INTERNATIONAL ATOMIC ENERGY AGENCY
UNITED NATIONS EDUCATIONAL, SCIENTIFIC AND CULTURAL ORGANIZATION
INTERNATIONAL CENTRE FOR THEORETICAL PHYSICS
I.C.T.P., P.O. BOX 586, 34100 TRIESTE, ITALY, CABLE: CENTRATOM TRIESTE

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

INTERNATIONAL CENTRE FOR SCIENCE AND HIGH TECHNOLOGY
c/o INTERNATIONAL CENTRE FOR THEORETICAL PHYSICS 34100 TRIESTE (ITALY) VIA GRIGNANO, 9 (ADRIATICO PALACE) P.O. BOX 586 TELEPHONE 040-224572 TELEFAX 040-224575 TELEX 460449 APH I

SMR.648 - 55

SECOND AUTUMN WORKSHOP ON MATHEMATICAL ECOLOGY

(2 - 20 November 1992)

"Natural Selection and the Dynamic Coexistence of Defective and Complementing Virus Segments"

E. Szathmary
Roland Eotvos University
Dept. of Plant Taxonomy and Ecology
H-1083 Budapest
Hungary

These are preliminary lecture notes, intended only for distribution to participants.

MULTICOMPARTMENT VIRUSES

Sean Nee's treatment: J. Mol. Evol. (1987) 25, 27; 281

complete virus:

$$W_C = K_C q^L$$

- L: genome length
- q: copying fidelity
- K_C: number of copies made within a cell.
- W_C: fitness

incomplete viruses (coviruses)

$$W_I = K_I q^{L/2} R$$

- R: probability of complementation
- $K_{I_1} \stackrel{?}{=} K_{I_2}$

I increases in frequency if:

$W_I > W_C$, i.e. $\boxed{R/q^{L/2} > K_C/K_I.}$

What is the upper limit for $R/q^{L/2}$?

Junk molecules must be complemented doubly:

$$W_J = K_J R^2$$

I-J equilibrium is possible if:

$W_J < W_I$; i.e. $\boxed{R/q^{L/2} < K_I/K_J.}$

Fixation of I is possible if

$$\boxed{1 > K_C/K_I < K_I/K_J \gtrless 1}$$

$\gtrless$?

VIRUS DYNAMICS BASED ON THE "STRUCTURED DEME" MODEL OF WILSON (1975, 1980)

Szathmáry, E. J. theor. Biol. (1992) 157, 383-406.

Virus (V) and Defective Interfering (DI) Particle

Dynamics in homogeneous environment:

$[V] = x$

$[DI] = y$

$$\dot{x} = a x^2 = a x x$$

$$\dot{y} = b x y \qquad b > a$$

Average subjective frequencies:

$$\rho_p = \sum_p' P_p p^2 / \sum_p' P_p p = p + \sigma_p^2 / p$$

as p sees itself

the relative frequency of trait groups where the relative frequency of V is p.

variance in relative frequency of V across all trait groups

$$\rho_q = p - \sigma_{pq} / q$$

Let N be the fixed cell size, then IF distribution of viruses is binomial:

$$\sigma_p^2 = p(1-p)/N \quad \sigma_{pq} = pq/N$$

Dynamics of relative frequencies in the GENE POOL:

$$\dot{p} = a_p N p_p - p\bar{w}$$
$$\dot{q} = b_q N p_q - q\bar{w}$$

V wins if

$$N < b/(b-a)$$

V and D1 coexist if

$$N > b/(b-a) \qquad \hat{p} = a/[(b-a)(N-1)]$$

If $N = 2$, then pairwise interaction:

game equation:

$$\begin{array}{c} \\ V \\ D1 \end{array} \begin{array}{c} \begin{array}{cc} V & D1 \end{array} \\ \begin{bmatrix} 2a & a \\ b & 0 \end{bmatrix} \end{array}$$

- V wins, $\hat{p} = 1$ is ESS if $2a > b$
- Mixed ESS $\hat{p} = a/(b-a)$ if $2a < b$.

Same can be proven, using Cohen & Eshel (1976), assuming:

- Poisson distribution
- no fixed coinfection group size.

Expected coinfection group size ~ multiplicity of infection (m.o.i).

- Mutation-selection balance can be calculated
- Alternative model for interference possible:

Competitive exclusion of V-DI by a resistant virus (R):

$$\dot{p} = a_p N p_p - p w$$
$$\dot{q} = b_q N p_q - q w$$
$$\dot{r} = a_r N r_r - r w$$

assuming multinomial distribution

- Payoff matrix:

	V	DI	R
V	aN	a	a
DI	$b(N-1)$	0	0
R	a	a	aN

- using Stadler & Schuster (1990):

- R cannot invade when rare!

- Mutation terms are necessary:

$$\dot{p} = a_p N p_p (1 - \mu - \xi) - p\bar{w}$$
$$\dot{q} = b_q N p_q + a_p N p_p \mu - q\bar{w}$$
$$\dot{r} = a_r N r_r + a_p N p_p \xi - r\bar{w}$$

- R successfully invades a D+V system.

Stable coexistence of coviruses (C):

homogeneous system

$$\dot{x} = a_x x x_y$$
$$\dot{y} = b_y y x_y \qquad a \neq b$$

$$\dot{p} = a_p N p_p N q_p - p\bar{w}$$
$$\dot{q} = b_q N p_q N q_q - q\bar{w}$$

simplifies to [Using Hofbauer & Sigmund (1988)]:

$$\dot{p} = a(pN+q) - pw$$
$$\dot{q} = b(qN+p) - qw$$

$a \neq b$ competition of segments.

STABLE COEXISTENCE:

$$\hat{p} = \frac{bN - a(N-2) + \sqrt{a^2N^2 - 2ab(N^2-2) + b^2N^2}}{2(a-b)(N-1)}$$

if $b > a$. $\hat{p} = 1/2$ if $b = a$.

- Similar result with bivariate Poisson and varying coinfection group size.

The establishment of coviruses (C) against a Virus (V):

$$\dot{p} = b_p N p_p N q_p + b_p N r_p - pw$$
$$\dot{q} = b_q N p_q N q_q + b_p N r_q - qw$$
$$\dot{r} = a_r N r_r - rw \qquad (b > a)$$

C segments are DIs of V.

- After internal equilibration $p = q$.

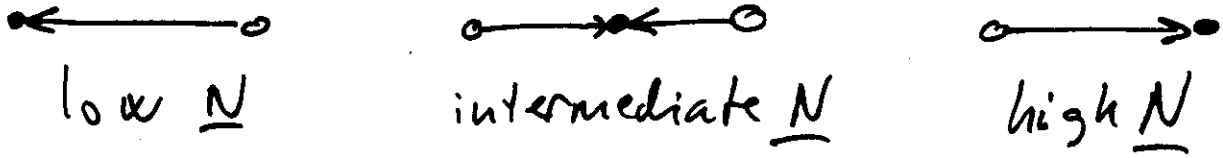
Let $x = p+q = 2p$. new variable:

$$\dot{x} = bx(x^2N/4 - x^2/4 + x(2+r)(N-1) - xw$$

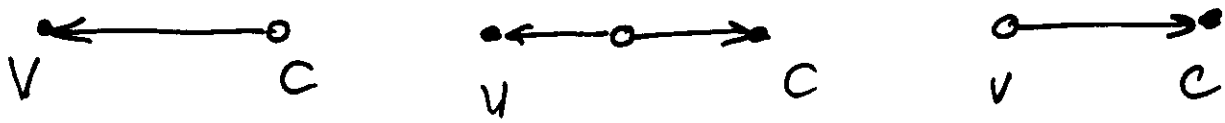
$$\dot{r} = ar(rN + 1 - r) - rw \qquad x + r = 1.$$

Equilibria:

- if $b > 2.78a$



- if $b < 2.78a$



C wins if N is high enough.

PLAYING THE FIELD IN VIRUS DYNAMICS

Two types of particle: V and D).

$$\dot{x} = x\left[\sum_{m=0}^{n-1}\binom{n-1}{m} x^m (1-x)^{n-1-m} b_{m+1} - dn - c - \Phi\right]$$

- x: relative frequency of V
- b_{m+1}: personal benefit if m+1 members cooperate (are V's)
- dn: d: nonspecific decay rate
- c: cost of cooperation
- n: group size $\rightarrow$ "carrying capacity".

$$\Phi = x\left[\sum_{m=0}^{n-1}\binom{n-1}{m} x^m (1-x)^{n-1-m} b_{m+1} - c\right] - dn + (1-x)\left[\sum_{m=0}^{n-1}\binom{n-1}{m} x^m (1-x)^{n-1-m} b_m\right]$$

- Φ: mean fitness
- $(1-x)$: D's particles
- dn: specific "cost of commonness"

$$\delta_m = b_{m+1} - b_m$$

crucial Motro (1991) JTB

$$b_m = \beta m^s / (k + m^2)$$

δ_m has a hump

- benefit: { synergistic at low m (1); diminishing returns at high m (2)

(1) cost of rarity → Allee effect

(2) saturation of the cells' catalytic machinery

- Varying group size n:

total number of ~~cells~~ particles: N

total number of cells: C

Poisson distribution of n → $\lambda = N/C$

- formal dynamics:

$$\boxed{\dot{N} = \Phi N}$$ (c.f. coevolutionary models)

Rearrangements:

crucial role

$$\dot{x} = x(1-x)\left[\sum_{m=0}^{n-1}\binom{n-1}{m} x^m (1-x)^{n-1-m}\delta_m - c\right]$$

$$\dot{N} = N\left[\sum_{m=0}^{n-1}\binom{n-1}{m} x^m (1-x)^{n-1-m}\left(x b_{m+1} + (1-x) b_m\right) - xc - dn\right]$$

$$\dot{x} = x(1-x)\left[\sum_{n=1} e^{-\lambda}\lambda^n/n! \sum_{m=0}^{n-1}\binom{n-1}{m} x^m (1-x)^{n-1-m}\delta_m - c\right]$$

$$\dot{N} = N\left\{\sum_{n=1} e^{-\lambda}\lambda^n/n!\left[\sum_{m=0}^{n-1}\binom{n-1}{m} x^m (1-x)^{n-1-m}\left(x b_{m+1} + (1-x) b_m\right) - dn\right] - xc\right\}$$

- Vector field plots of the system without and with Poisson distribution:

$N = nC$ ↓

highly similar

- growth rate landscapes.

- possibility of oscillations and death

Discrete time version

- numerical solutions.
  - stable oscillations: small β and d
  - long-period (50 time step oscillations): higher β, d
  - $X(0)$ decreases: time to extinction decreases
  - apparent chaotic states (extreme sensitivity to initial conditions)
  - marked increase in β: self-arrest → extinction.

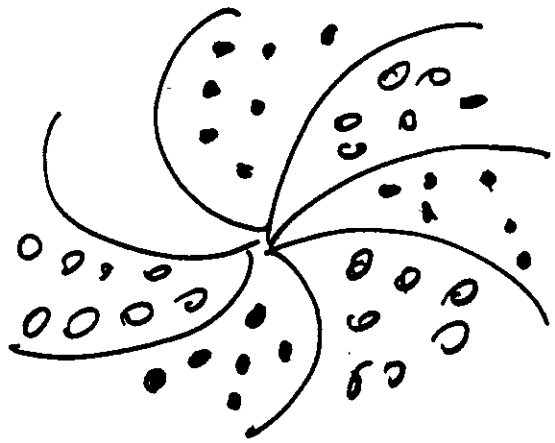
- Classical results in experiments in vitro
  - C appears constant
  - all dynamic phenomena

Palma & Huang (1974) J. Infect. Dis.

vesicular stomatitis virus (VSV)

THE ROLE OF SPATIAL HETEROGENEITY

1)

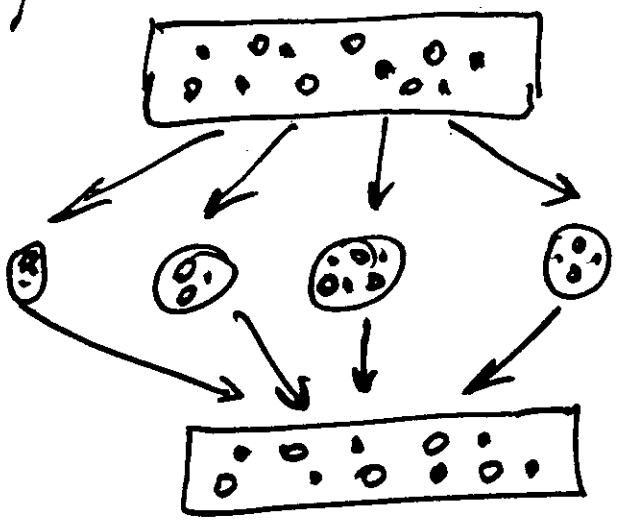


- self generated structures

"Cellular automaton"

Boerlijst & Hogeweg 19
Nowak & May 1992

2)

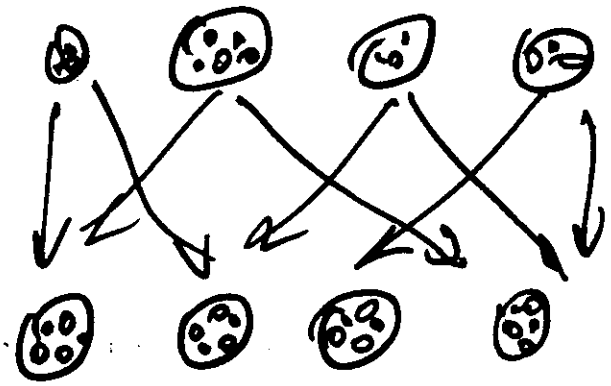


- structured deme

"trait group"

Wilson, 1980

3)



- group selection

(e.g. stochastic corrector model)

Szathmáry 1986

Szathmáry & Demeter, 1987.

