A theoretical construction of the genetic material

Elements of Biology

Summary

We shall construct a structure for the genetic material using a list of requirements derived from a limited number of phenomena that are assumed to be universal among living organisms. The construction leads to an ideal structure, characterized by specific symmetry and asymmetry elements. A comparison of this structure with the structure of the DNA double helix leads to a better intuitive understanding of its properties.

Part I:
Nature of the problem and preliminary considerations

Questions

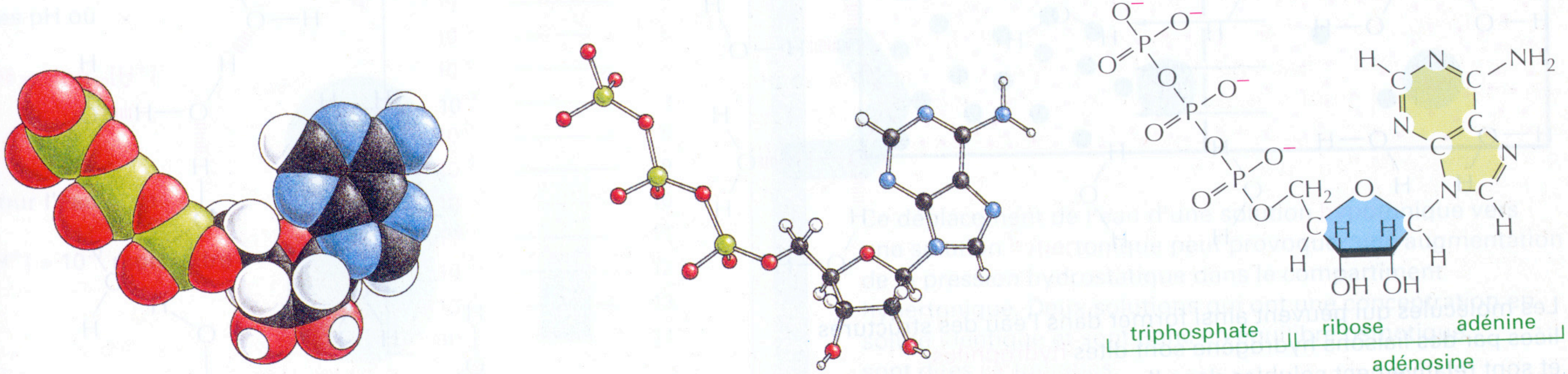
- Is the structure of the genetic material unique?
- Why is DNA such as it is and not otherwise?
- Is the structure of DNA the result of a “frozen accident” (as Crick said in 1968 of the genetic code)?
- Is the structure of DNA necessary or contingent?

Questions and Answers

J.D. Bernal 1963

Q. Are the forms of life necessary or contingent?

A. The simpler are necessary and the more complicated are not. Molecules such as adenine are apparently necessary. The form of any particular organism is not. It is contingent on the accidents of organic evolution.



(A) (B) (C)

Structure of genetic material

- We are not able today to demonstrate the the structure of DNA is necessary, especially at the level of its chemical structure.
- A goal of our constructive approach will be to provide a tentative and partial positive answer on the uniqueness of the structure of the genetic material.

Genes from matter?

- The gene can be viewed as a “black box” and considered solely as an information containing device, to be treated exclusively from a logical point of view. This provides the foundation of formal genetics, and needs not take into consideration the existence of a possible material support.
- The logical approach independent of any material support is not satisfactory. Fundamental biological knowledge on living matter calls for further conceptual developments.

A constructive approach for the genetic material

- We start from a functional definition, and aim at building a material structure that possesses the required functional properties.
- By constructing the structure we reach a better intuitive understanding of it.
- Comparison with von Neumann's approach to the building of a self-reproducing automaton (focus on the logical aspect).

Principles of design (1)

Two aspects:

1) What is the method used for the construction: what are the underlying principles?

2) What facts and concepts on living organisms are we going to use?

Principles of design (2): symmetry and asymmetry considerations

- Relate symmetry and invariance
- Construction of a Platonic object
- Relate symmetry to a lack of information (as in probability theory)
- Asymmetry and phenomena
- Asymmetry and life

Symmetry

Etymology: *syn-* "together" + *metron* "meter”:

1) Literally: having the same measure. Two geometric objects having the same (Euclidean) measure are *identical*. They are *different* otherwise. Two identical objects can be superimposed: this transformation is a particular geometric transformation (an isometry), which leaves the first object unchanged. Concept of *invariance*.

