRAPPING

$$n = n_0 + n_2 |E|^2 + \dots \qquad (n_2 > 0)$$

(Kerr medium)



The propagating beam shrinks until a limiting diameter is reached after a path of critical length

$$R_{sf} = \frac{a}{2} \sqrt{\frac{n_0}{n_2 |E|^2}}$$

(effective self-focusing length)

PHYSICAL MECHANISMS FOR REFRACTIVE INDEX CHANGES

	n_2 (e.s.u.)	τ (s)
Kerr effect (molecular orientation)	$10^{-11} \sim 10^{-12}$	$10^{-11} \sim 10^{-12}$
Molecular redistribution (libration)	$10^{-12} \sim 10^{-13}$	2×10^{-11}
Nonlinear electronic polarizability	$10^{-13} \sim 10^{-14}$	10^{-15}
Electrostriction	$10^{-11} \sim 10^{-12}$	$10^{-8} \sim 10^{-9}$
Thermal changes	$10^{-5} \sim 10^{-4}$	$10^{-1} \sim 1$

Coefficients for nonlinear indexes of refraction n_2 and the critical power level P for self-trapping
(Index of refraction $n = n_0 + n_2 E^2$, where E is in e.s.u.)

Material	$n_2 \times 10^{13}$ (Kerr effect)		$n_2 \times 10^{13}$ (electrostriction)	P (electrostriction) (MW)
Carbon disulfide	180	18	18	0.2
Benzene	49		13	0.25
Water		0.13	2	1.
Air (1 atm)			0.041	80.
(100 atm)			4.1	0.8
Glass (heavy silicate flint)			0.9	4.
Calcite			0.8	4.
Sapphire			0.2	20.

When nonlinear refraction compensates for the diffraction spreading completely, the beam is confined within an optical waveguide ("filament") where it propagates without divergencies
(self-trapping of the wave)

Self-focusing and self-trapping of the beams occur only when a critical power P_{cr} is exceeded

$$P_{c2} = \frac{(1.22)^2 \lambda^2 c}{256 n_2}$$

(as can be seen by simple arguments of geometrical optics)

RADIATION-MATTER interaction
(more informations than we can give)

PONDEROMOTIVE FORCES

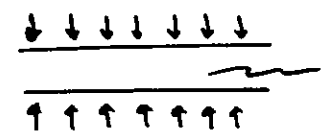
we investigate the effects of a self-trapped beam propagating in an aqueous solution of bio-molecules,

the unit volume force exerted by an electric field $\vec{E}$ in a medium with polarization $\vec{P}$ is

$$\vec{F} = \rho \vec{E} + (\vec{P} \cdot \vec{\nabla}) \vec{E} + \frac{1}{c} \frac{\partial \vec{P}}{\partial t} \times \vec{H}$$

$$(\vec{P} \cdot \vec{\nabla}) \vec{E} \simeq \text{const} \sum_K' \frac{(\omega_{0K}^2 - \omega^2)}{(\omega_{0K}^2 - \omega^2)^2 + \delta_K^2} \nabla E^2$$

SELF-FOCUSING enhances ∇E^2



when $\omega < \omega_0$ the force is attractive

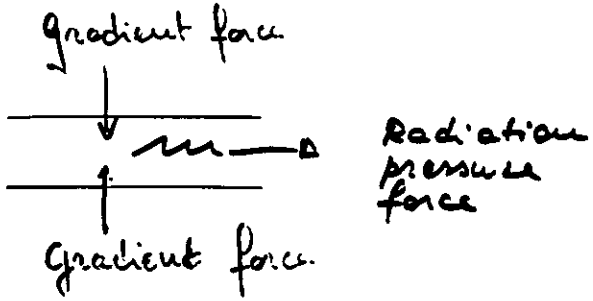
FREQUENCY-DEPENDENT SELECTIVE ATTRACTION

changes in concentrations ⇒
⇒ self-association ⇒
⇒ polymerization of biomolecules in solution by ordering mechanisms
(RINGSDORF, Mainz)

RADIATION PRESSURE

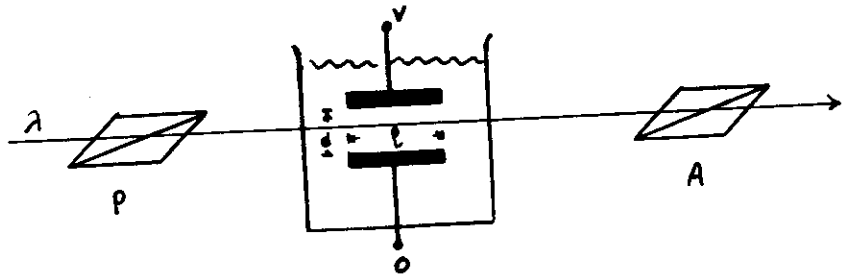
If electric polarization waves are transverse then

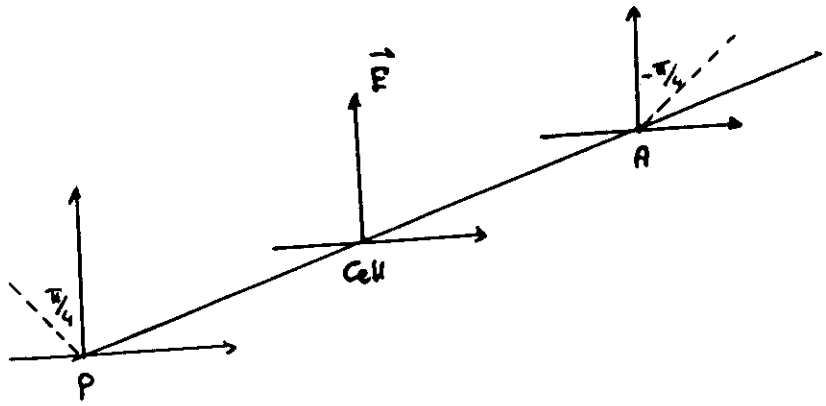
$\frac{1}{c}\frac{\partial \vec{P}}{\partial t} \times \vec{H}$ is parallel to the propagation direction