ıfection groups is above a certain minimum (Szathmáry, 1992). An analogous
: was treated by Michod (1983) showing by a trait group model that DI molecules
ld be controlled by population structure imposed on prebiotic replicators.
Maynard Smith (1983) criticized Wilson's model mainly for semantic reasons. He
ıted out that it is incorrect to refer to it as a model of genuine group selection.
: term group selection ought to be spared for cases where the units of evolution
lergoing multiplication, heredity, and variation, are in fact the groups and not
individuals. In Wilson's model it is the change in gene frequency from one global
)l to the next one in time that we calculate, rather than the change in group
ıuency from one set of groups to the next one in time. Leigh (1938) expressed the
ıe opinion: "I mean by group selection the differential mortality and replication
groups, which to my mind seems meaningful only if one can single out ancestors
descendants of groups. I do not think that the trait-group selection of Wilson

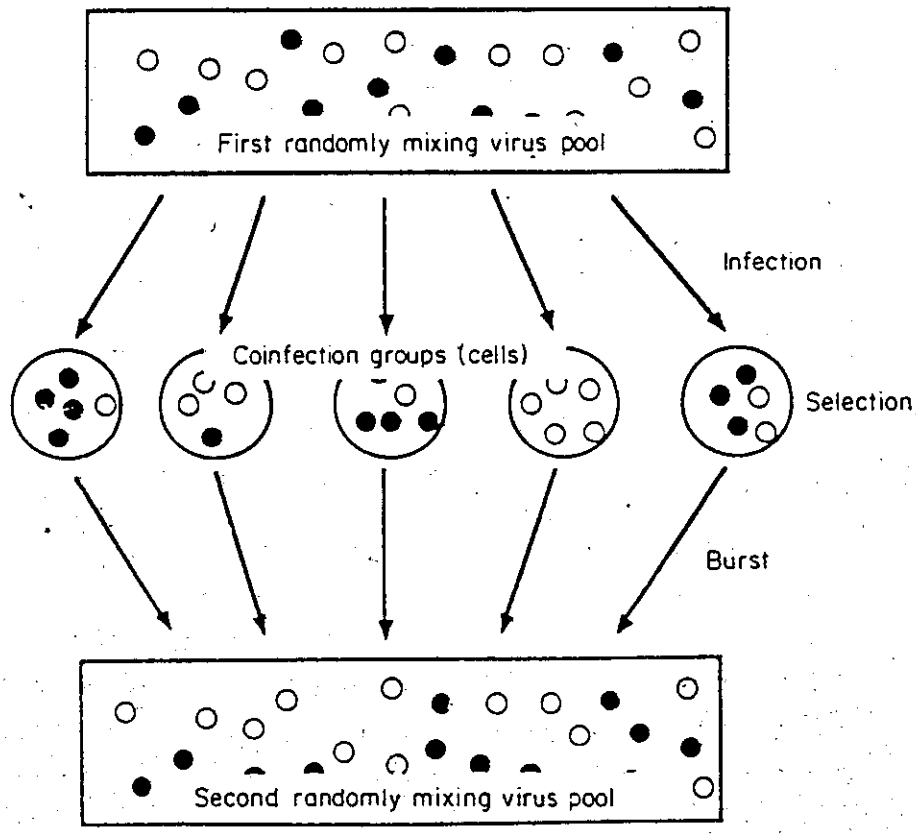


FIG. 1. A "structured deme" of coviral replication. (From Szathmáry, 1992).

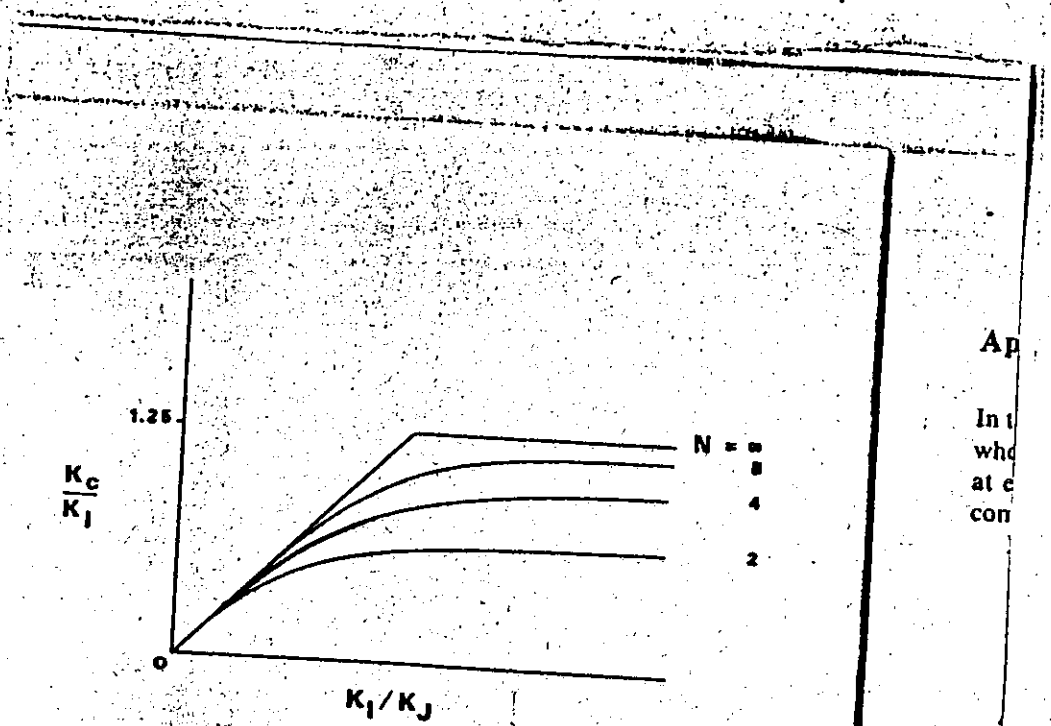


Fig. 2. It is assumed that replication fidelity is 0.8 and that complementation probability, R, is given by $R = 1 - \exp[-N(1 - p)/2]$, where N is the transmission multiplicity and p is the proportion of junk in the population. For a particular transmission multiplicity, fixation will occur in the dotted region below the corresponding curve.

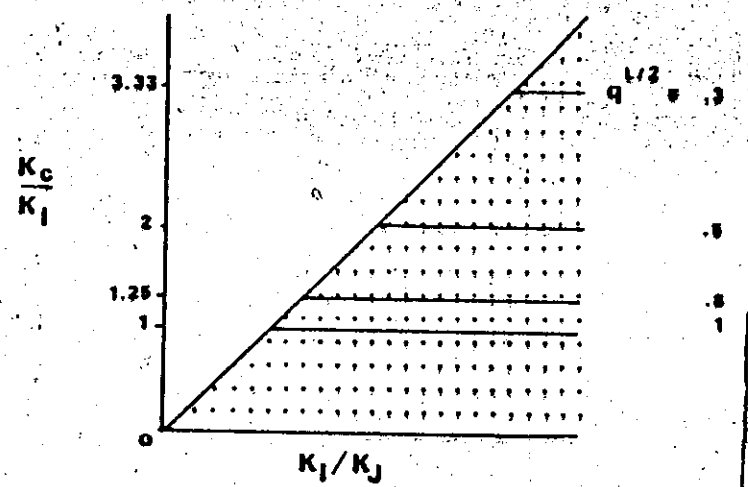


Fig. 1. The dots show the region of $(K_I/K_J, K_C/K_I)$ parameter space for which the fixation condition, $R/q^{1/2} > K_C/K_I$, can possibly be satisfied for some combination of R and $q^{1/2}$. When the condition is satisfied, the complete virus is entirely eliminated from the virus population. Multicompartmentalism cannot possibly evolve in the undotted region of the picture. Each horizontal line corresponds to a particular replication fidelity. The line intersects the K_C/K_I axis at the inverse of this fidelity. For a particular replication fidelity, fixation is only possible in the dotted region below the corresponding line. In this region, multicompartmentalism will evolve if transmission multiplicity, hence R, is sufficiently high.

functions: to resist Muller's ratchet (the loss by chance of the optimal genome class), and the reduction of mutational load when deleterious mutations act synergistically.

In the following I deal mainly with the conditions for dynamical coexistence of virus particles that are either defective or complementing each other. The primary examples considered in detail are the selection of defective interfering (DI) viruses in competitive situations, and the successful establishment and stable coexistence of co-viruses. Defective interfering particles are deletion mutants that are capable of replication only when complemented by the wildtype virus but then interfer with the reproduction of the latter. DI viruses arise spontaneously during replication. High moi increases the DI:standard ratio in cultures. Holland (1990) gives a useful summary of DI genome characteristics. Table 1 gives a list of DI-like genomes and multicompartment viruses.

TABLE 1

Defective viral genomes and multicompartment viruses from Holland (1990) *and Matthews* (1979), *respectively*

DEFECTIVE VIRAL GENOMES
Integrated defectives (e.g. defective lysogenic viruses)
Satellite viruses and RNAs
coliphage satellite
plant virus satellites (e.g. TNV, virusoids)
human satellite viruses (e.g. AAV)
Pseudovirions (containing host genome segment)
Helper-virus dependent DI viruses of
RNA viruses
Negative-strand RNA viruses
Positive-strand RNA viruses (picorniaviruses, alphaviruses)
Reoviruses
DNA viruses
Papovaviruses, Herpesviruses
MULTICOMPARTMENT VIRUSES
With two segments
Pea enation mosaic
Como
Tobra
Nepo
With three segments
Alfalfa mosaic
Ilar
Bromo
Cucumo

TNV, Tobacco necrosis virus; AAV, adeno-associated virus.

Bangham & Kirkwood (1990) constructed a deterministic model of a virus–DI system, tracking the numbers of standard virions, DI particles, uninfected cells, and cells infected by standard virons, DI particles, and both. They found that the initial moi of DI is decisive. Increased yield of the standard virus is possible only if the initial moi of DI particles is sufficiently low. The final yield of both viruses is dominantly influenced by this number. If it is too high, this can result in the disappearance of DI and standard viruses together ('self-curing'). The model accounts for the

product of the concentration of V and DI, since V provides the replicative machinery and DI provides the template [Fig. 1(a)]. In order to be consistent, replication of V should depend on the product xx or x^2, as in eqn (1a), since there the replicative machinery as well as the template is provided by V itself [Fig. 1(b)].

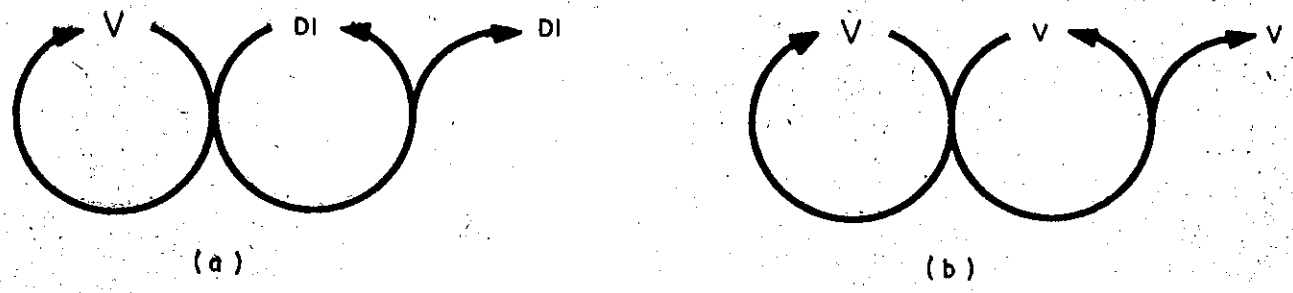


FIG. 1. Reproduction scheme for defective interfering (a) and wildtype (b) particles. The formal stoichiometry of the system indicates that V acts as a "catalyst" in the reproduction of two templates: V and DI, both of which are autocatalytic.