2) Having the right proportion, harmonious

Symmetry (2)

Mathematics of symmetry: group theory

The set of all symmetry transformations of a given object constitutes a mathematical group (the symmetry group)

Examples:

For a rectangle or a square (discrete groups)

Continuous groups: special orthogonal group SO_3 of rotations in a 3D space

Symmetry (3)

Physical **symmetries** and **conservation laws**
(for continuous transformations)

The equations of motion of Newtonian mechanics are invariant under:

- Space translation
- Time translation

The invariance results from the physical assumption that a given quantity (absolute spatial position, absolute time) is not observable.

Each invariance is associated a conservation law:

- Space translation with the conservation of the momentum
- Time translation with the conservation of energy

Symmetry and invariance (1)

Physical sciences have taught us that invariance expressed in conservation laws has its origin in symmetry.

The very concept of heredity implies invariance. Since the physical carrier that we want to build has some properties of invariance, it must possess characteristic associated symmetries.

Symmetry and design

Principle of design:

We want to introduce as many symmetry elements as possible in the structure.

In doing so, we do not construct a existing structure *a priori*, but rather an ideal, Platonic form.

Symmetry and **lack** of information

There exists a general relation between symmetry and absence of information. In probability theory for instance, we can predict the outcome of the tossing of a coin by stating that there is equal chance of finding head or tail. This is also the reasoning that confers the status of a “law” to the observations of Mendel.

We look for a structure that contains (genetic) information. Therefore we shall be looking for a structure having specific asymmetry features.

“All a priori statements in physics have their origin in symmetry”

H. Weyl, Symmetry, Princeton University Press (1952)

Asymmetry and phenomena (Curie)

« C’est la dissymétrie qui crée le phénomène »

“Asymmetry creates phenomena”

P. Curie. 1894. J. Phys. 3ème série, Tome III p.393

Curie's asymmetry principle (1894)

http://gallica.bnf.fr/

« La symétrie caractéristique d'un phénomène est la symétrie maximale compatible avec l'existence du phénomène.

Un phénomène peut exister dans un milieu qui possède sa symétrie caractéristique ou celle d'un des intergroupes de sa symétrie caractéristique.

Autrement dit, certains éléments de symétrie peuvent exister avec certains phénomènes, mais ils ne sont pas nécessaires. Ce qui est nécessaire c'est que certains éléments de symétrie n'existent pas. C'est la *dissymétrie* qui crée le phénomène. »

Curie’s asymmetry principle (1894)

http://gallica.bnf.fr/

Relates Asymmetry with phenomenon

Or equivalently

Symmetry with Non observable (TD Lee, 1981)