Further energy is available to support and control polymerization processes

Kerr cell

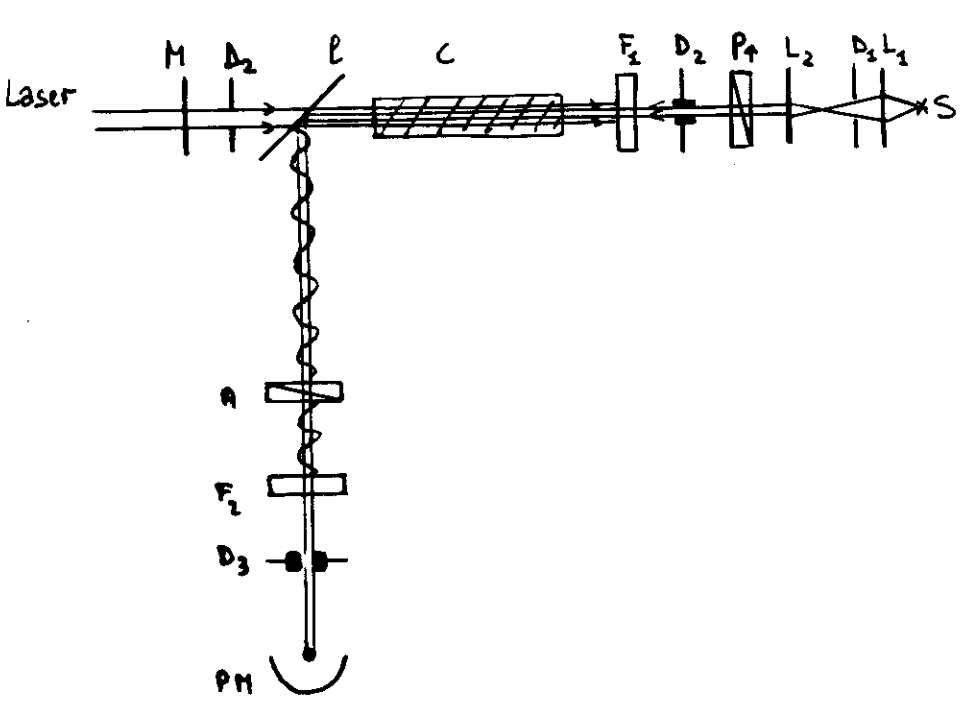




$$(n_s - n_o) = K\lambda\left(\frac{V}{d}\right)^2 \frac{1}{9\cdot 10^{9}} \quad \propto \delta$$

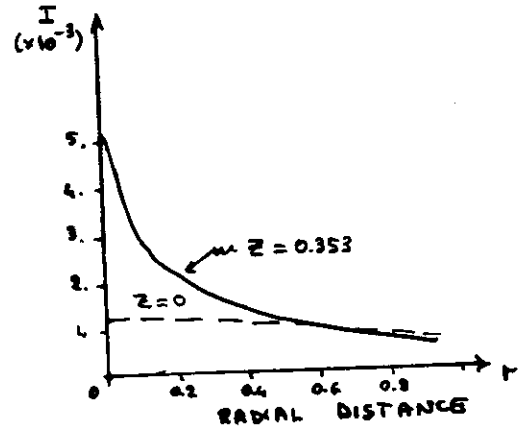
$$\delta = \frac{1}{\lambda} 2\pi l \Delta n$$

Birefringences measure

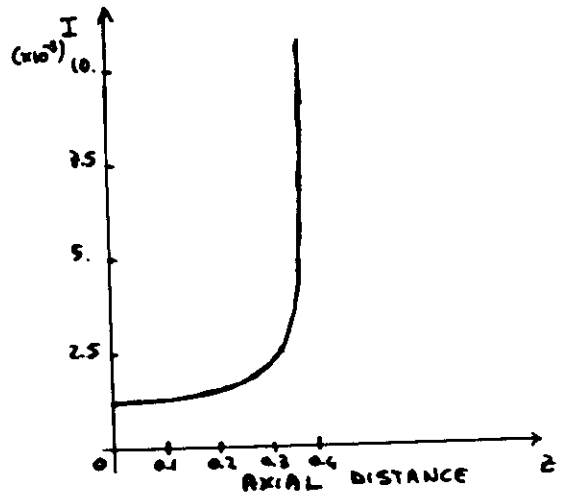


S	Xenon arc lamp	l	glass
L_1, L_2	lenses	M	laser mirror
P, A	polarizers	PM	photomultiplier
D_1, D_2, D_3	diaphragms (ϕ: 7mm)		
F_1, F_2	filters (5000 Å)		
C	liquid cell (19cm)		

G. Mayer & F. Gires (1964)



- Calculated intensity of beam I vs radial distance r for z = 0.353
For comparison the Gaussian initial profile (z = 0) is shown dashed



- Calculated intensity of beam center I vs. z

NONLINEAR POLARIZATIONS

(static and time-dependent)

