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Review

The Boltzmann equation in molecular biology

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ABSTRACT

In the 1870's, Ludwig Boltzmann proposed a simple equation that was based on the notion of atoms and molecules and that defined the probability of finding a molecule in a given state. Several years later, the Boltzmann equation was developed and used to calculate the equilibrium potential of an ion species that is permeant through membrane channels and to describe conformational changes of biological molecules involved in different mechanisms including: open probability of ion channels, effect of molecular crowding on protein conformation, biochemical reactions and cell proliferation. The aim of this review is to trace the history of the developments of the Boltzmann equation that account for the behaviour of proteins involved in molecular biology and physiology.

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1. Introduction

1.1. Notion of probability

In the mid 19th century, the physicists who studied thermodynamics were divided into two schools. According to the first one, the entropy of a gas increased with the occupied volume. According to the second theory, the evolution of a system towards its equilibrium corresponded to the passage from an initial state to another, statistically more probable. This latter interpretation was based on the existence of atoms, molecules and the notion of probability, which at this epoch were not yet recognised. These two propositions were theoretically possible but had not been demonstrated. It is Ludwig Boltzmann (1844–1906) who proposed in the 1870s the equation:

$$S = R\,M\,\mathrm{Ln}\,W, \tag{1}$$

where: S is the entropy, expressed in joules per kelvin ($J\ K^{-1}$), corresponding to the agitation of molecules as a function of

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temperature, R is the gas constant, M is the mass of an hydrogen atom (=1/N, where N is the Avogadro's number) and W is the probability to find a molecule in a given state.

Several years later, developments of the original Boltzmann equation were applied to describe the equilibrium potential of ions in cells and more recently, the properties of macromolecules as a function of their environment. Moreover, the Boltzmann equation has been applied to describe complex cell biological behaviours such as the cell size–proliferation relationship. While some recent developments of the Boltzmann equation remain speculative, they can describe several biological mechanisms that are exposed in the following sections.

1.2. Boltzmann's constant

At the end of the 19th century, most physicists did not accept Eq. (1). It is only in 1899 that Max Planck (1867–1947) introduced the Boltzmann constant (k = R/N) and proposed a new formulation of the Boltzmann equation (Eq. (2)) that is engraved on Boltzmann's tombstone in Vienna:

$$S = k \, Ln \, W. \tag{2}$$

This equation is schematised in Fig. 1 where two compartments are separated by a partition pierced by an aperture. If at a temperature of zero kelvin, particles (neutral molecules or atoms) are introduced in compartment 1, they are immobile and do not diffuse into compartment 2. In contrast, when the temperature is superior to zero kelvin, the particles are agitated because of the Brownian movement and diffuse from compartment 1 towards compartment 2. At equilibrium, the probabilities (p) of finding a particle in the two compartments are equal. If one takes the exponential of the two terms of Eq. (2) and if one expresses S as a function of the particle energies (u_1 and u_2) in both compartments and temperature and W in term of probability (p), one obtains particle fluxes from one compartment towards the other ($f_{1\rightarrow2}$) and ($f_{2\rightarrow}f_1$) so that:

$$f_1 \rightarrow f_2 = p_1 \exp(u_1/kT) \tag{3}$$

$$f_2 \rightarrow f_1 = p_2 \exp(u_2/kT). \tag{4}$$

At equilibrium, which is reached faster as the temperature is raised, $f_1 \rightarrow {}_2 = f_2 \rightarrow f_1$ and $u_1 = u_2$. Consequently, $p_1 = p_2$ that gives the relative probabilities:

$$\frac{p_1}{p_2} = \exp \frac{(u_1 - u_2)}{kT}. \tag{5}$$

It is worth noting that Eq. (5) is equivalent to Eq. (2) with $(u_1 - u_2)/T = S$ and $p_1/p_2 = W$. The scheme of Fig. 1 is equivalent to a cell where intra- and extracellular media are identical. The cell membrane corresponds to the partition and the protein mediated particle pathways correspond to the aperture.

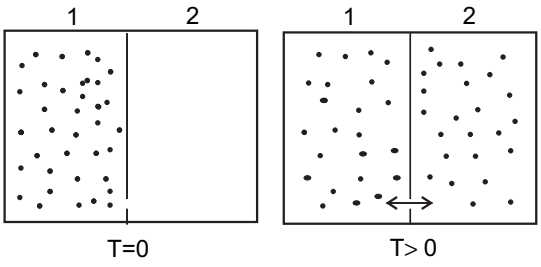

Fig. 1. Steady-state probability, at T = 0 and T > 0, to find a particle in compartments 1 and 2 separated by an aperture when the particles are introduced in compartment 1.

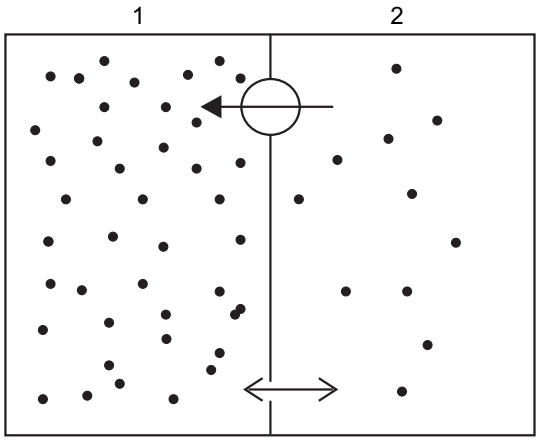

Fig. 2. Steady-state probability (at T > 0) to find a particle in compartments 1 and 2 separated by an aperture when particles are actively pumped from compartment 2 to compartment 1.

1.3. The Nernst equation

In 1888, Walther Hermann Nernst (1864–1941) developed an equation that allows to determine the equilibrium potential (reversal potential) of an ion species that is permeant through specific membrane pathways (channels). This equation is derived from the Boltzmann equation (Eq. (5)) for electrical charged particles.[1]

In cells, the concentrations of solutes are generally different in intra- and extracellular media because membrane pumps and transporters impose them. This notion in schematised in Fig. 2 where pumps and transporters concentrate the particles in compartment 1. At equilibrium, the unidirectional fluxes through channels and pumps are equal and the relative probability to find a particle in one compartment is described by Eq. (5). In another words, the probability to find a particle in compartment 1 is:

$$\frac{p_1}{p_1 + p_2} = \frac{\exp(u_1/kT)}{\exp(u_1/kT) + \exp(u_2/kT)}, \tag{6}$$

which gives:

$$\frac{p_1}{p_1 + p_2} = \frac{1}{1 + \exp[(u_2 - u_1)/kT]}. \tag{7}$$

If in Eq. (5), one replaces the relative probabilities by concentrations (c) and the elementary energies by their molar energies (U), one obtains:

$$\frac{c_1}{c_2} = \exp \frac{U_1 - U_2}{NkT}. \tag{8}$$

Apart from the difference of units: concentrations in place of probabilities and molar energies in place of entropy, one sees that Eq. (1–8) are equivalent. For this reason, they are indifferently called the "Boltzmann equation".

Let us now consider that the particles are electrically charged. For example, if one takes the case of potassium ions (K^+) that are 30–40 fold more concentrated in the cytoplasm than in the extracellular medium due to the Na^+–K^+ATPase, which for simplification we consider as electroneutral. Because of this concentration difference, K^+ ions have tendency to outflow from the cell by chemical diffusion. However, because of their electric charge, their

[1] It should be noted that the Nernst equation has been formulated in its actual form after Planck introduced Boltzmann's constant.