It is apparent that in the present model V forms a one-membered hypercycle (Eigen, 1971; Eigen & Schuster, 1978*a*): V catalyses the template replication of itself (double or second-order autocatalysis; Fig. 2). The quadratic growth term without an ecological constraint leads to strange behaviour: x reaches infinity in finite time. Various problems associated with such models (cf. Szathmáry *et al.*, 1988; Szathmáry, 1989*a*, 1991) suggest that care should be taken when applying them in modelling realistic systems: I shall come back to this problem in section 6.

2.1. A STRUCTURED DEME MODEL WITH FIXED COINFECTION GROUP SIZE

The mode of application of the structured deme model to our case is schematized in Fig. 3. I therefore assume that the gene pool becomes completely mixed when the viruses leave the cells after burst ["burst size" simply indicates the average number of all virus particles produced by a cell; cf. Bangham & Kirkwood (1990)]. Complete mixing (lack of viscosity) is assumed *within* coinfection groups as well. The number of cells and the size of the gene pool are very large.

We are interested in the dynamics of the relative frequency p of V and q of DI. To this end we must consider the overall help that an *average* virus gets from the others, averaged over all trait groups (cells; see Wilson, 1980 for the general description of the method). We assume that the per capita fitness of V is ...

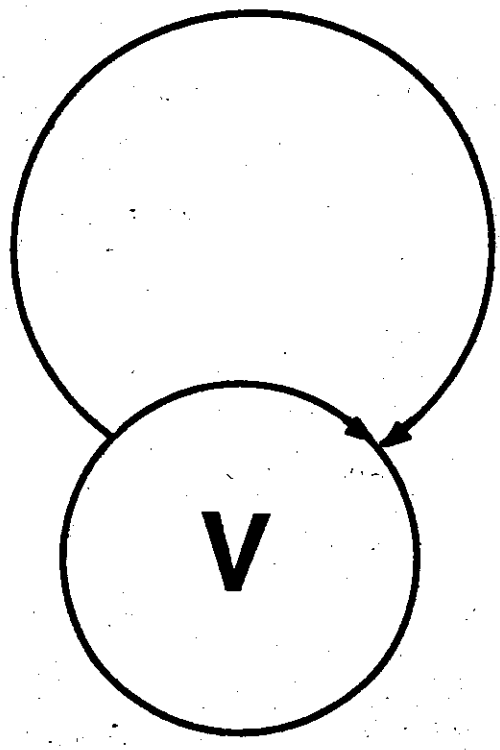


FIG.2. Reproduction of the wildtype virus V as a one-membered hypercycle: the two arrows indicate double autocatalysis, since V is a template and reproductive machinery at the same time.

is the average subjective *frequency* of V as V sees it. Thus, the per capita aid for an average V individual by other V's is proportional to the average subjectve *number* of V across trait groups as V sees it. p_p is a weighted average of the following form:

$$p_p = \sum_p^I P_p p^2 \Big/ \sum_p^I P_p p = p + \sigma_p^2/p \qquad (2a)$$

where P_p is the relative frequency of trait groups in which the relative frequency of V is p, and σ_p^2 is the variance in the relative frequency of V across all trait groups. Note how the variance increases the average subjective frequency of V to itself. Similarly, the average subjective frequency of V as DI sees it is

$$p_q = p - \sigma_{pq}/q \qquad (2b)$$

16

where μ and ξ are the mutation rates from V to DI and R, respectively. It is obvious that the edges V–DI and V–R cannot have fixed-points any more: whenever V is present, both DI and R must appear through mutations. There are only two fixed-points on the boundary of the simplex: the point $q=1$ and $r=1$. The former is unstable and the latter is stable.

The simplex interior is hard to analyse analytically. But, the exact details do not matter as far as we can decide whether R can successfully compete against V–DI. To this end consider the system (13) of the V–DI mutation-selection balance, which is a sub-system of (23). Imagine that in the beginning $r=0$ and ξ is zero, thus V and DI coexist. Then switch on ξ instantly. Will the system now reach the point $r=1$? If there is an attractor (any kind of attractor) in the simplex interior, then the basin of this should be separated from that of point $r=1$ by a separatrix. This separatrix may

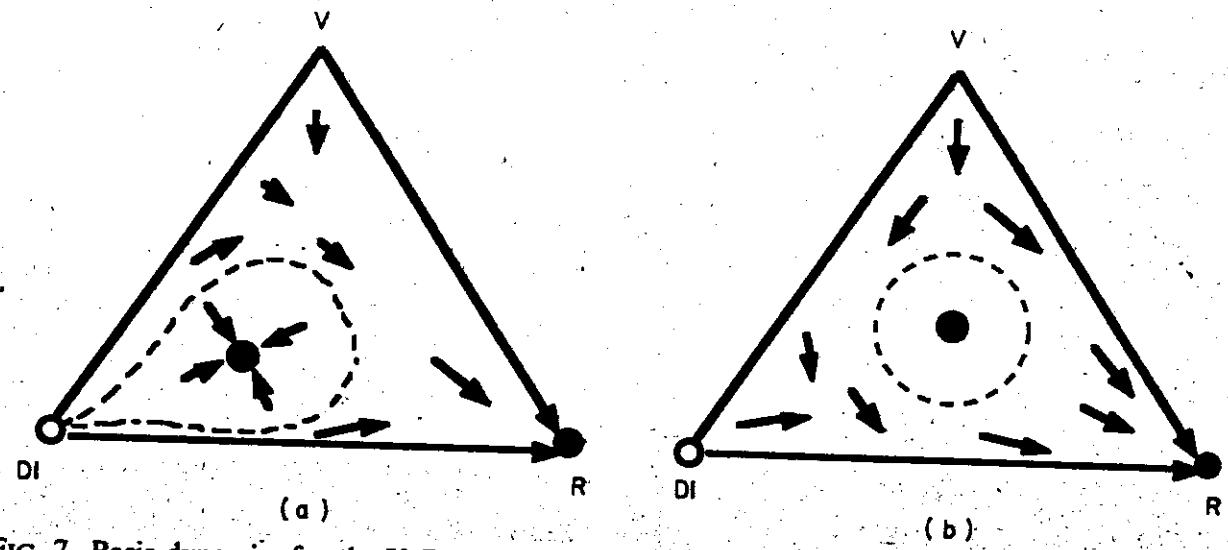


FIG. 7. Basic dynamics for the V–DI–R system with recurrent mutations. As there are only two fixed points on the simplex boundary, the point where R is alone should be accessible from the vicinity of the V–DI edge, even if there is a stable point with a certain domain of attraction in the simplex interior.

touch the simplex boundary at equilibrium points only (Fig. 7). Clearly, $r=1$ is excluded, since the separatrix cannot reach into this basin of attraction. The only choice is $q=1$, or a separatrix which does not touch the boundary at all (which must be an unstable limit cycle). In any case, the interior of edge V–DI will be a repellor, and its immediate vicinity will belong to the basin of attraction of the point $r=1$. It is concluded that when there is a measurable mutation rate from V to R, the latter competitively excludes the V–DI pair; in accord with the experiments.

4. The Stable Coexistence of Coviruses (C)

Coviruses are segmented, multicompartment viruses, where several or all segments, often each of th

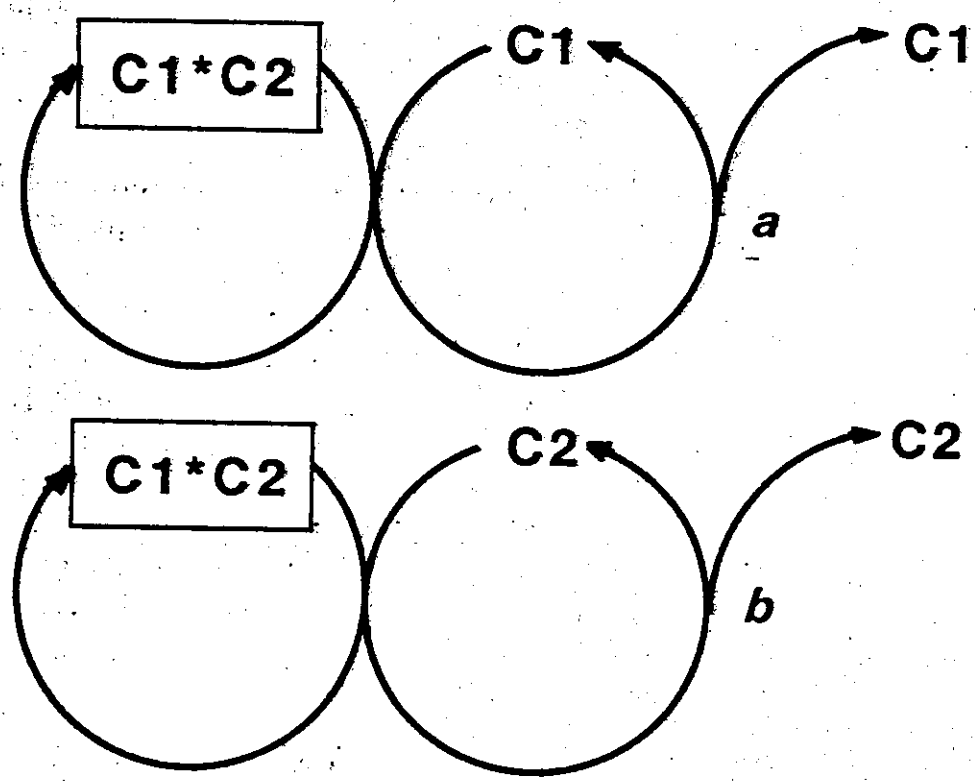


FIG. 8. Templates and reproductive machineries of coviruses. The former can be *either* segment C1 or C2, but the latter must be some complex of C1 *and* C2. Rate constants are indicated.

where w is the average fitness:

$$w = apNp_pNq_p + bqNp_qNq_q. \tag{25c}$$

Expanding the subjective frequencies we obtain:

$$\dot{p} = apq(pN+q)(N-1) - pw \tag{26a}$$

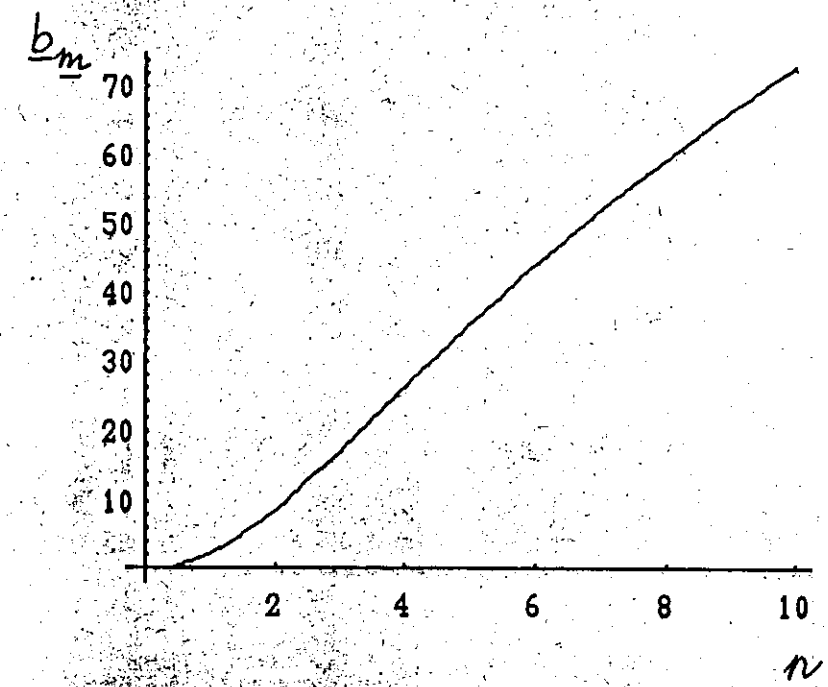
$$\dot{q} = bpq(qN+p)(N-1) - qw. \tag{26b}$$