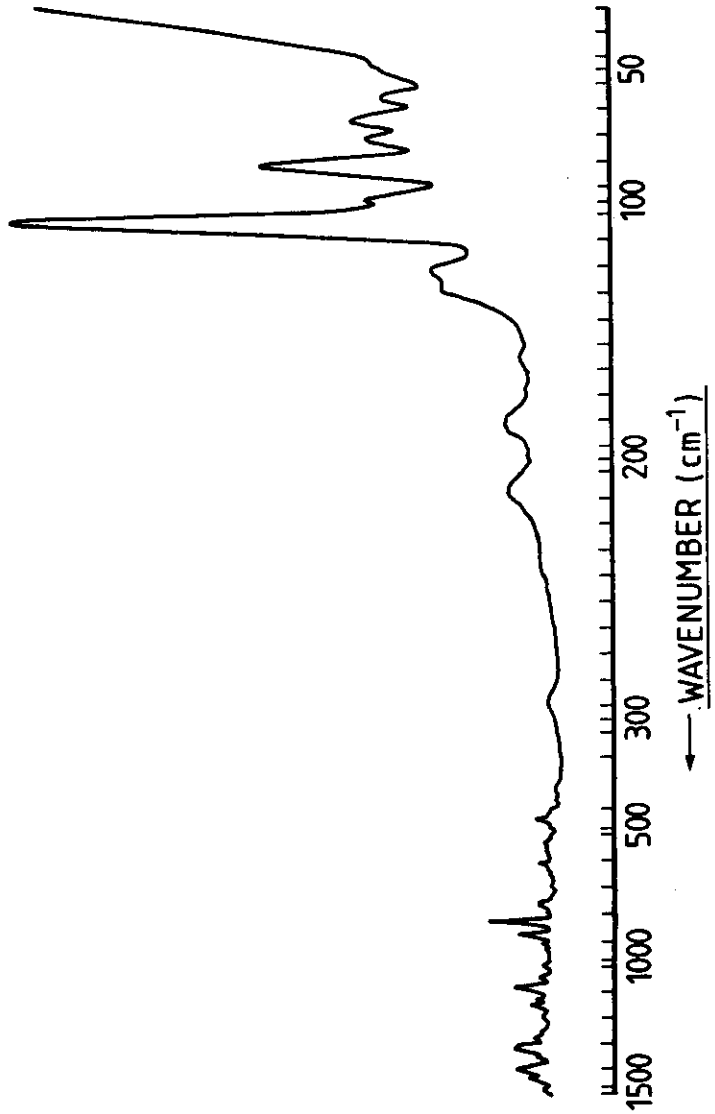
$P_i = \sum_{k=1}^{3} \alpha_{ik} E_k$

Scalar approximation

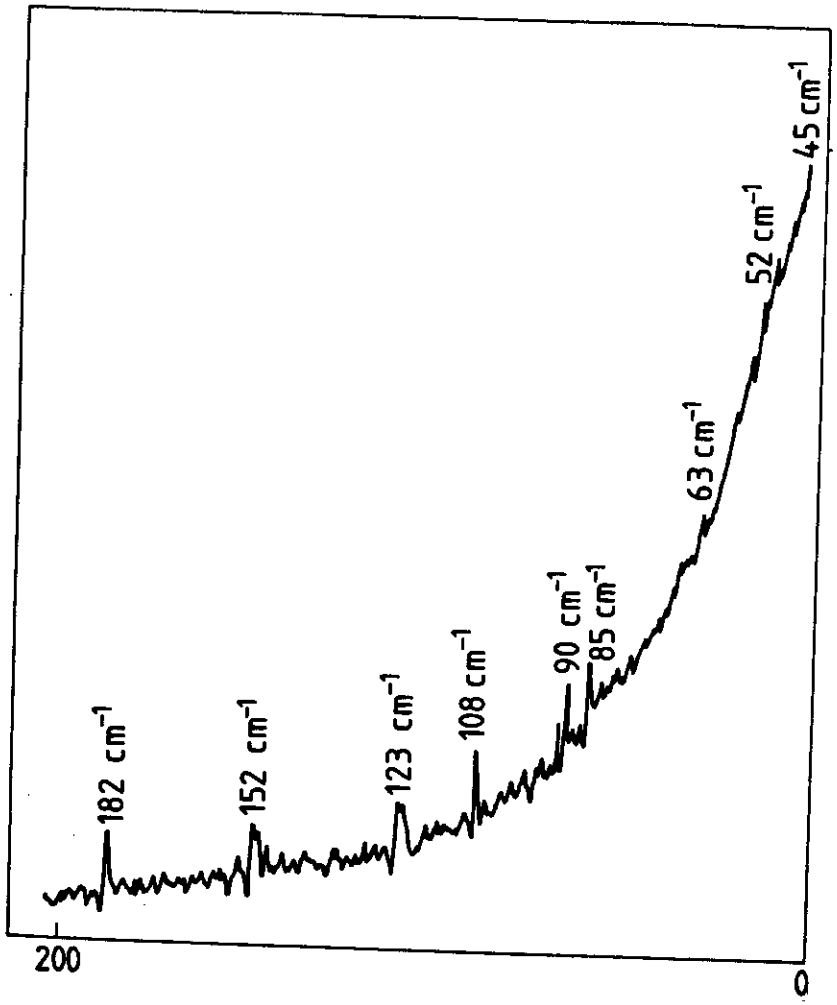
$E = E^0 + E^\omega \cos(\omega t)$ $\qquad P = P^l + P^{nl}$

$P^l = \alpha E \; ; \; P^{nl} = \chi E^2 + \vartheta E^3$

		NONLINEAR POLARIZATION			
Electrical	χ	$\chi E^0 E^0$	—	—	—
	ϑ	$\vartheta E^0 E^0 E^0$	—	—	—
Electro-optical	χ	—	$2\chi E^0 E^\omega$	—	—
	ϑ	$\frac{3}{2}\vartheta E^0 E^0 E^0$	$3\vartheta E^0 E^0 E^\omega$	$\frac{3}{4}\vartheta E^0 E^\omega E^\omega$	—
Optical	χ	$\frac{1}{2}\chi E^\omega E^\omega$	—	$\frac{1}{2}\chi E^\omega E^\omega$	—
	ϑ	—	$\frac{3}{4}\vartheta E^\omega E^\omega E^\omega$	—	$\frac{1}{4}\vartheta E^\omega E^\omega E^\omega$
		Static	Fundam.	II Armonic	III Armonic