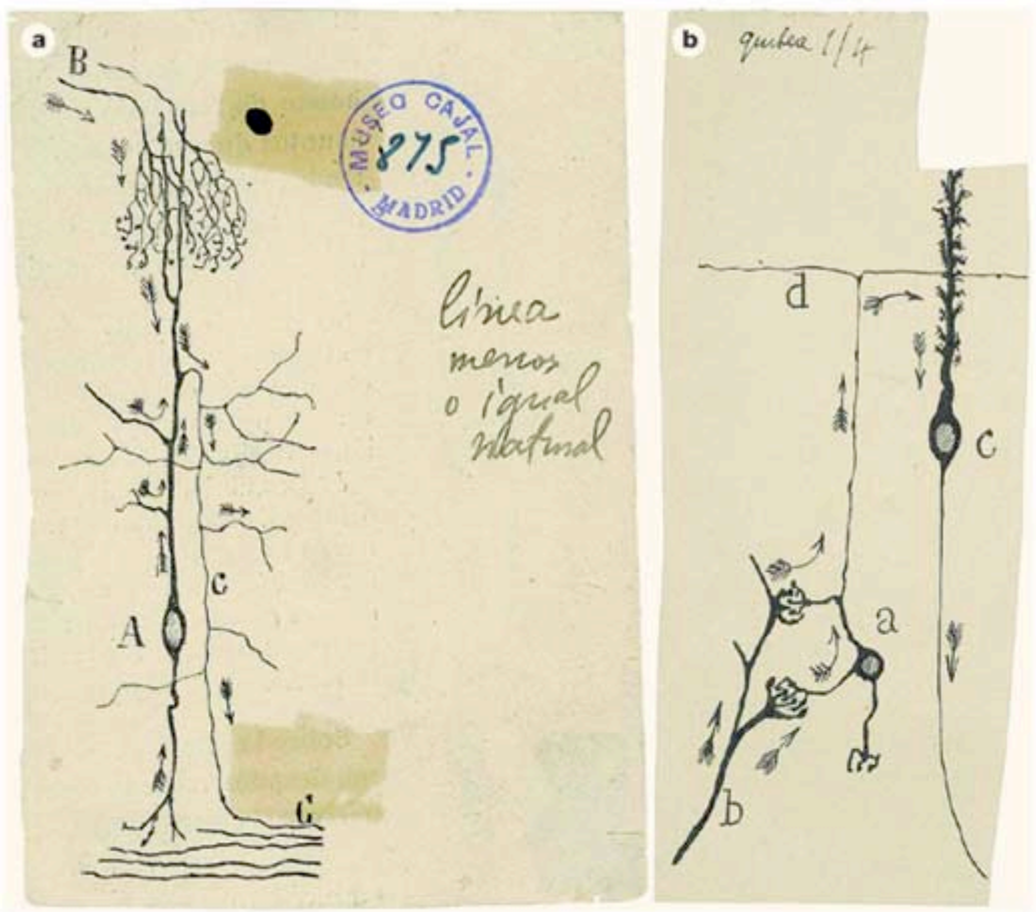
Phenomena

Phenomena can be classified according to their characteristic symmetry.

The analysis of the essence of a phenomenon is the analysis of this phenomenon based on symmetry considerations alone.

Two illustrations

Phenomena and symmetry: Dynamic polarization of the neuron Ramon y Cajal (1888)



Phenomena and symmetry: plus William James (“forward direction”) plus van Gehuchten. Stigler’s Law of Eponymy

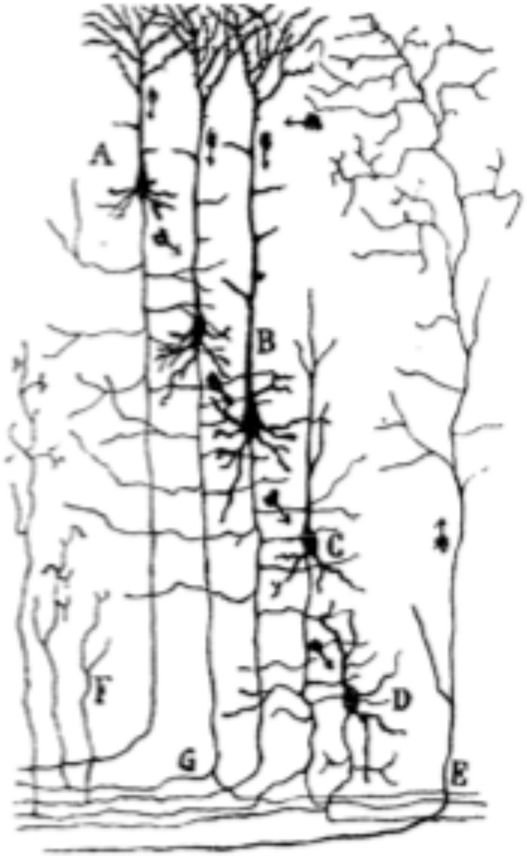


Fig. 16.

Schéma montrant la marche probable des courants et les connexions nervoso-protoplasmiques dans les cellules de l'écorce cérébrale.

A petite cellule pyramidale ; *B* grande cellule pyramidale ; *C* et *D* corpuscules polymorphes ; *E* fibre terminale venue d'autres centres ; *F* collatérales de la substance blanche ; *G* cylindre axe bifurqué dans la substance blanche.

Brownian motion of colloids (H.C. Berg)

Asymmetry and Brownian motion

Is Brownian motion compatible with a homogeneous (divisible *ad infinitum*) structure of matter?

No.

(The Curie Principle is related to Leibniz Principle of Sufficient Reason.)

Asymmetry and Brownian motion

The existence of Brownian motion is sufficient to establish the atomic structure of matter (Perrin, 1909).

This phenomenon requires a lack of symmetry (the symmetry of scale invariance).

Application of Curie's asymmetry principle

Asymmetries characterize phenomena.

→ We want to construct the genetic material based on its characteristic asymmetries.

Asymmetry and life

Must the genetic material be chiral?

Two aspects:

1) Can one explain the chirality of living matter?
2) Is the existence of chiral living matter compatible with an achiral genetic material (an epigenetic chirality?)