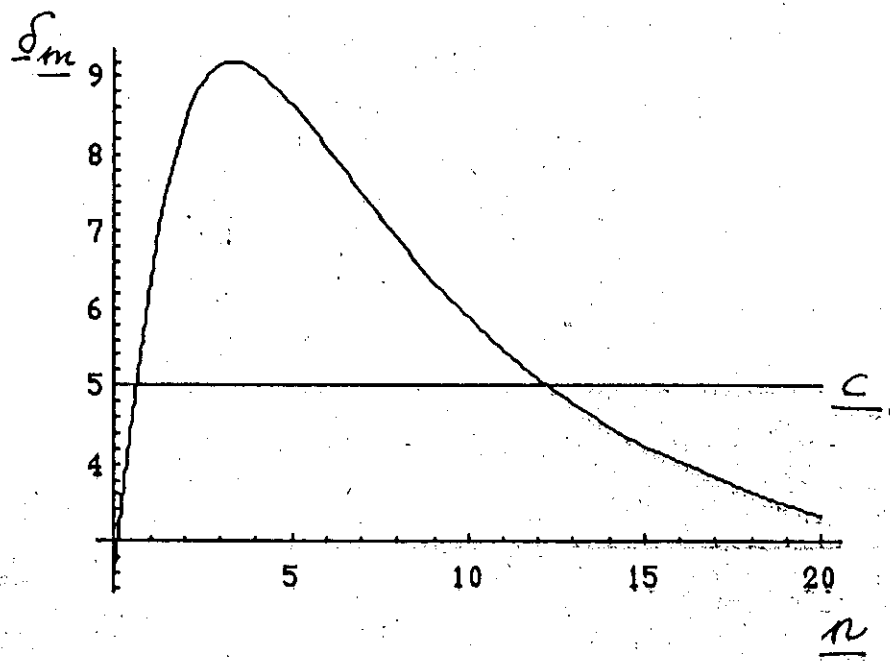
From the theory of dynamical systems we know (Hofbauer & Sigmund, 1988) that if we divide the *growth terms* in (26) by $pq(N-1)$ and modify w accordingly, the direction of the flows and the position of stable equilibria on the C1–C2 simplex will not change (a velocity transformation). Thus we obtain the system (which becomes linear in the basic growth terms):

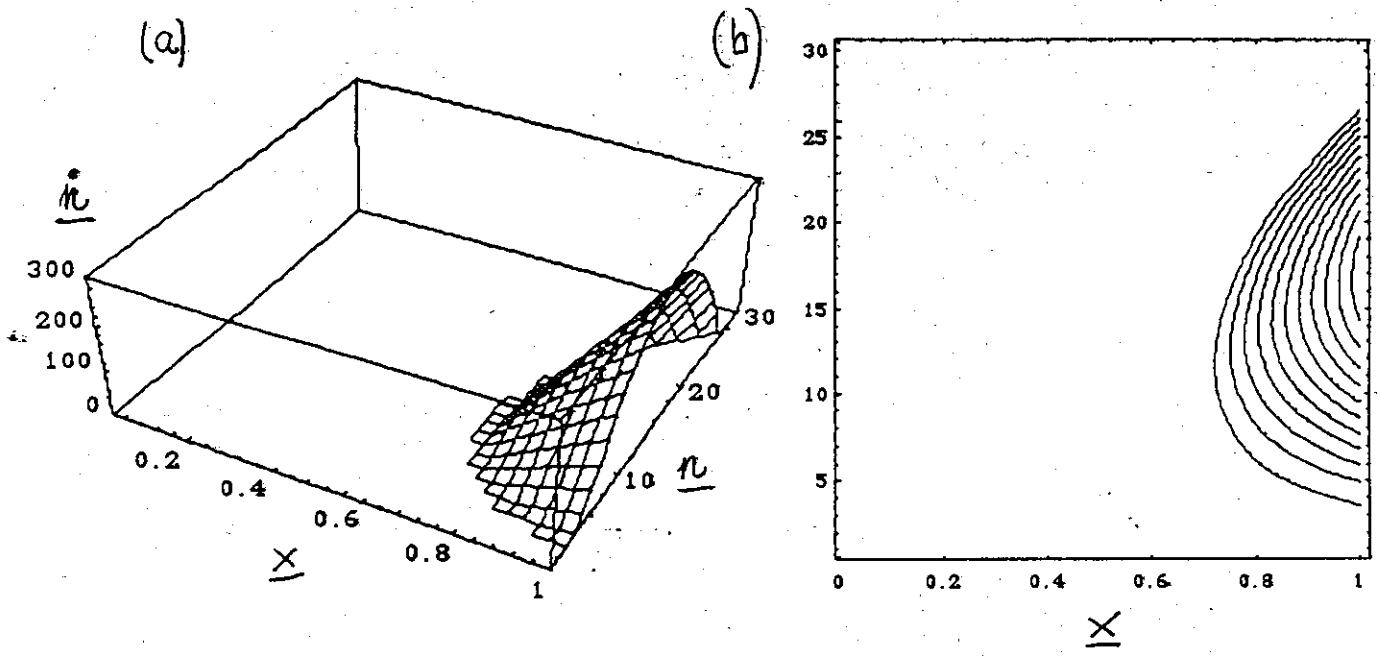
$$\dot{p} = a(pN+q) - pw \tag{27a}$$

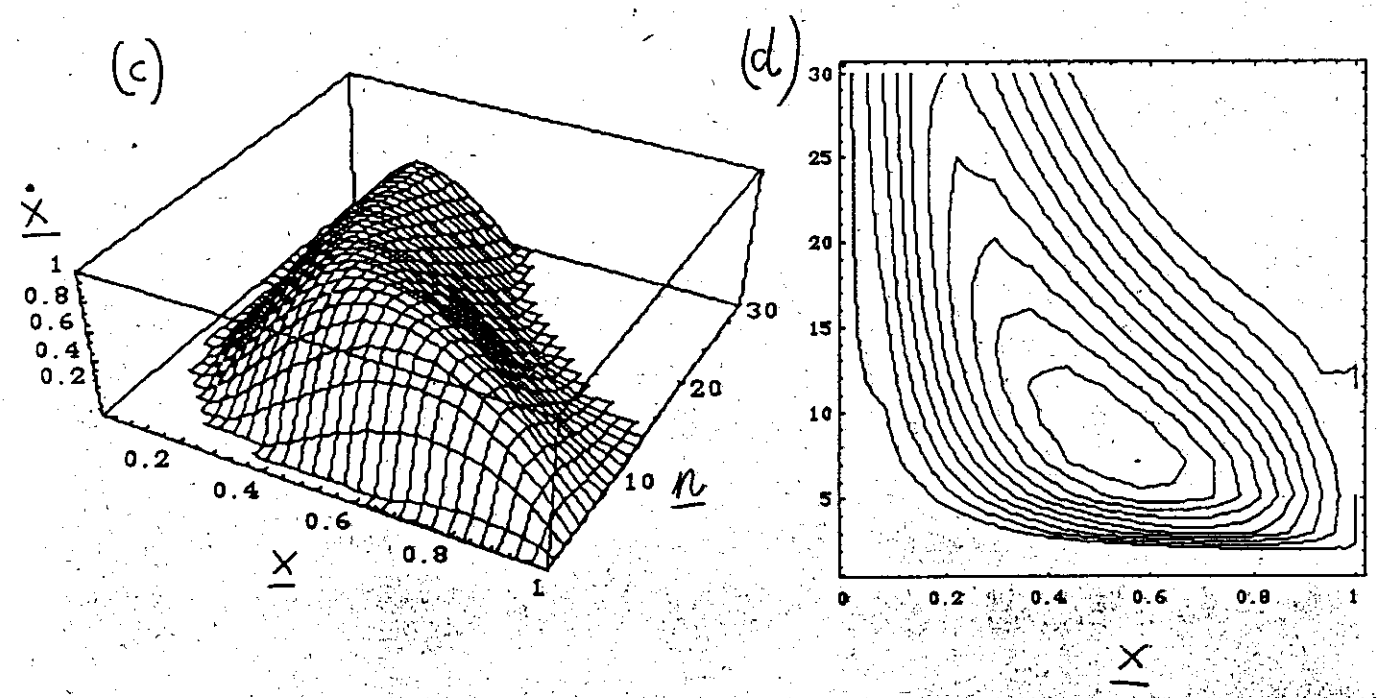
$$\dot{q} = b(qN+p) - qw \tag{27b}$$

from which it is apparent that both components can invade when rare irrespective of the sign of $(a-b)$. (Note that when N tends to infinity, the terms in brackets become pN and qN, respectively, and the whole system approaches the competition of the Malthusian replicators.) The position of the *stable internal equilibrium* is:

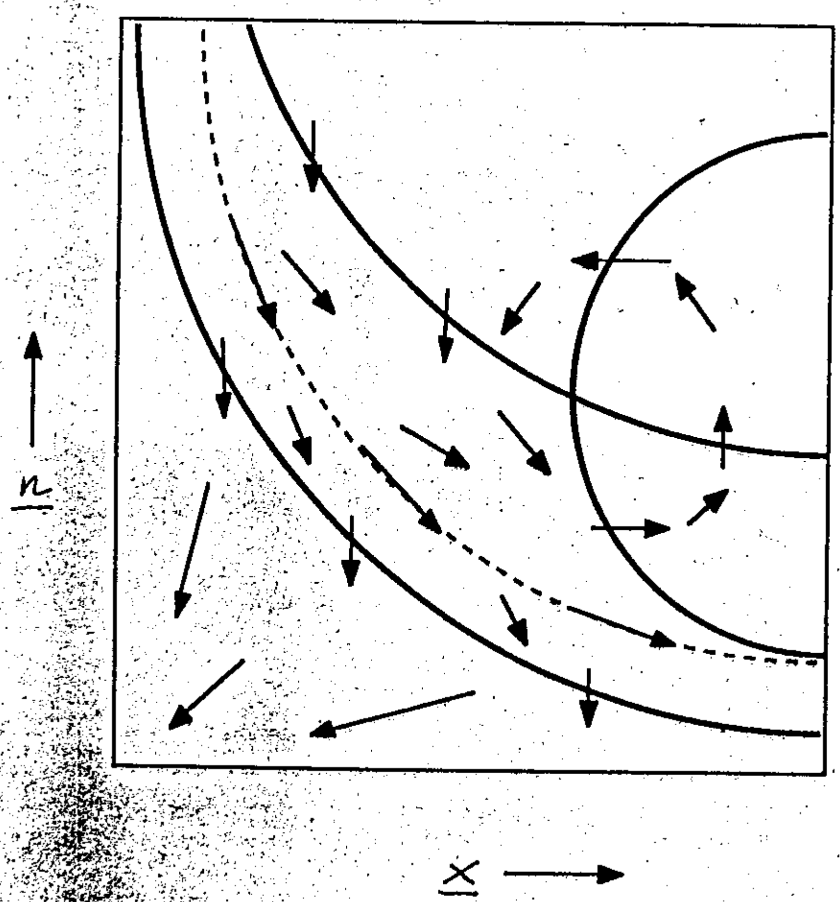

b_m
70
60
50
40
30
20
10
2
4
6
8
10
n


δ_m
9
8
7
6
5
4
c
5
10
15
20
n

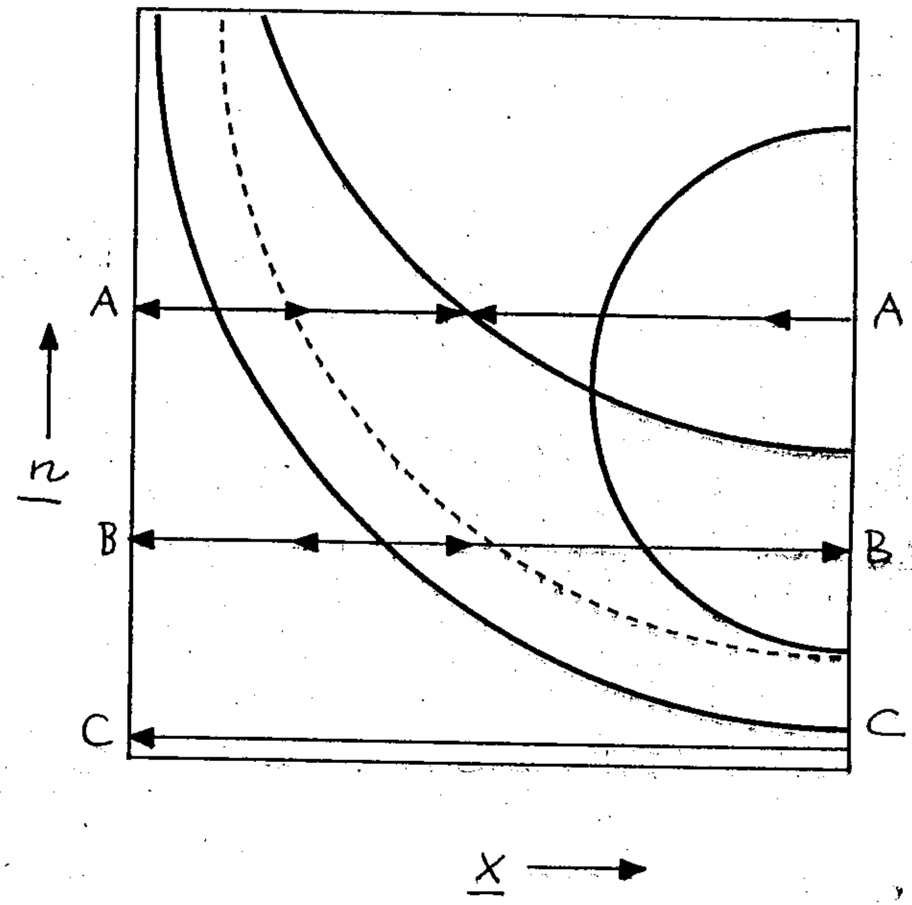

(a)
(b)
$\dot{n}$
300
200
100
0
0.2
0.4
0.6
0.8
1
X
30
20
10
n
30
25
20
15
10
5
0
0.2
0.4
0.6
0.8
1
X