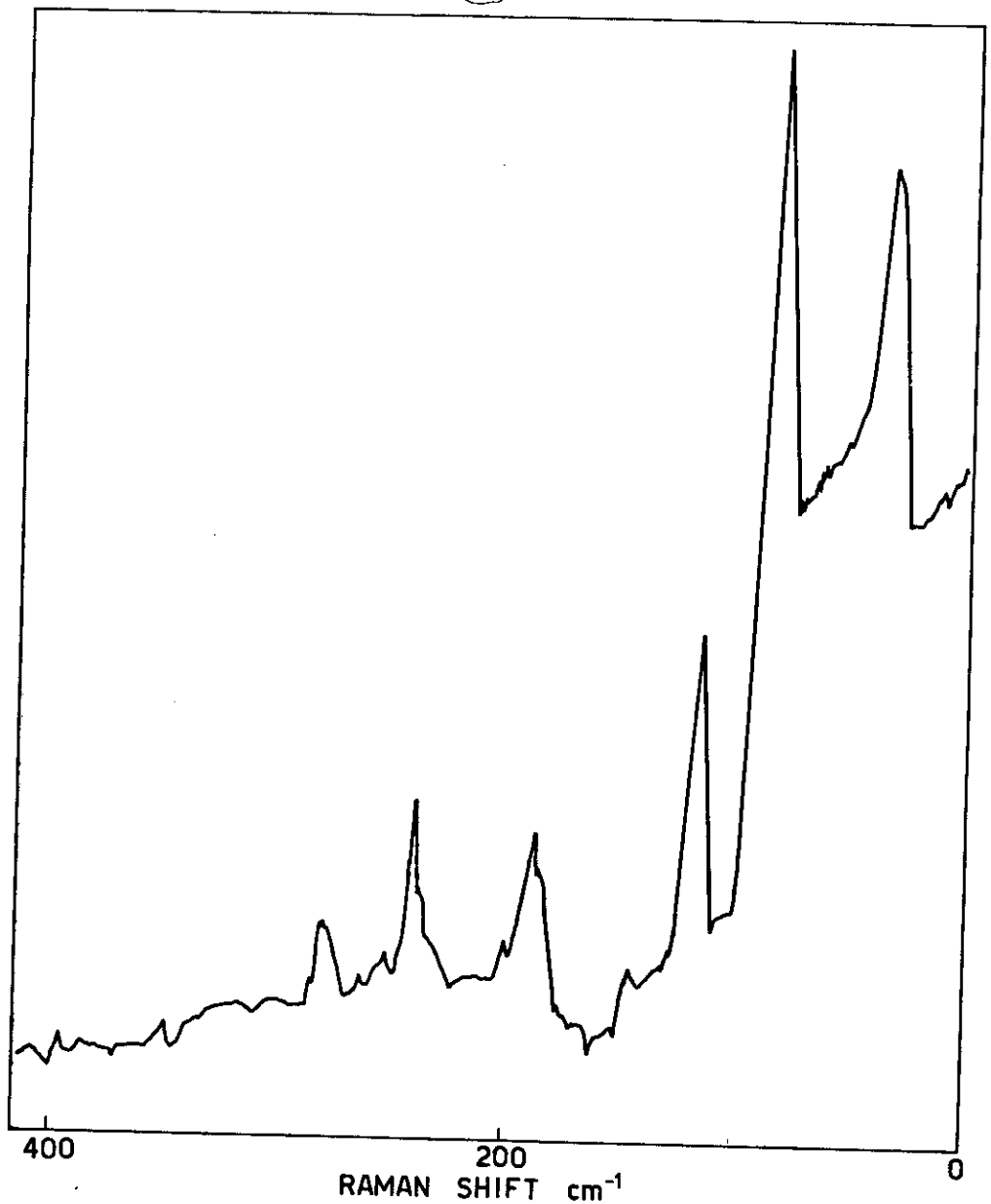


Raman spectrum of L-glutamine
(From E. Del Giudice, S. Doglia, M. Milani and M.P. Fontana
Cell Biophysics 6 (1984))

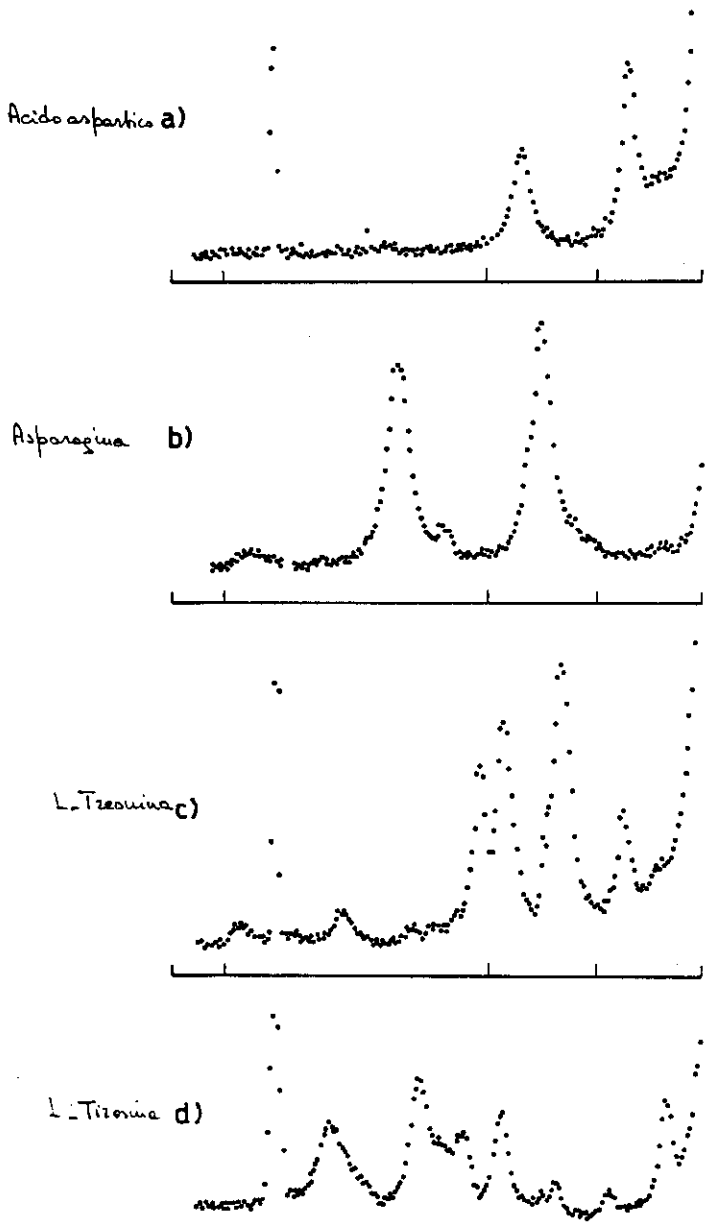


The Raman shift spectrum, between 30 and 200 cm^{-1} of non-synchronized cultures of E. Coli in Davis minimal medium.

From S.J. Webb, Phys. Rep. 60 (1980) 201



A low frequency Raman shift spectrum obtained with cultures E. Coli in which lines at 45 and 85 cm^{-1} became very strong. From S.J. Webb, Phys. Rep 50 (1980) 201



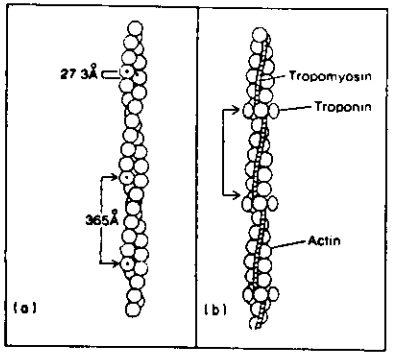
CELL CYTOSKELETON

A complex network of filaments is found in the cytoplasm

i) MICROTUBULES (tubulin)
ii) MICROFILAMENTS (actin)
iii) MICROTRABECULAE (mainly actin)

- lability of structures
- dynamical dependence (cell cycle, environment, ...)
- treadmilling
- lack of attachment to the membranes

privileged channel for molecular transport and chemical reactions



F-actin structure showing arrangement of G-actin monomers as deduced from X-ray diffraction and electron microscopy studies.

Highly schematic model of thin filament showing bound tropomyosin and troponin. There is one tropomyosin and one troponin for every seven G-actin monomers.

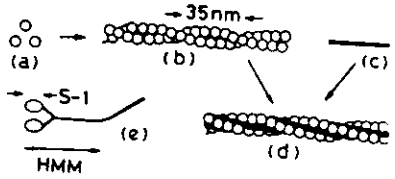


Illustration of the structures of muscle proteins.

Structural basis of F-actin

G-actin is globular in shape (Fig. 1a). Its molecular weight is about 42k daltons. G-actin polymerizes into F-actin under physiological salt concentrations (Fig. 1b). Based on observations by electron microscopy, a "pearl-and-necklace" model is proposed for the ultrastructure of F-actin. F-actin is a two-stranded helical polymer. The half pitch of the helix is 35 nm and within this length, there are 13 G-actins. The total length of F-actin varies according to polymerization conditions and, roughly speaking, is longer than 1 μm. As might be supposed from its structure, F-actin is rather stiff. Electron micrographs show the images of gradually curved F-actin. Tropomyosin is a rodlike protein (Fig. 1c). When tropomyosin molecules are added to the solution of F-actin, they bind to F-actin and settle in the grooves of F-actin helix forming tropomyosin strands (Fig. 1d). Myosin has two heads called subfragment-1 (S-1) and binds to F-actin in the absence of ATP. Partial digestion by some kind of proteases produces heavy meromyosin (HMM) and also S-1 (Fig. 1e).