Principles of design

2) What facts and concepts on living organisms are we going to use?

- How do we define life?

  Can we define life in terms of invariance only?

  NO (concept of adaptation to environmental change)

- Should we limit ourselves to data pertaining to the physiology of the living organisms that exist today?
- Is there a need to use the theory of evolution?

  YES

The theory of evolution

Two statements:

- All living organisms descend from a common ancestor.
- The evolution of life is the result of the process of natural selection.

A role for the theory of evolution (1)

Peas, bacteria, elephants and humans all have a common ancestor. The transmission of hereditary information is not perfect: invariance dominates on a short time scale, and change on a long one. Change (or **mutation**) must be possible in the material element, as an unfrequent event. The genetic material must have a physical structure that is particulate. Some of its components will remain invariant in the transmission process; others will undergo (unfrequent) changes.

A role for the theory of evolution (2)

The theory of evolution provides a support for inductive reasoning. When we make an observation for a **given living organism**, we can use the concept of common descent to try to generalize this observation to all living organisms. This would be much harder otherwise. Such generalizations are common in cytology and biochemistry.

Universal features of life: cytology

- All living organisms are made of cells.
- The process of cell division (called mitosis in certain cases) is universal among living organisms.
- All cells come from a previous cell.
- The last common ancestor was unicellular organism.

Cell division and the transmission process

- The hereditary material present in the mother cell is found again in each daughter cell: the transmission process during cell division implies a **duplication** process.
- The duplication process has two aspects. It can be viewed as a metabolic (chemical) process, by which the initial structure is copied.
- It also implies the transport (segregation) of each of the two final structures to the daughter cells.
- Here we shall take into account this transport phenomenon to understand the duplication process.

A role for the theory of evolution (4)

- Stability of the structure searched:

  The duplication process has been going on since the appearance of life on earth. Furthermore, the permanency of biological structures can be observed on **geological time scales**. The components expected to remain invariant in the transmission process have an exceptional stability.

  We shall try to build a structure as stable as is possible.

Elements of bacterial physiology

Choice of *Escherichia coli*

Bacterial Growth: characterization of the **exponential growth** and its dependence on simple chiral compounds (Thesis of Monod 1942). Implication for the duplication process of the genetic material.

Brownian motion and life: *E. coli* motility (HC Berg)

Stages of growth

- Lag
- Exponential
- Maximal
- Decrease

Definition:

Growth rate: number of division per hour (speed of growth per unit of density)