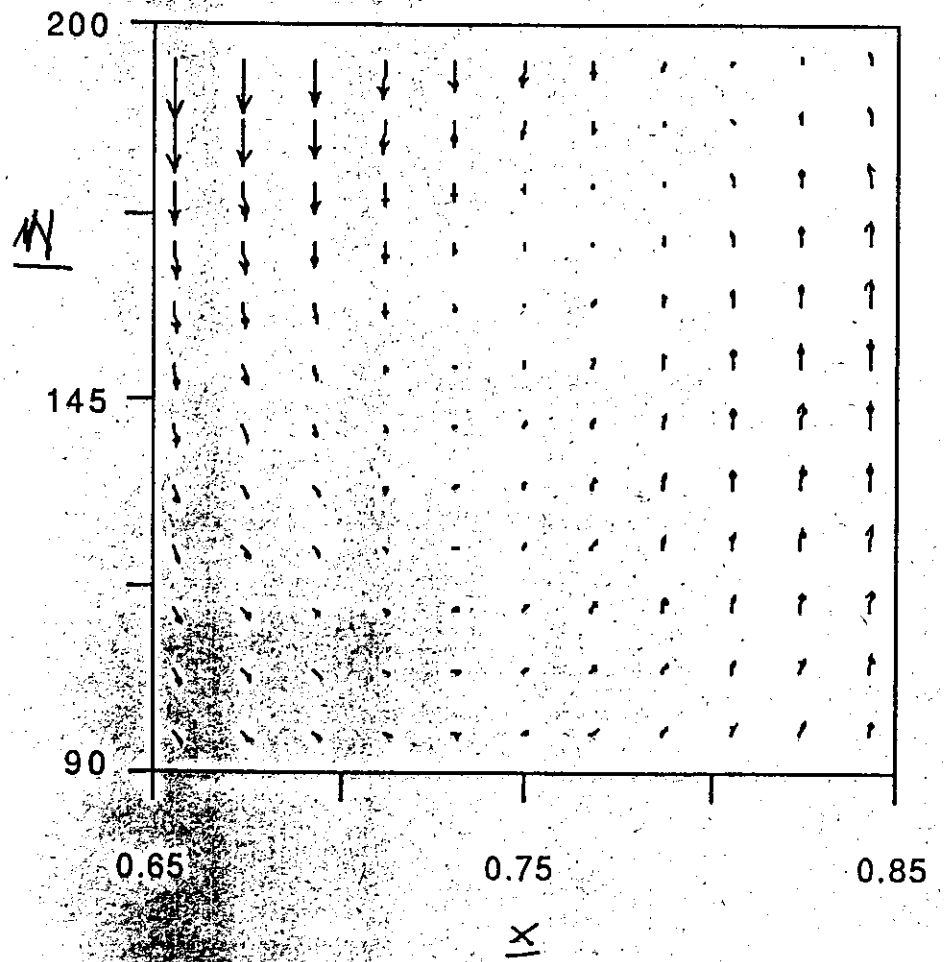

(c)
(d)
$\dot{X}$
1
0.8
0.6
0.4
0.2
0.2
0.4
0.6
0.8
1
X
30
20
10
n
30
25
20
15
10
5
0
0.2
0.4
0.6
0.8
1
X

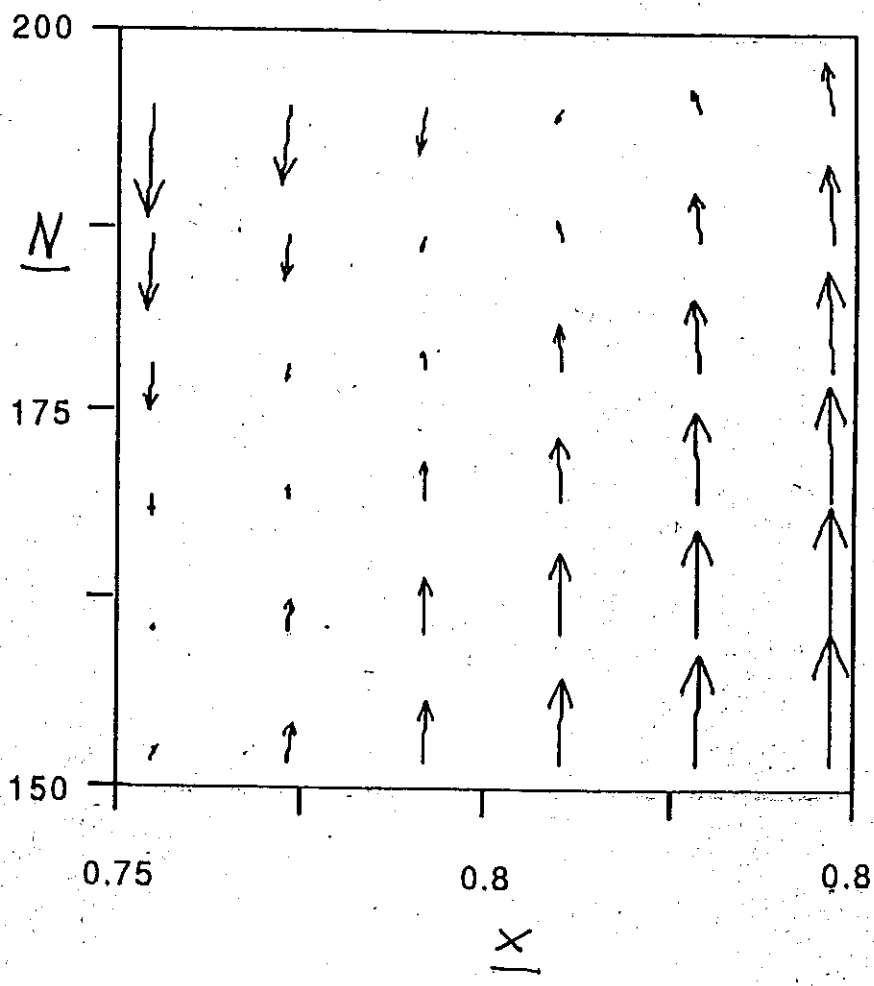
(a)

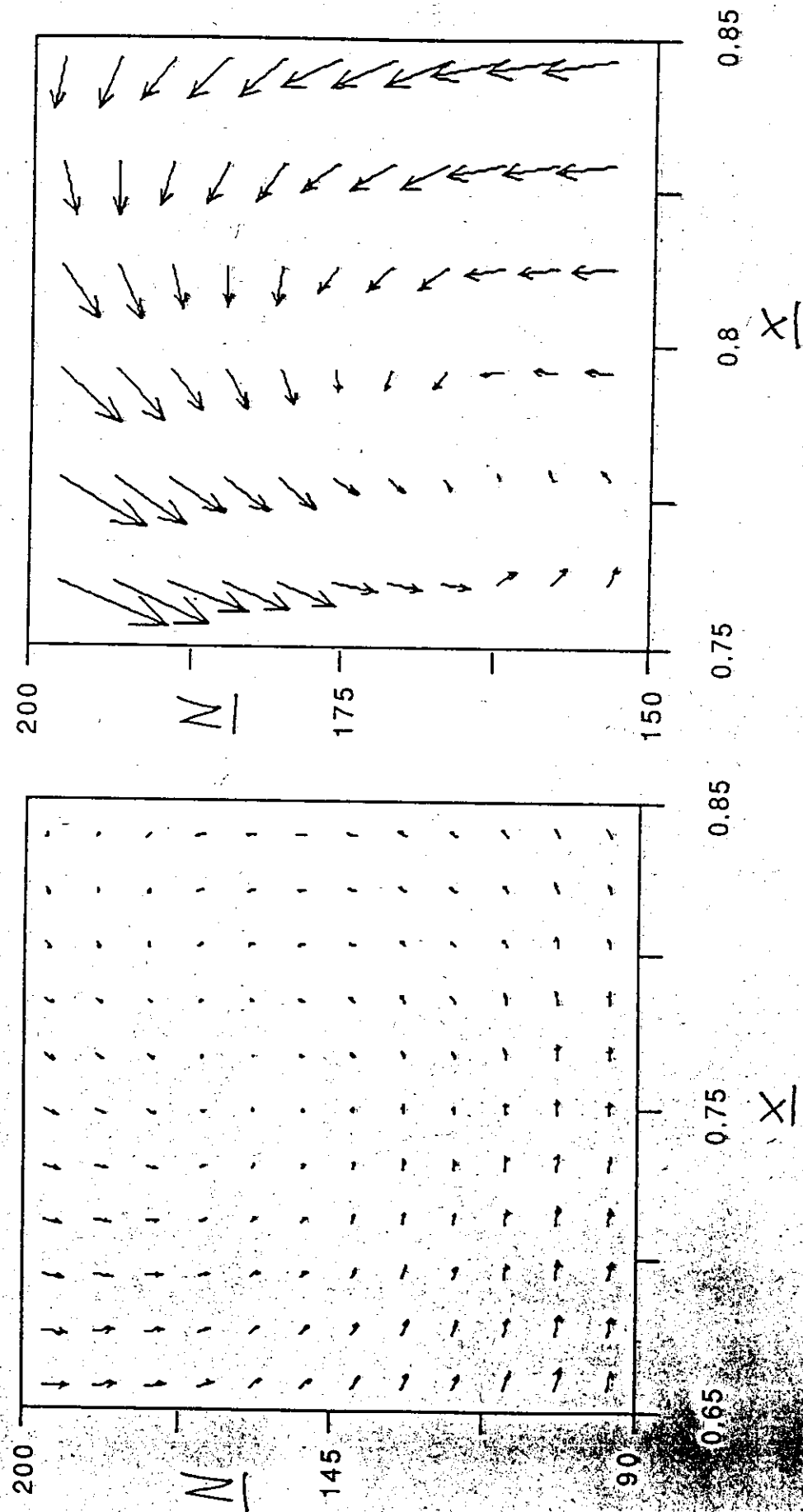


(b)