.. STRUCTURE OF THE CYTOPLASMIC MATRIX

A. Ribosomes

Ribosomes not bound to the endoplasmic reticulum ('free' ribosomes) occupy a considerable proportion of the cytoplasmic ground substance, with densities of about 2,000 particles μm^{-3}. They are not necessarily free to move or diffuse independently, since many are associated in helical groups of about 5-30 ribosomes, forming polysomes. Each polysome is held together by a single strand of mRNA and each ribosome will have associated with it a growing polypeptide chain.

B. Microtubules

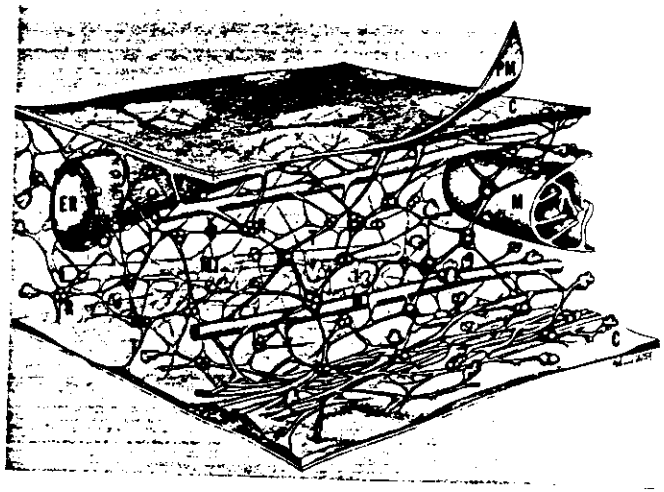
Microtubules are cylindrical proteinaceous structures, 24 nm in diameter and often many micrometres in length. They frequently lie parallel to each other in arrays of a few to several hundred. Microtubules are found in all eukaryote cells, in a wide variety of situations, such as the cell cytoplasm, the mitotic spindle, just beneath the plasma membrane and the axonemes of cilia and flagella.[15] They are associated with various cell activities ranging from the apparently static maintenance of cell shape to the rather slow movements of chromosomes and the more rapid beating of cilia and flagella. Stationary microtubules may also be associated with the movement of adjacent cytoplasm (Fig 7).

C. Filamentous structures

The cytoplasm of many animal cells contains a great variety of filamentous structures which are only now being clearly defined and understood. Microfilaments (Fig. 7.) are one type of filament that appears to be universally important, occurring in plants and animals, where they were first studied as the thin actin filaments of muscle fibres. In non-muscle cells these microfilaments occur singly or in parallel assays; they are especially evident in cells showing saltatory and cytoplasmic streaming motions[16] and in the advancing edge of moving cells.[17] These cytoplasmic movements are clearly visible at the light microscope level, as a flow of particles that are sufficiently large to be resolved. Typical flow rates range from 1-50 $\mu m\ sec^{-1}$. There has been an intensive search over many years to identify the cellular system that converts cellular energy to cytoplasmic movement.[18] A great deal of circumstantial evidence points to the involvement of the microfilament system in the generation of this flow.

D. Cytoplasmic gel

The ground cytoplasmic substance contains many macromolecules, metabolites and ions in an aqueous environment. Little is known of their specific movements within this gel, although it is assumed that the smaller move in response to concentration gradients, which may be generated by cellular metabolism. Many of the components of this gel are readily soluble in water and ionise or possess surface charges. This forms a gel with complex mechanical and internal surface charge properties that affect the movement of both cell organelles and the simple molecular components of the cytoplasm. In the microscale of the cellular environment we need to be aware that it is very doubtful that random diffusion events can occur; the local viscosity may be in the range 1-10 centipoises while the self-diffusion coefficient of water is reduced by a factor of about 2[19]. Clearly this will effect our interpretation of data from LLS systems.



ROWLANDS experiments on erythrocytes

— ❦ —

- enhanced rouleau formation in metabolically active cells (blood red cells)
- dependence of the attraction upon the presence of selected molecules in the medium
- dependence of the attraction upon different (ken?) properties of the same molecule
- formation of contractils when red cells are pulled apart
- presence of end gap (i.e. contractils are not attached on the red cells)
- species specificity

experimental evidence for the existence of Fröhlich coherent electric vibrations

LEGENDS TO FIGURES

Fig. 1 Rouleau formation in normal blood.

Fig. 2 The end cells of a six-cell rouleau have been gently aspirated into the glass micropipettes seen left and right. The pipettes were then drawn apart. The contractils are not resolved by light microscopy. In this picture their presence is inferred by the distortion of the shape of the cells in the chain. On release of the negative pressure in the pipettes a normal-looking six-cell rouleau reforms.

Fig. 3 a) Distribution of the erythrocytes on the floor of the haemacytometer chamber at the beginning of an experiment. The darker rings are small rouleaux seen on end. There are also two prominent fuzzy spots which are artefacts.
b) The same field of view about an hour later. Note the diminution in the total number of rings and the presence of larger rouleaux (pseudo-rectangles) which have fallen onto their sides.

Fig. 4 Scanning electron microscope picture of a rouleau extended as in Fig. 2. The macromolecular solution was slowly replaced with isotonic glutaraldehyde while tension was maintained on the pipettes. After

being fixed by the glutaraldehyde the specimen was washed in distilled water, dried overnight and then gold-shadowed. [Line lower right is 5 μm long]

Fig. 5 As in Fig. 4 but at higher magnification. The break in the middle is artefactual but the discontinuities where the contractils meet the drawn-out cell membrane are always present. [Line above the identification numbers is 5 μm long]

Fig 6 Similar to Fig. 2 but with the pipettes moved out of line. As this is done the line of the contractils remains coincident with the line joining the centres of the spherical portions of the cells held by negative pressure in the pipettes.

Fig. 7 As in Figs. 2 and 6. The negative pressure in the upper pipette has been reduced in magnitude. The point on the cell held in the upper pipette moves freely, with no lag, over the cell surface as the pipettes are rapidly moved out of and into alignment.