Typical growth of a bacterial culture

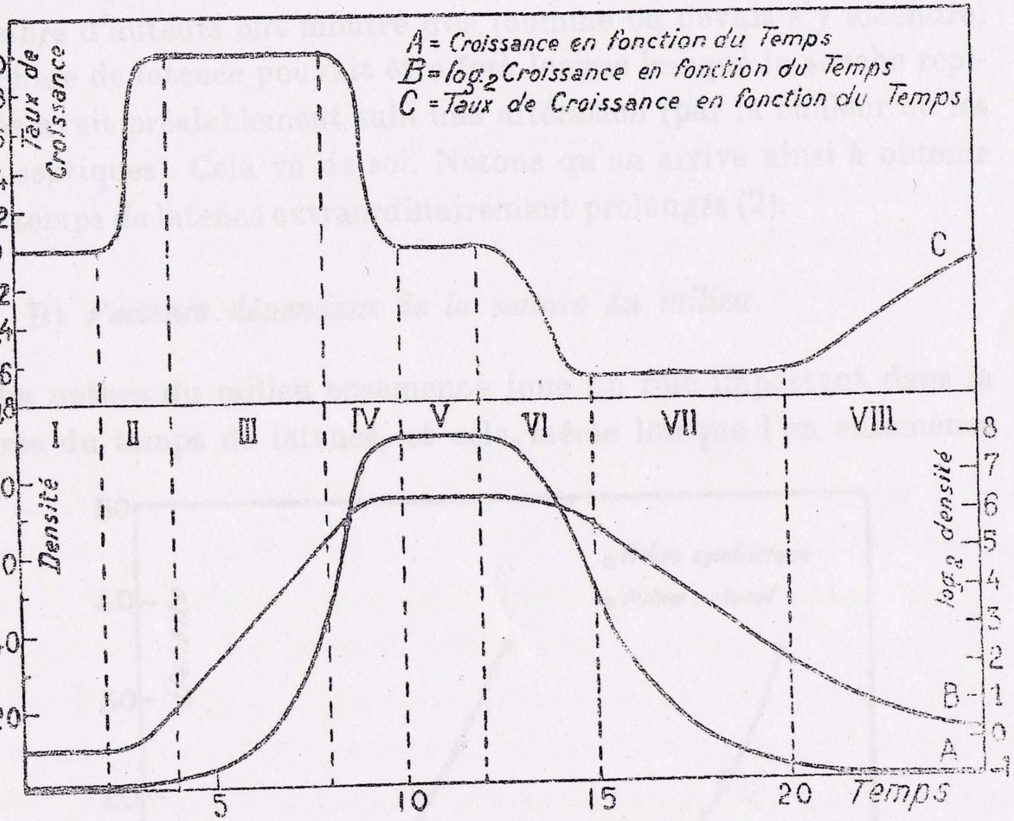


Fig. 1. — Croissance typique d'une culture bactérienne (en coordonnées normales et semi-logarithmiques) et variations du taux de croissance au cours des différentes phases. Les chiffres romains désignent les phases successives dont les limites sont indiquées par les traits interrompus verticaux (v. texte p. 6).

Exponential growth is an experimental fact

A constant growth rate

« Lorsque rien ne s'oppose à leur croissance, que tous les aliments nécessaires sont présents en concentration suffisante, ou plus exactement en excès, la culture croît à taux constant, et la vitesse de la croissance est proportionnelle à la densité de culture. On sait depuis MALTHUS que dans ce cas la courbe de croissance est une exponentielle ».

After n generations the density x of the culture is :

$x = x_0 2^n = x_0 2^{\mu t}$ where μ is the growth rate

Fitness and growth rate

Definition: fitness is the Malthusian parameter of an exponential growth

Fisher, R. A., 1930, “The Genetical Theory of Natural Selection”, Dover, New York (2d ed. 1958).

The growth rate

Study of the growth rate (in the exponential phase) as a function of

- The concentration of “food”
- The concentration of carbohydrate (in a synthetic medium)

The nature of the carbohydrate.

Growth rate (1)

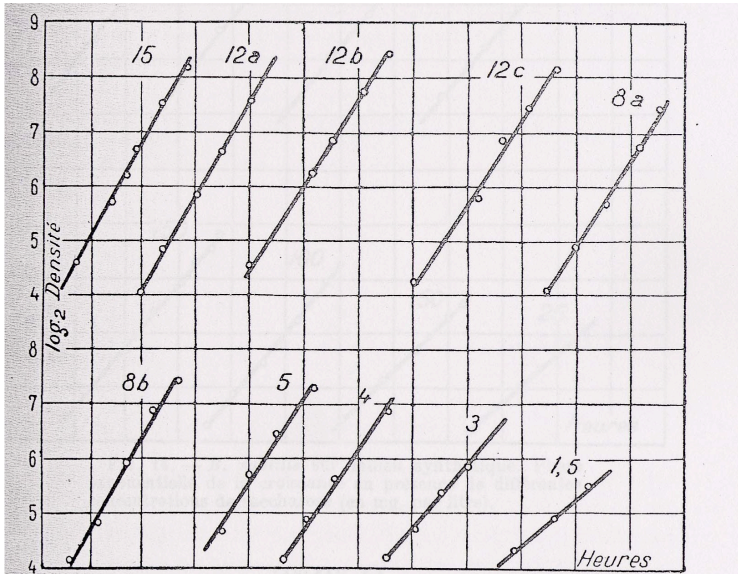


FIG. 13. — *B. subtilis* sur bouillon de cervelle de veau. Phase exponentielle de la croissance sur différentes concentrations de bouillon, indiquées en unités arbitraires.

Concentration initiale	Taux de croissance	Temps de division
15	1,67	36′
12 *a*	1,72	35′
12 *b*	1,67	36′
12 *c*	1,65	36′
8 *a*	1,65	36′
8 *b*	1,67	36′
5	1,64	37′
4	1,43	42′
3	1,18	52′
1,5	0,87	69′

The growth rate has an upper limit. It diminishes only for very low concentrations of food.

Growth rate (2)

Role of the nature of the carbohydrate.

Fitness is a **function of the environment** and depends on a **metabolic efficiency**

Taux de croissance et temps de division des cultures de B. subtilis en milieu S suivant la nature de la source carbonée.