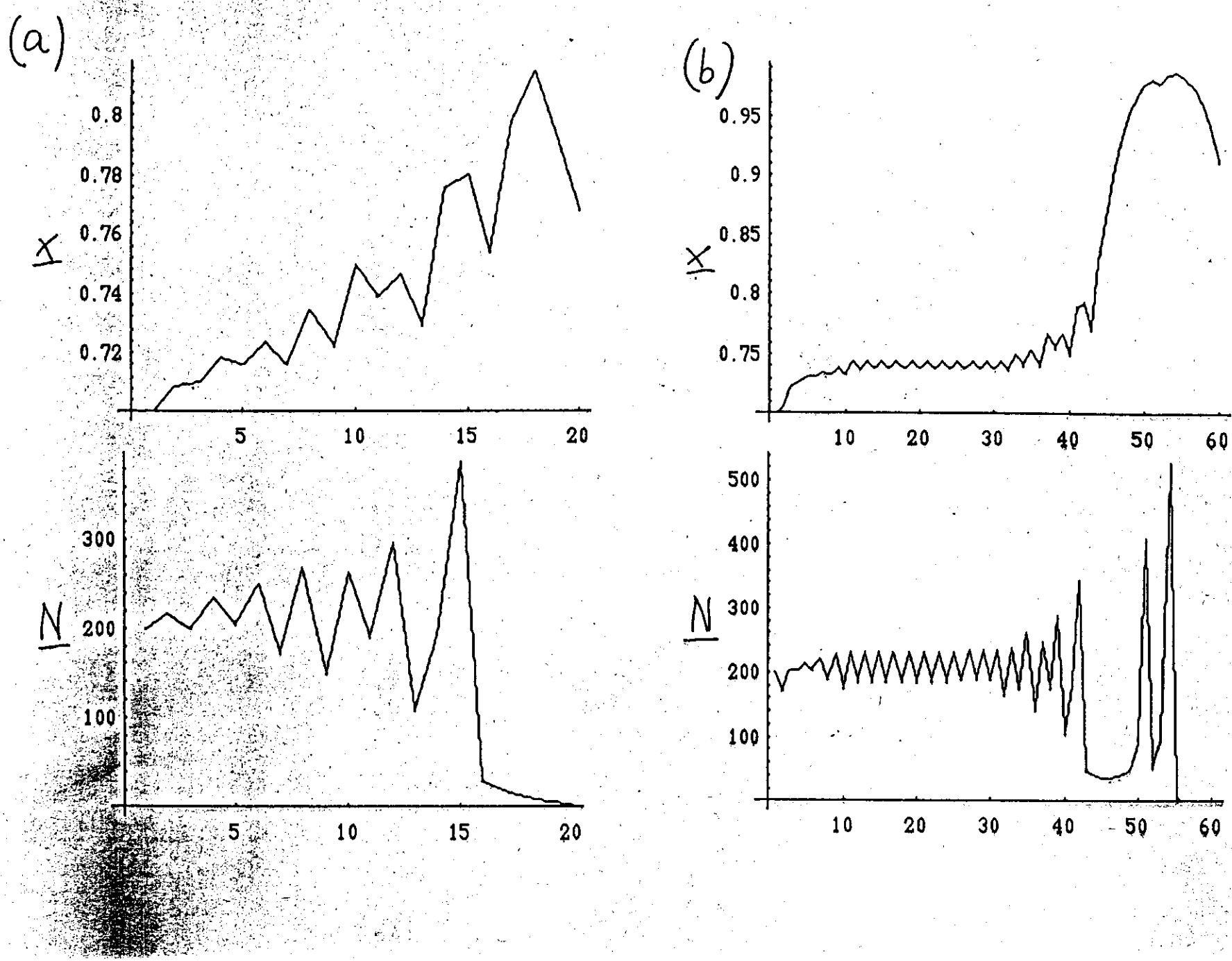


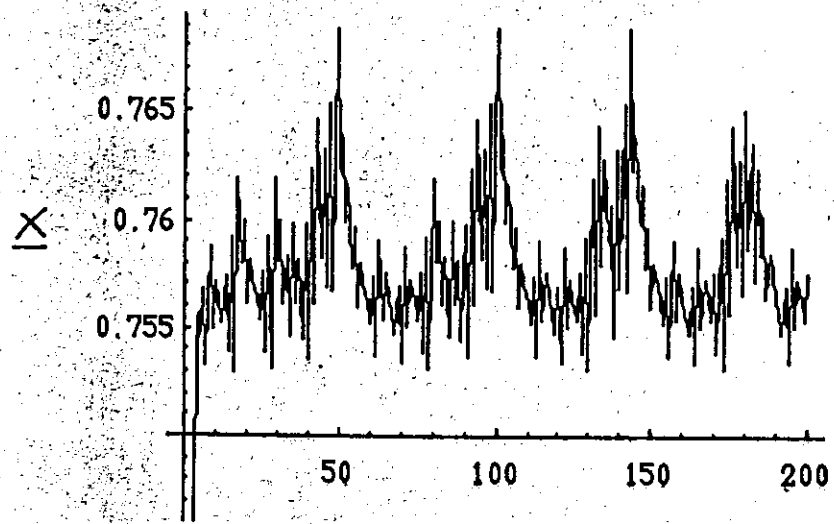

200
N
145
90
0.65
0.75
0.85
X

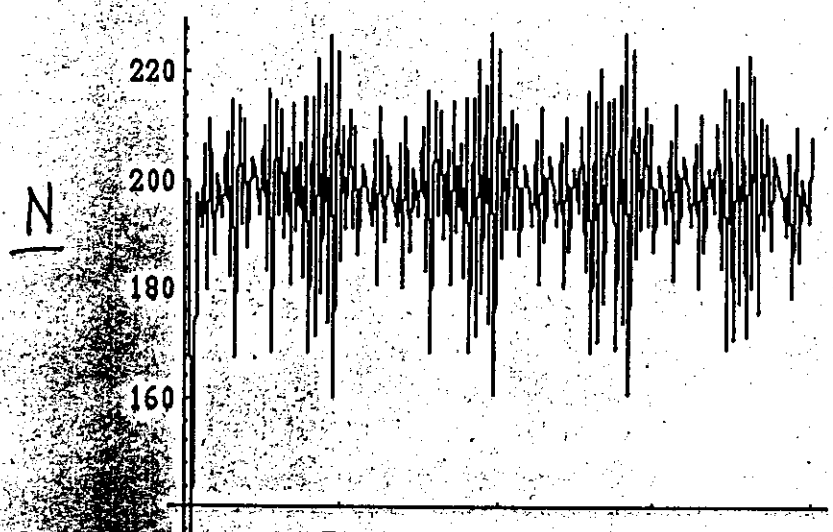

200
N
175
150
0.75
0.8
0.85
X

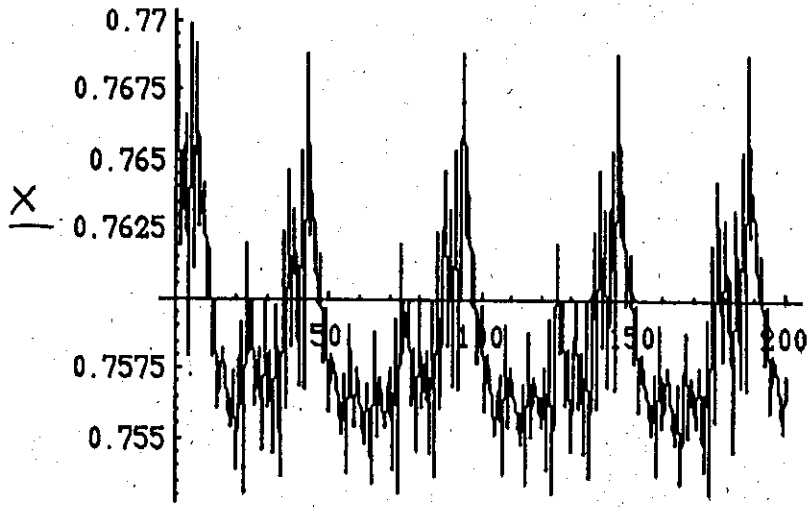

0.85
0.8
X
0.75
200
175
150
N

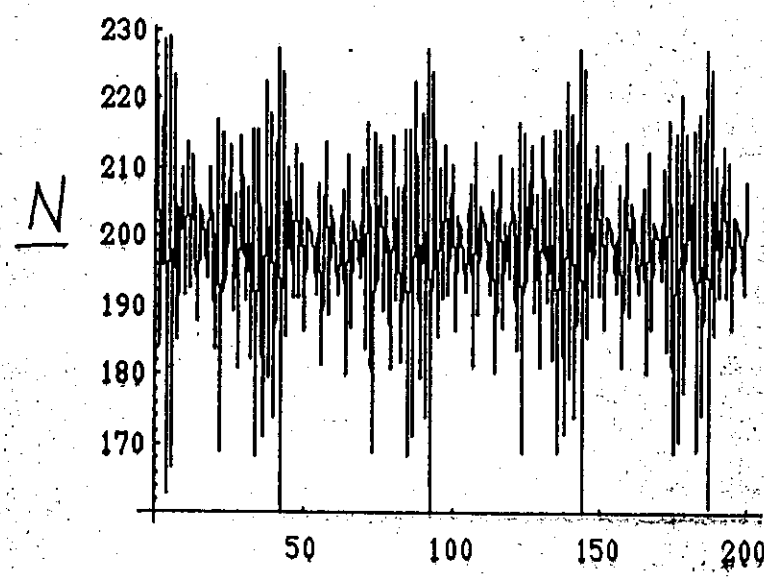
0.85
0.75
X
0.65
200
145
90
N

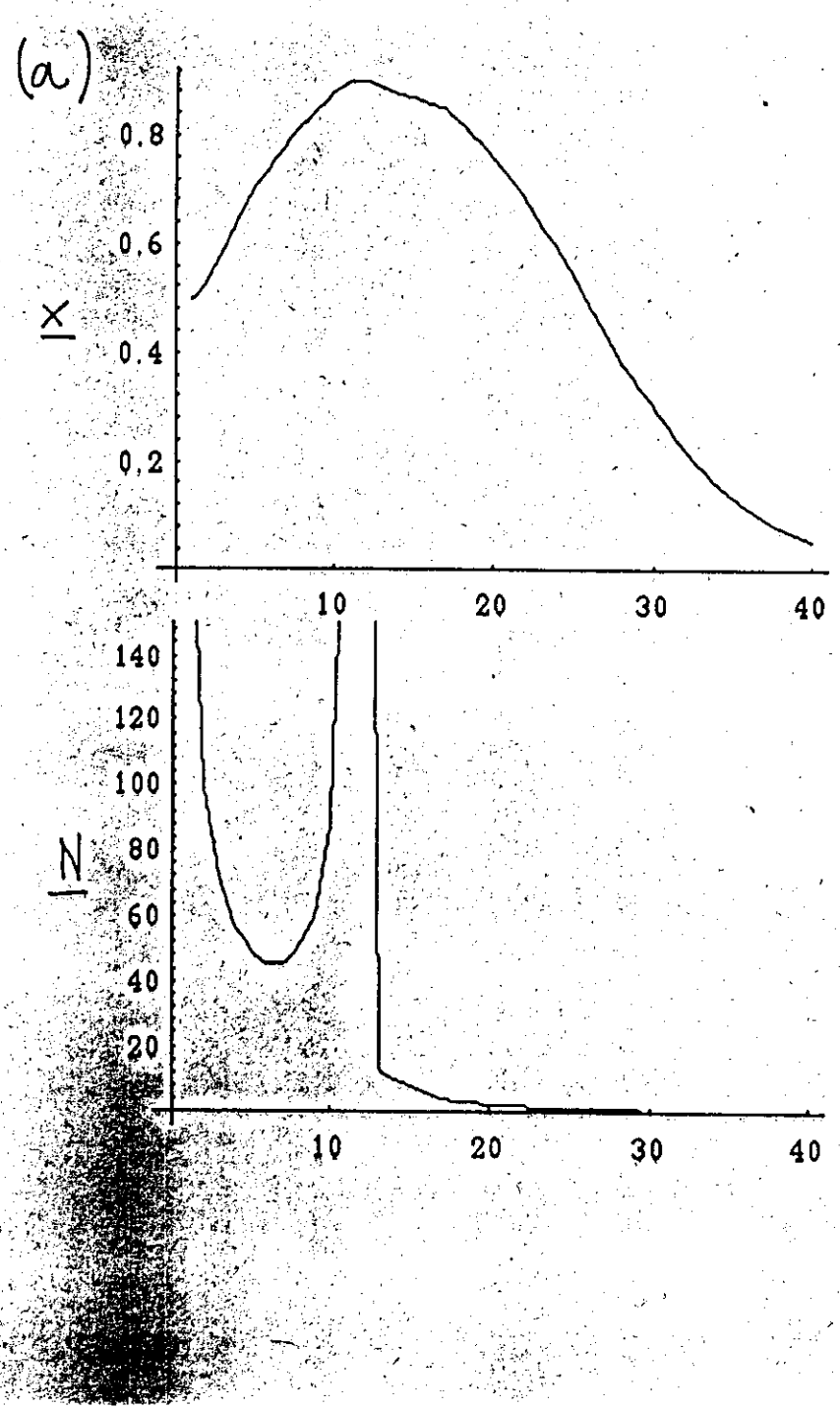

(a)
X
0.8
0.78
0.76
0.74
0.72
5
10
15
20
N
300
200
100
5
10
15
20
(b)
X
0.95
0.9
0.85
0.8
0.75
10
20
30
40
50
60
N
500
400
300
200
100
10
20
30
40
50
60