(71)

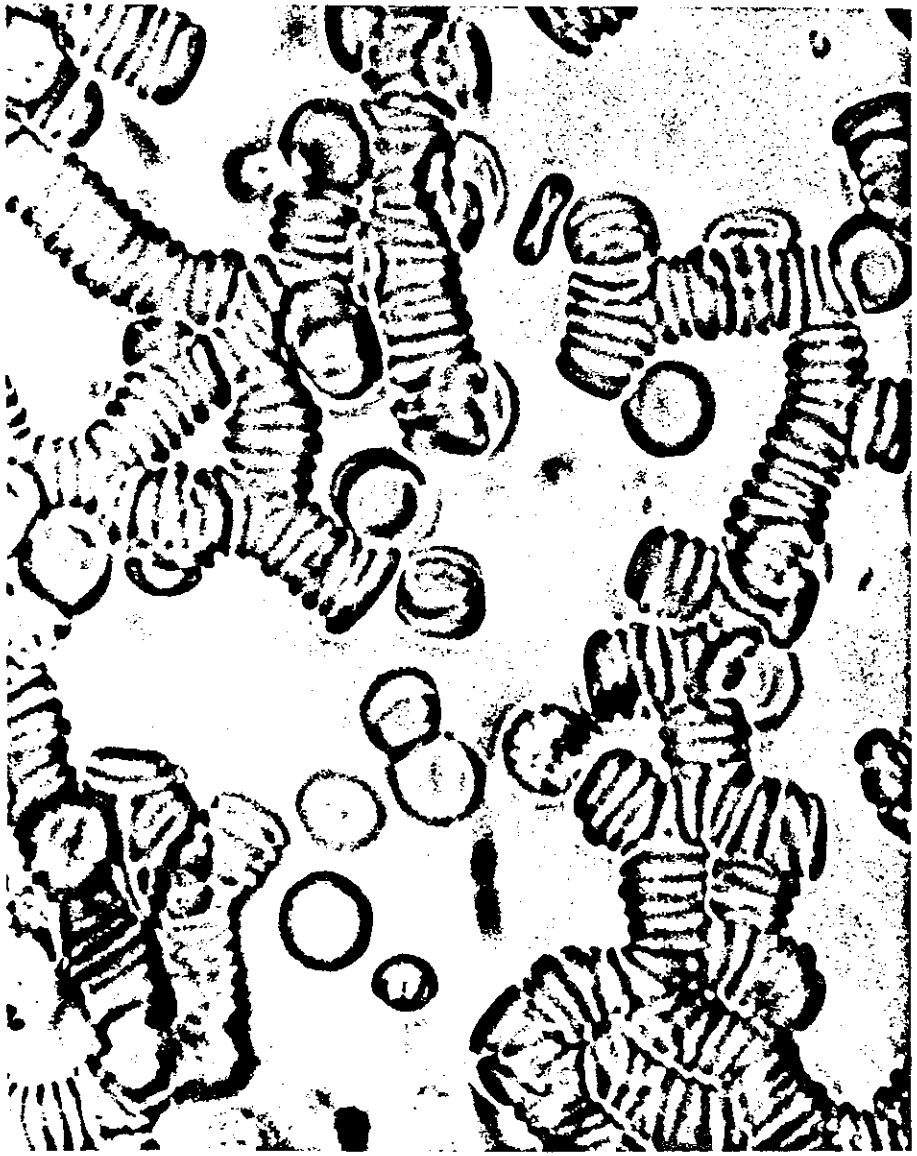


Fig 1

(72)

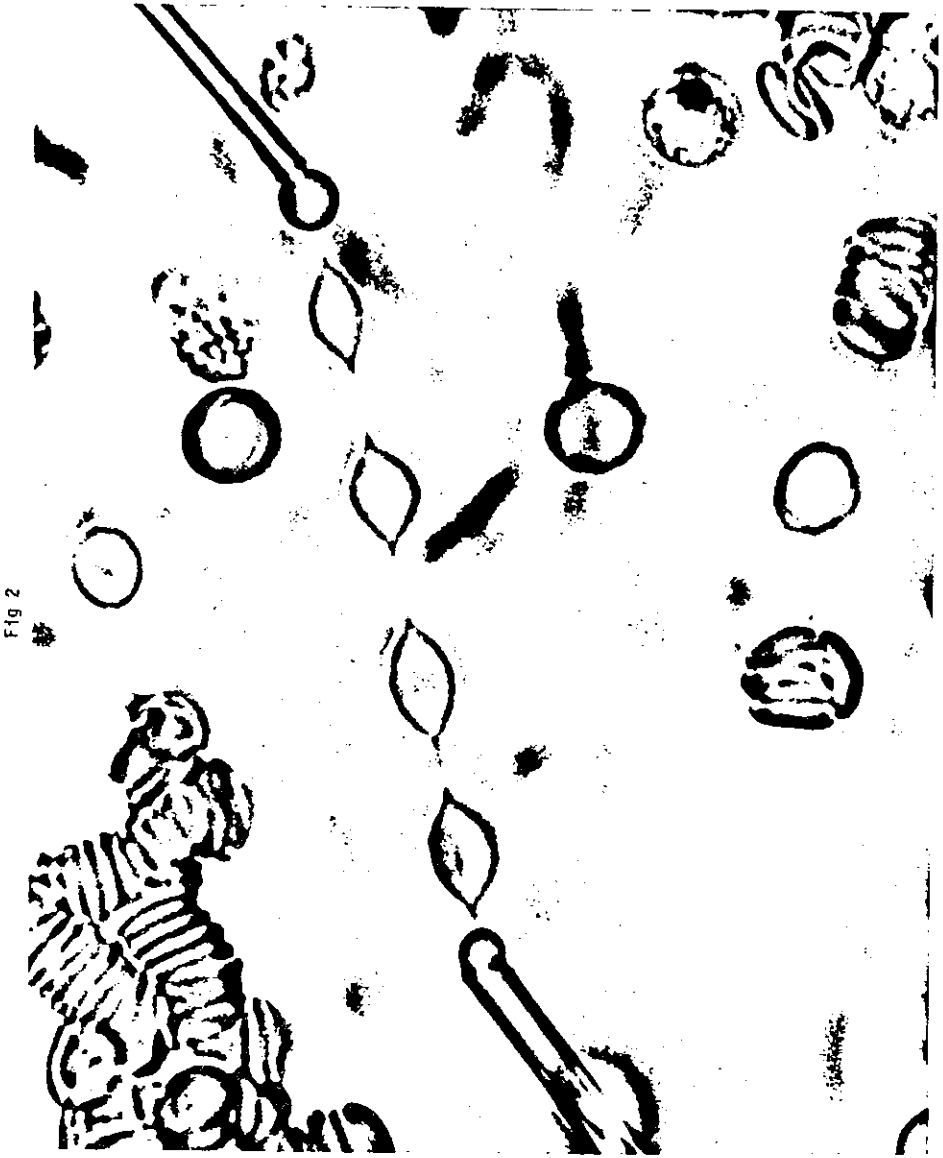
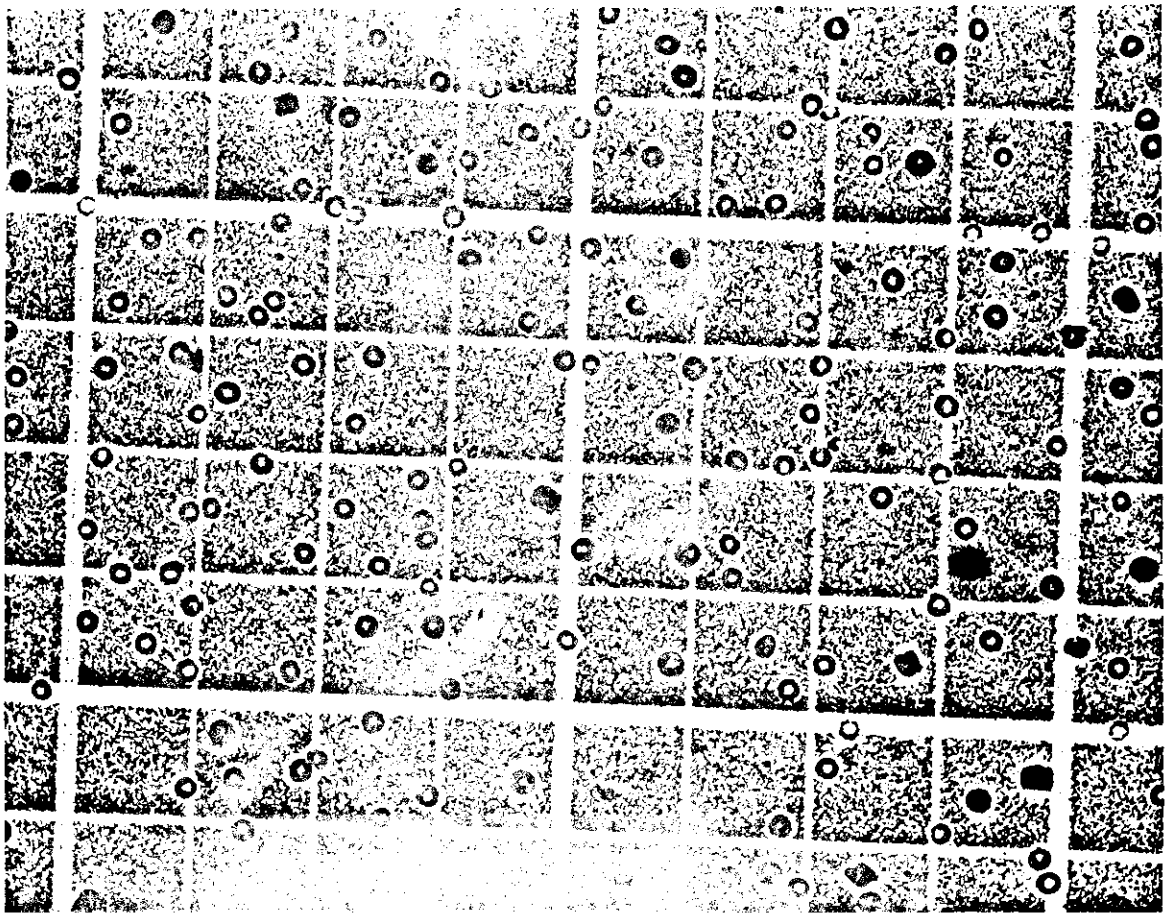