Source carbonée	Taux de croissance (nombre de divisions à l'heure)	Temps de division (en minutes)
Polyalcools :		
Glycérine	1,31	46′
Mannite	1,10	55′
Sorbite	1,25	48′
Inosite	1,09	55′
Hexoses :		
Glucose	1,21	50′
Fructose	1,22	49′
Mannose	1,05	57′
Pentoses :		
Arabinose	0,84	71′
Disaccharides :		
Saccharose	1,25	48′
Maltose	1,00	60′
Trisaccharide :		
Raffinose	0,67	90′
Polysaccharide :		
Dextrine	0,87	69′

Brownian motion and life (1)

Two questions arise at the microscopic level:

1) Is Brownian motion due to specific properties of living matter?

   No, as shown by Robert Brown in 1828

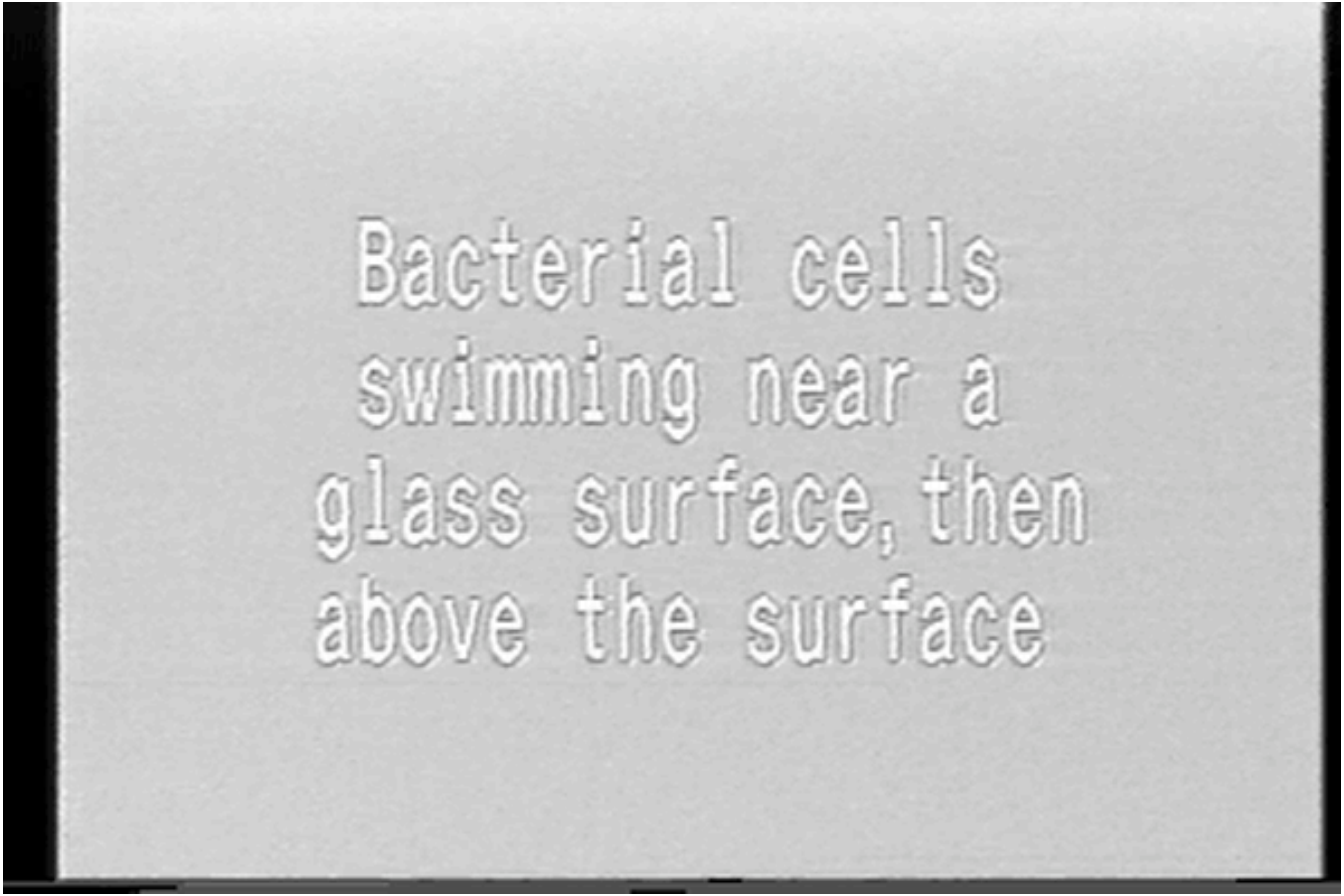
2) Can the movements of cells be explained in terms of Brownian motion?