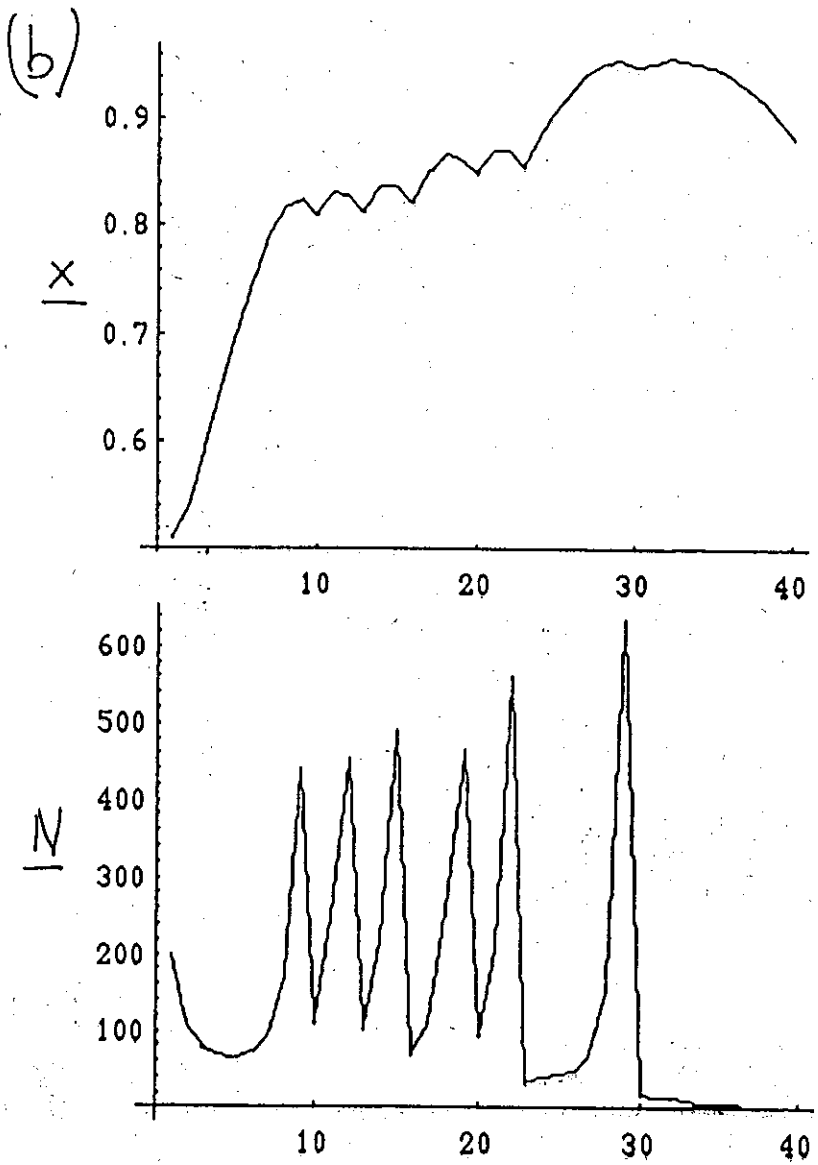

X
0.765
0.76
0.755
50
100
150
200

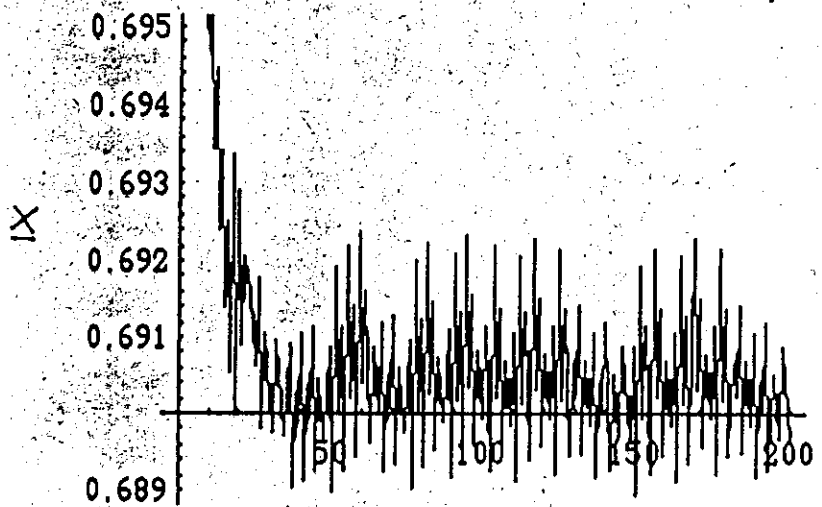

N
220
200
180
160
50
100
150
200

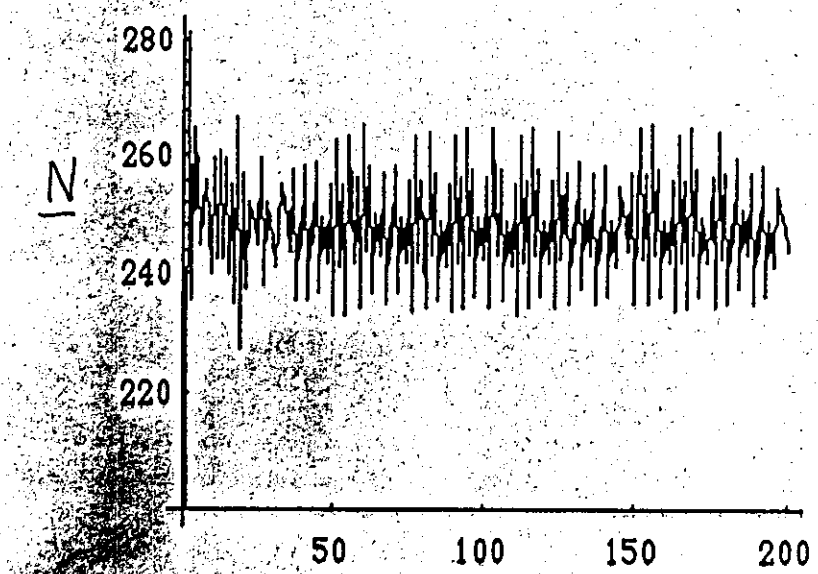

X
0.77
0.7675
0.765
0.7625
0.7575
0.755
50
100
150
200

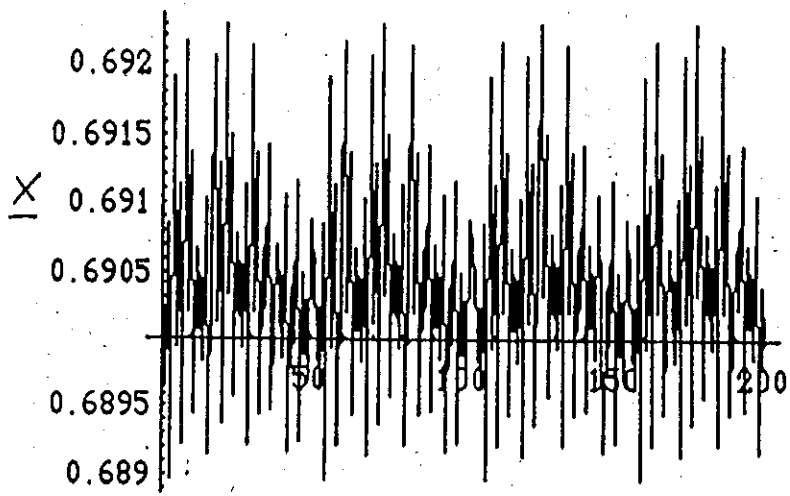

N
230
220
210
200
190
180
170
50
100
150
200

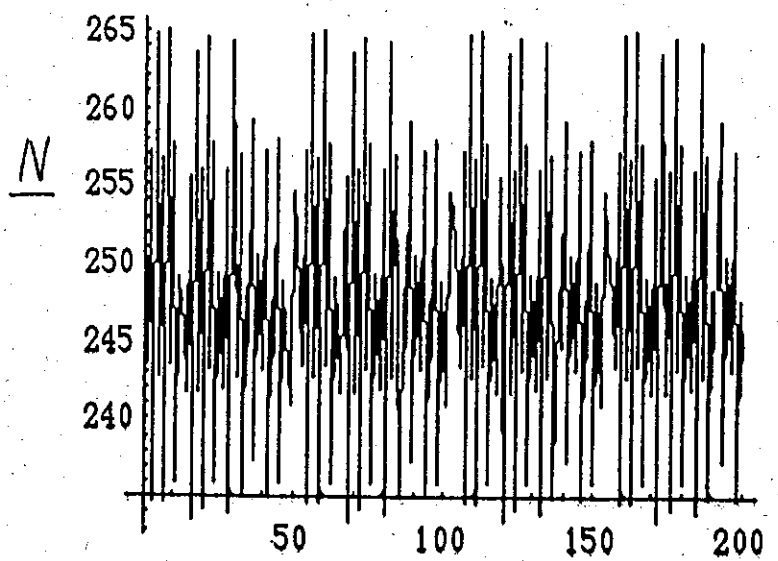

(a)
0.8
0.6
x
0.4
0.2
10
20
30
40
140
120
100
N
80
60
40
20
10
20
30
40

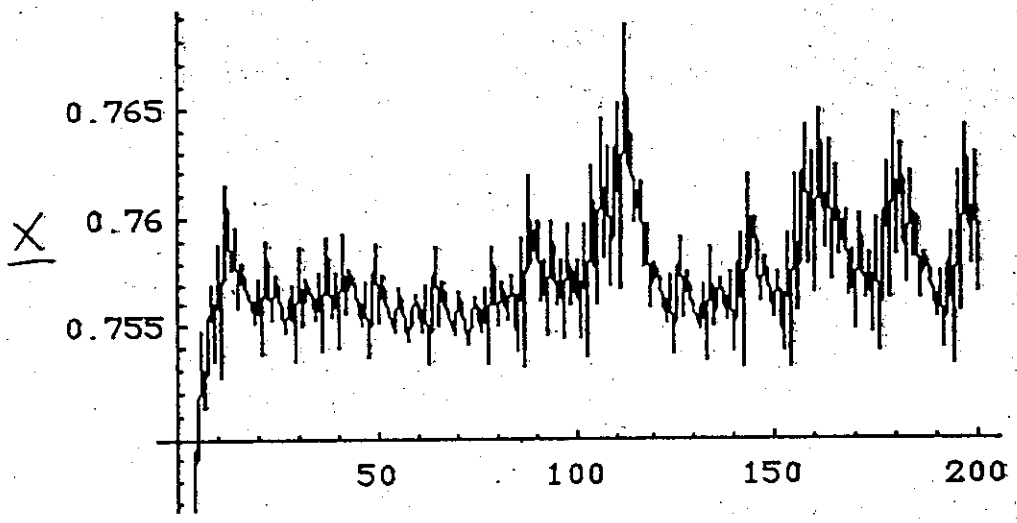

(b)
0.9
0.8
x
0.7
0.6
10
20
30
40
600
500
400
N
300
200
100
10
20
30
40

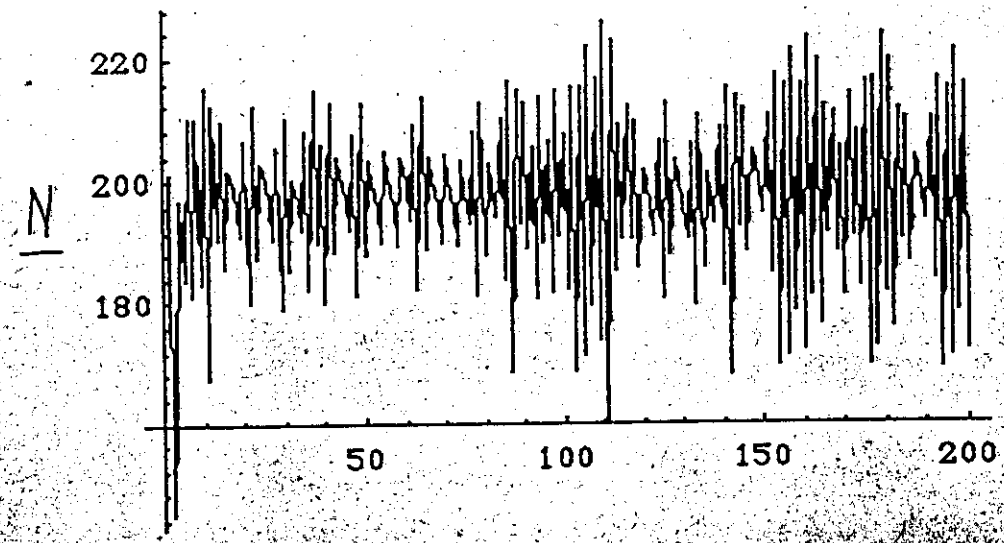

X
0.695
0.694
0.693
0.692
0.691
0.689
50
100
150
200

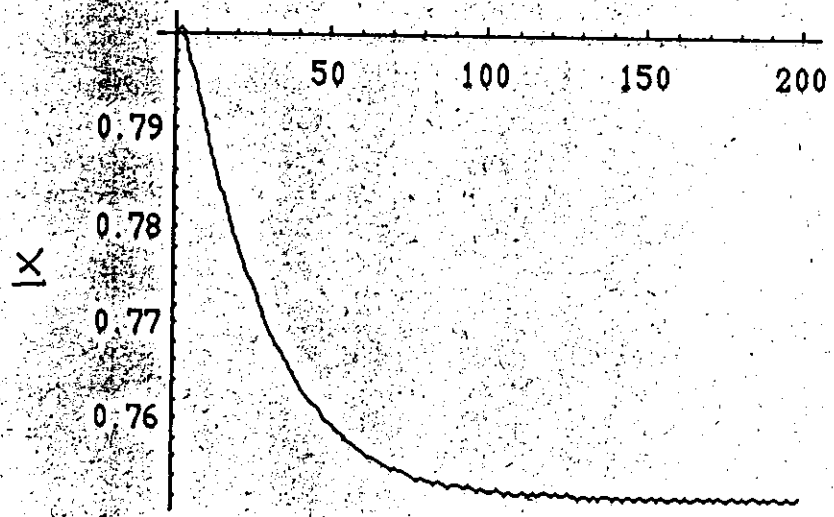

N
280
260
240
220
50
100
150
200

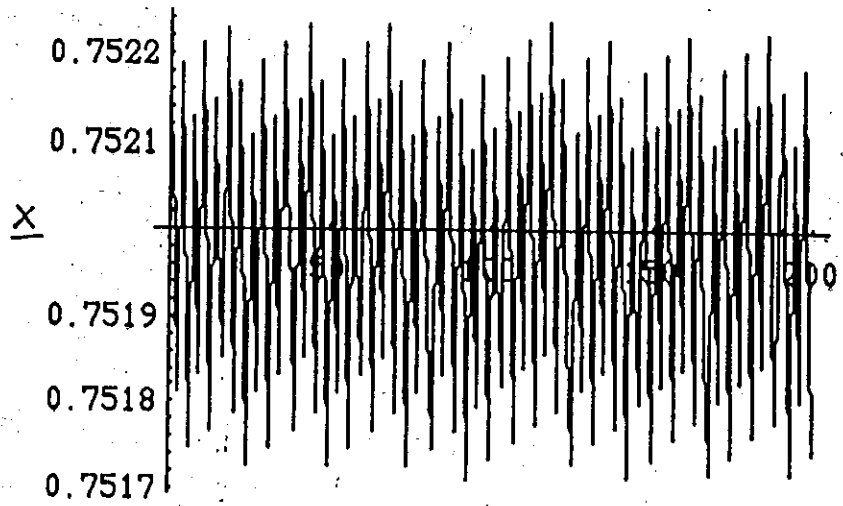

X
0.692
0.6915
0.691
0.6905
0.6895
0.689
50
100
150
200

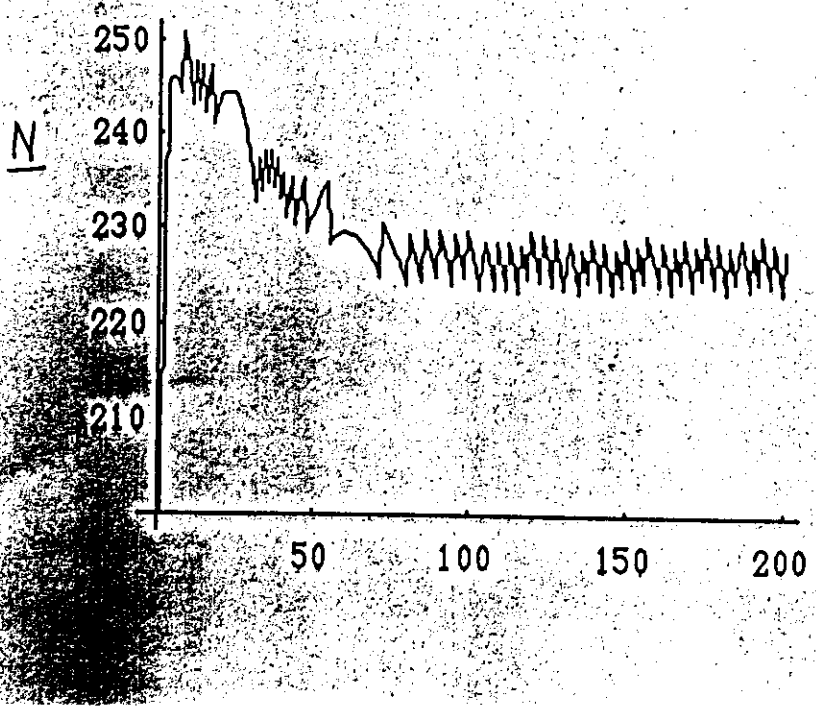

N
265
260
255
250
245
240
50
100
150
200

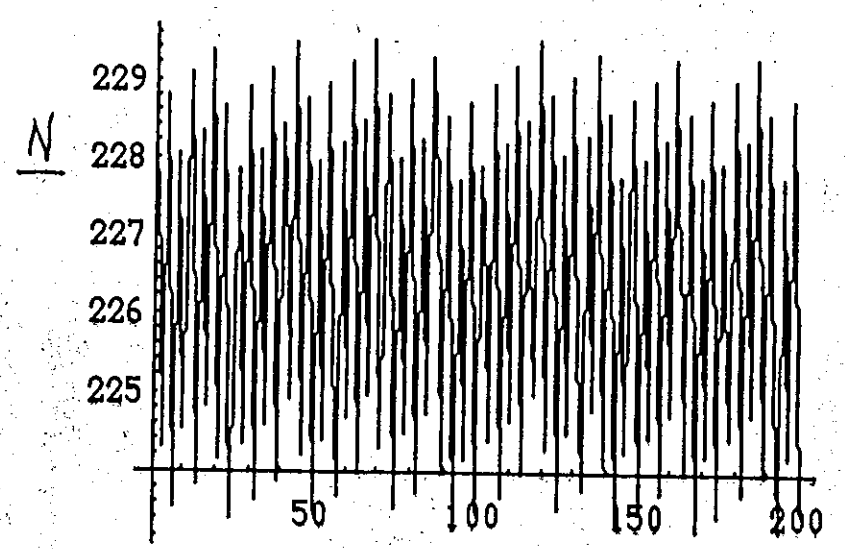

0.765
X
0.76
0.755
50
100
150
200


220
N
200
180
50
100
150
200


50
100
150
200
0.79
0.78
0.77
0.76
X


0.7522
0.7521
X
0.7519
0.7518
0.7517


250
240
N
230
220
210
50
100
150
200


229
228
N
227
226
225
50
100
150
200

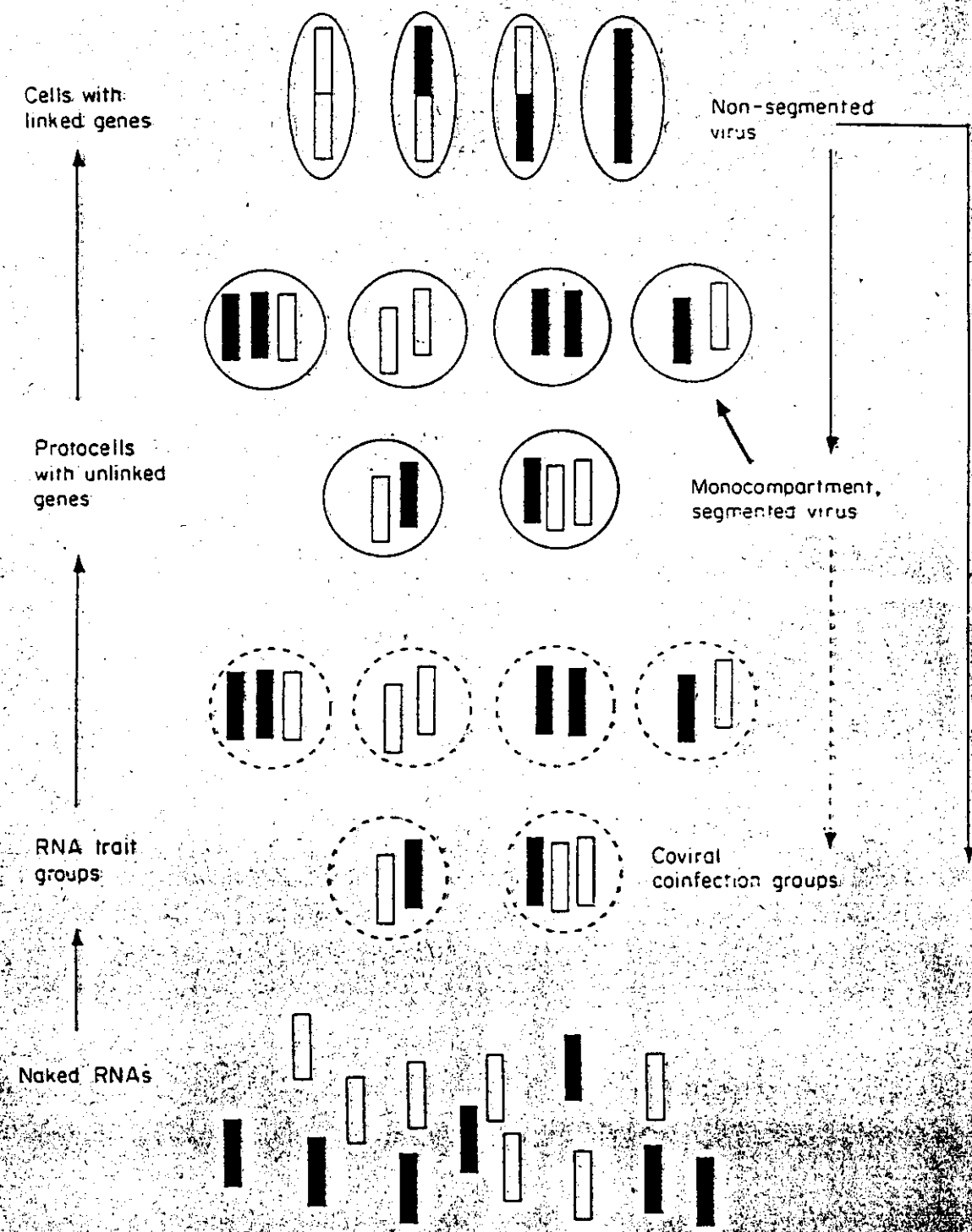


FIG. 2. From genes to compartments and back. Black and white indicate different alleles. The scheme illustrates the origin (upwards) and dissolution (downwards) of compartments.