Fig 2

Fig 3a

(13)

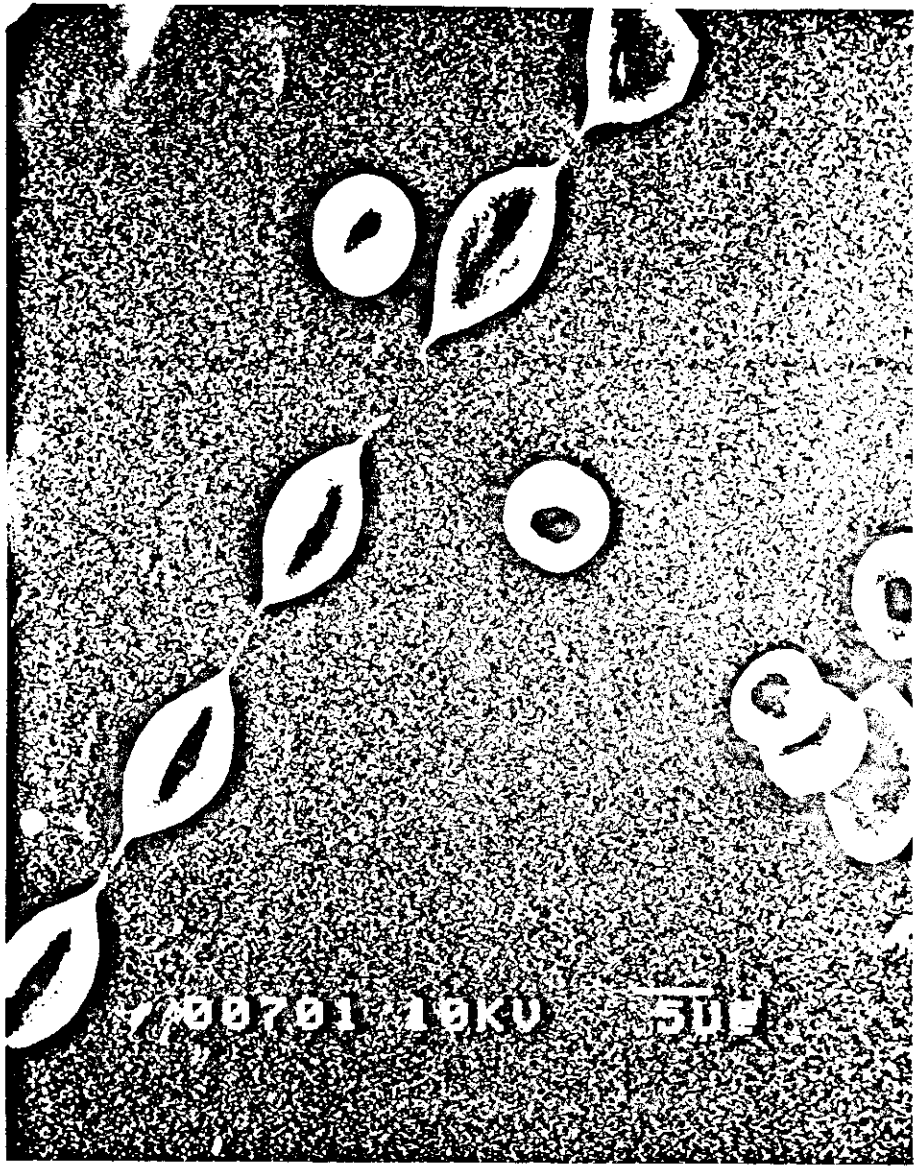
Fig 3b



(14)