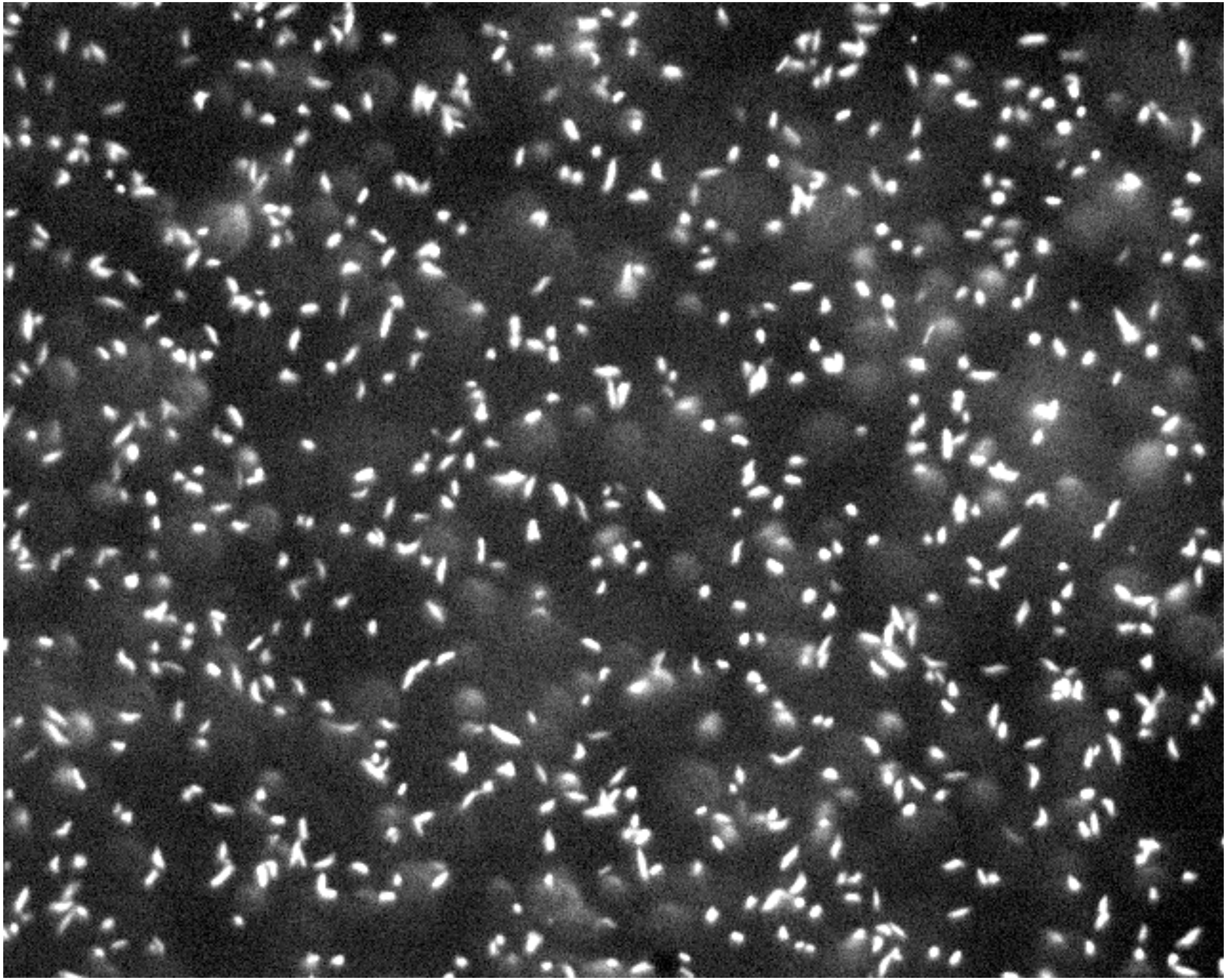
Brownian motion and life (2)

Study of *Escherichia coli* in an isotropic medium at rest (Berg and Brown, 1972):

On a long time scale, the motion is diffusive, with a mean-squared displacement linear in time. However, the measured effective diffusion coefficient is **three orders of magnitude larger** than that calculated using the Sutherland-Einstein relation for a particle of the size of *E. coli!* Dead bacteria are found to diffuse as expected.