zation of the mono-compartment influenza virus definitely denies a hypercycle with eight specific replicases, contrary to previous suggestion (Eigen & Schuster, 1982).

types in their template composition. These compartments are treated as mutants (Fig. 11).

Everything is now ready for constructing an Eigen eqn (1) *at the compartment level*. Amplification factor A_i for the ith type compartment can be calculated from the obvious relation $A_i = \ln(2)/\tau_i$, where τ_i is the compartment's generation time. The factors Q_i and w_{ij} can be calculated from the stochastic distribution.

We have arrived at the conclusion that, despite internal competition, selection at the compartment level leads to a stable protocellular quasi-

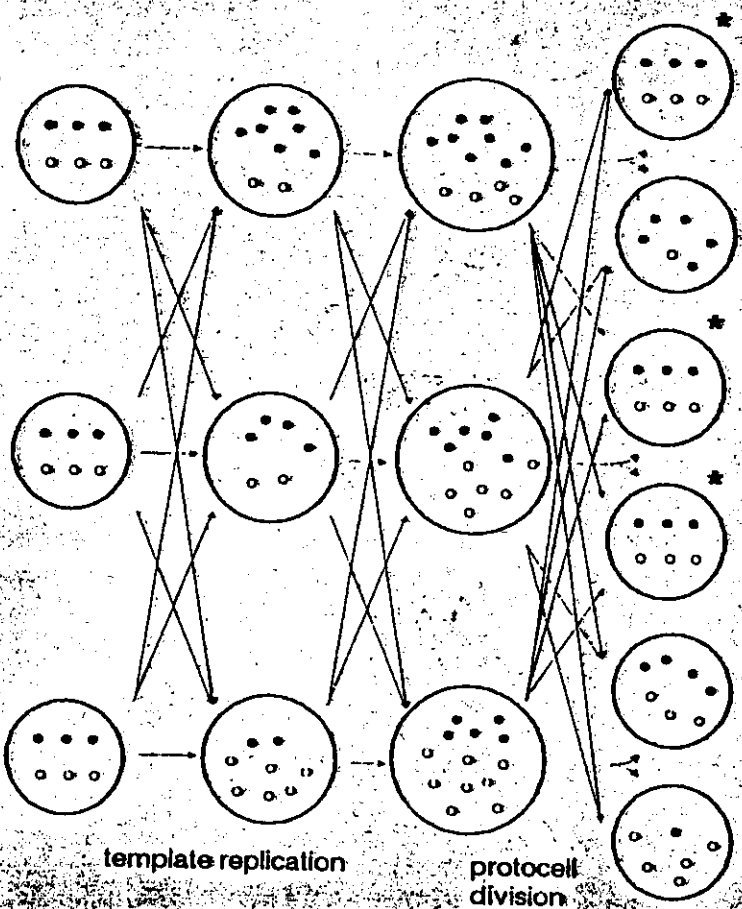


Fig. 11. Schematic representation of the stochastic corrector mechanism. Solid and open circles indicate two different templates, both being necessary for compartment growth. Here the optimal initial composition is three copies of each kind. Replication as well as template allocation in cell division are stochastic processes. Despite the tendency that the solid templates replicate faster, due to stochastic effects the best compartment type (marked by asterisks) recurs. Finally, a self-reproducing compartment distribution (quasispecies) emerges. Reproduced from Szathmáry (1989).