(75)

Fig 4



(76)

Fig 5

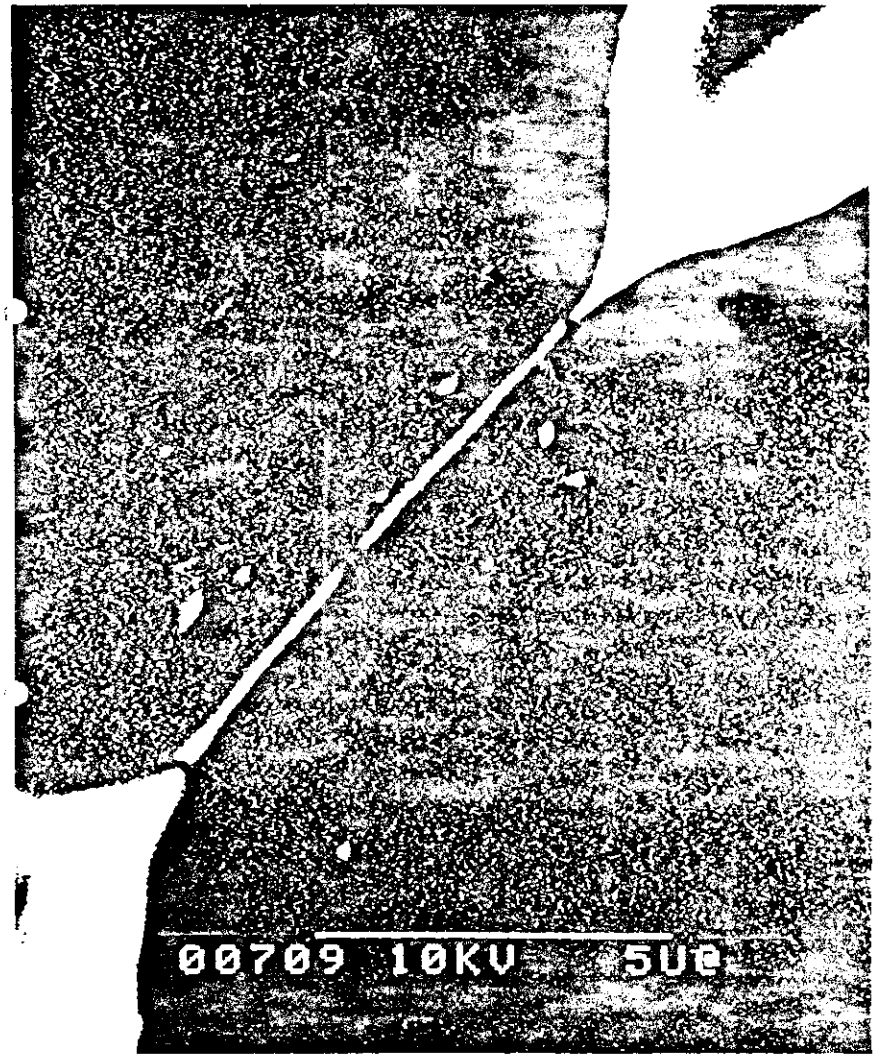
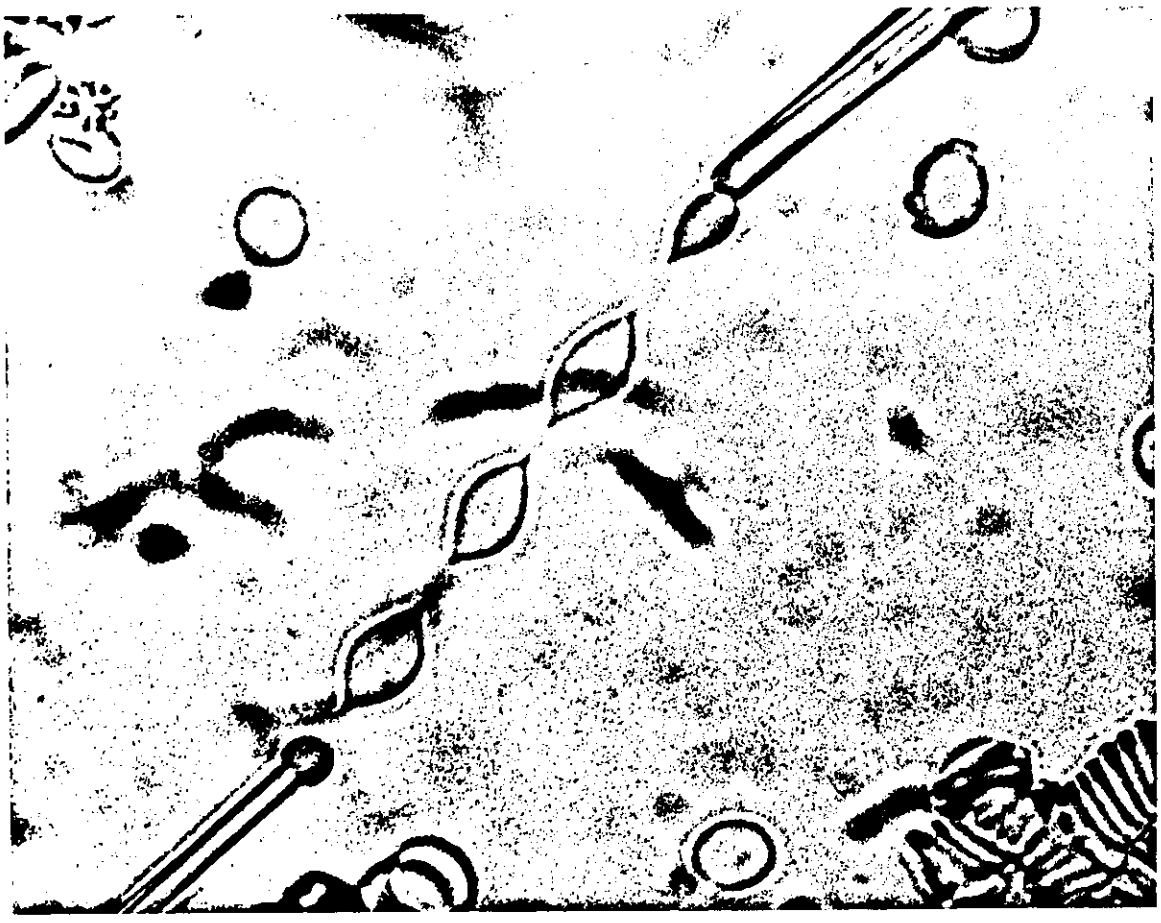


Fig 6

Fig 7



(79)

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