Motility of E. coli (H.C. Berg)





Brownian motion and life (3)

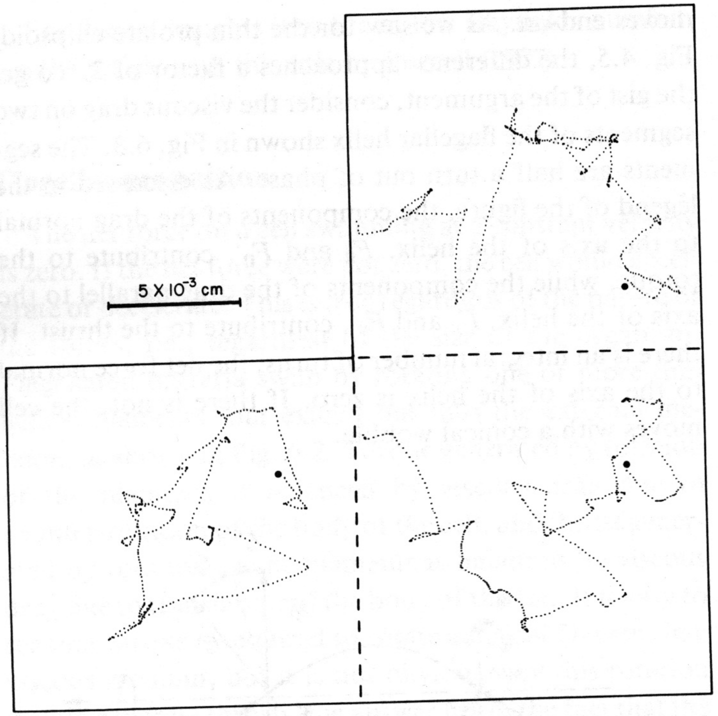


Fig. 6.4. A digital plot of the displacement of a wild-type bacterium, *E. coli* strain AW405, executing a random walk in a homogeneous, isotropic medium. The plots are planar projections of a three-dimensional path. If the left and upper panels are folded out of the page along the dashed lines, the projections appear in proper orientation on three adjacent faces of a cube. Observation began at the end of the path denoted by the large dot and continued for about 30 sec. There are 12.6 dots/sec; the bar is 5×10^{-3} cm long. The cell swam at a speed of about 2×10^{-3} cm/sec. Run intervals were relatively long, about 1 sec on the average, and tumble intervals were relatively short, about 0.1 sec on the average. There were 26 runs and tumbles. The tracking was done at 32°C in a medium of viscosity 0.027 g/cm sec. The data are from Berg and Brown (1972). A stereo pair of this track is shown in Fig. 7 of Berg (1978).

The bacteria “run” in straight lines for about one second at with a contant velocity of about 30 μm/s, and then change direction at random.

Brownian motion and life (4)

- The bacteria move in a medium where inertial forces can be neglected in front of viscous forces. Because of this, in the regime where the bacteria run at constant velocity, there must exist a continuous impetus.
- Thus, there must exist a miniature motor, a device that dissipates energy to perform this mechanical work. The only energy available to *E. coli* is of chemical origin. This chemical energy has to be dissipated in a locally anisotropic environment to provide the observed directionality of the motion (Curie's principle)
- Such miniature motors are clearly advantageous in chemotaxis. The advantage is twofold. From a kinetic point of view it allows the bacteria to explore more of its surrounding. The availability of mechanical energy above k_BT permits to bypass obstacles.

Transport of the genetic material during cell division

Can this transport phenomenon rely on Brownian motion alone?

Two arguments are in favor of a role of miniature motors in the process:

1) Clearly, the use of miniature motors would be advantageous in the transport since there would exist an available chemical energy in addition to the thermal energy.

Transport of the genetic material during cell division (2)

2) (Weak) When we observe cell division on agar plates, the cells are immobile (no Brownian motion) and growth at constant rate corresponds to a movement of the cell material at a constant velocity. Therefore, the transmitted genetic material is also transported at constant velocity.

Our conclusion is that there should exist miniature motors that move the genetic material during cell division. This implies that is necessary to design the structure of the genetic material to **interact efficiently** with these motors.

Symmetry (4)

Four fundamental types of symmetry in physics

1) Continuous space-time symmetries

2) Discrete symmetries

3) Internal symmetries

4) Permutation symmetries
(FD or BE statistics)