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Stability and sustainability: Efficacy of ATP (adenosine triphosphate) relative to GTP, CTP and UTP substantiated by principle of least variance

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ABSTRACT

The unstable bonds of ATP (adenosine triphosphate) are investigated in relation to those for the GTP, CTP and UTP. Two existing efficacies *Eff A*: *GTP* > *UTP* > *CTP* > *ATP* and *Eff B*: *ATP* > *UTP* > *CTP* > *GTP* can be substantiated, respectively, by two least variance inequalities *Var A*: $\Delta R_{GTP} > \Delta R_{UTP} > \Delta R_{CTP} > \Delta R_{ATP}$ and *Var B*: $\Delta R_{ATP} > \Delta R_{UTP} > \Delta R_{CTP} > \Delta R_{GTP}$. The verification involves computing the *R*-integrals and their variances ΔR from the nanometer displacements of the molecules of the S49 wild-type lymphoma cells. They are relevant to the coupling of the β_2-adrenoreceptor (β_2AR) to G_s protein, expressed as β_2AR-Gα_s.

Application of the least variance principle, *Eff A* and *B* is identified with the NTP (nucleoside 5′-triphosphates). They can *enhance* or *inhibit* the agonist-stimulated AC (adenylyl cyclase) activity. *Eff A* is found to be more stable with a longer sustaining time than *Eff B*. These findings are consistent with the behavior of potentially reactive molecules.

Corrective measures of ATP production can be used as an adjustment at the molecular scale to compensate for the unstable character of the ATP molecules. Quantitative assessment of the reactive process of ATP can also provide information on the breakdown of RNA and DNA. A possible approach is to couple the use of energy-release and non-equilibrium thermodynamics with the principle of least variance.

1. Introduction

When the sustaining time of the reactive molecules of ATP (adenosine triphosphate) is short, the biochemical reaction is said to be unstable. The corresponding energy state of the cells could change constantly, unable to reach thermodynamic equilibrium. The continuously and discontinuously exchange of flux of energy between the ATP and its surrounding correspond to the manifestation of thermodynamic non-equilibrium, uncommon in application. The wide use of the Gibb's free energy [1,2] for estimating the energy associated with the generation of ATP should not be interpreted as an endorsement for non-equilibrium. The Gibbs free energy does not consider spatial–temporal effects at the different scales. Moreover, non-homogeneity and non-equilibrium are not synonymous. Strictly speaking, *non-equilibrium refers to strong space–time dependency while equilibrium refers to negligibly weak space–time dependency*. The former and latter may correspond, individually, to non-homogeneous system and homogeneous system that can be further distinguished as local inhomogeneity in contrast to global homogeneity.

Biochemical reactions are intrinsically multiscale. The ATP macromolecule consists of single molecule entities at the nano or smaller scales. Scaling breakdown can occur from macro to micro and/or micro to nano, or from nano to pico [3,4]. Physical systems are dual scale. The dual scale segments can be connected by transitional functions for multiscale applications that are necessary intrinsic to biochemical reactions that involve energy loss.

Heat is dissipated by all biochemical reactions of the cells. The conversion of protein to carbohydrates causes "tissue respiration" which is a molecule called ATP, used by cells for energy. A glucose molecule is needed to produce ATP plus carbon dioxide, water and heat energy that is passed onto the blood. ATP can inhibit muscle contraction [5] by breaking down protein molecules. The ATP concentration inside the cell is about 1–10 mM (molecular unit) [6]. The multifunctional aspects of ATP can be further elaborated by the two efficacies [7] involving its interaction with GTP (guanosine triphosphate), UTP (uracil triphosphate), and CTP (cytoskeletal protein) with the G_s proteins. More specifically, GTP is used as an energy source in protein synthesis and for energy transfer within the cell, while CTP is essential for the structure and organization of cells. The UTP is a high energy molecule that acts as a precursor

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for the assembly of RNA (RiboNucleicAcid). The efficacies are referred to as *Eff A* and *Eff B*, identified, respectively, as *GTP > UTP > CTP > ATP* and *ATP > UTP > CTP > GTP*. The inequalities are connected with the NTP (nucleoside 5′-triphosphates), enhancing or inhibiting the agonist-stimulated AC (adenylyl cyclase) activity. These results can serve as the a posteriori conditions for deriving the weighting functions in the application of the principle of least variance [8]. The stability and sustainability of the ATP molecules in relation to GTP, UTP and CTP offer quantitative assessment of ATP for regulating biochemical pathways. To this end, use was made of the single-molecule, motion-based DNA sequencing of RNA polymerase [9]. ATP imbalances may be detected for taking corrective measures at an earlier stage. The sustaining time of, say of the order of minutes, for ATP can serve as a reference for determining the relative sustaining times of GTP, UTP and CTP.

Because of the multiscale character of biochemistry reactions of the ATP molecules, the use of non-equilibrium thermodynamics should be regarded as the rule rather than the exception. The current method of "Molecular Dynamics" is limited to equilibrium behavior. ATP reactions are highly non-equilibrium and unstable. Work on "non-equilibrium molecular dynamics" has been done based on the concept of Ideomechanics [10].

2. Sustainable molecular structures of nucleotide adenine for motion-based DNA sequencing

All molecular structures have a sustaining time after which they can change. This behavior applies to ATP that is consumed and replenished continuously in the cell by the energy-requiring (endothermic) processes and the energy-releasing (exothermic) processes. ATP regulates the main energy supply for the majority of cellular functions. This includes the synthesis of macromolecules for the DNA, RNA and proteins. This involves the transport of the GTP, CTP and UTP molecules. Their functions can be summarized as

- ATP (adhenosine triphospate) regulates the energy that carries out many of the body's functions. Sustainable time is about couple of minutes.
- GTP (guanosine triphosphate) transfers energy within the cell and is used in protein synthesis.
- **CTP** (cytoskeletal proteins) is responsible for the structure and organization of all cells. The metabolic enzyme CTP synthetase forms filaments, important to metabolic enzymes.
- **UTP** (uracil triphosphate) is a precursor for the assembly of RNA (RiboNucleicAcid).

2.1. Motion-based DNA sequencing

A method for tracking the transcription of single molecules of *Escherichia coli* RNA polymerase (RNAP) can be found in [9]. The scheme makes use of DNA sequencing and has identified 30 out of 32 bases in less than 3 min of observation time for four molecules. Figs. 1–4 inclusive show the records of transcriptional position versus time for a single molecule of RNAP under four limiting nucleotide conditions. These data are reproduced from [9] with permission [11]. Positions of expected pauses used for record

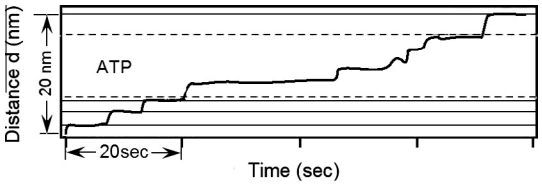

Fig. 1. ATP molecule for 2.5 μM-A and 1 mM-C.G.U.

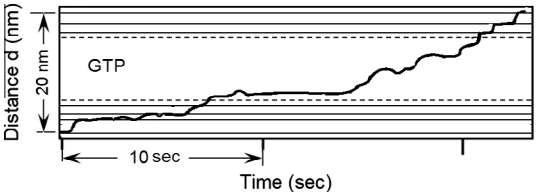

Fig. 2. GTP molecule for 2.5 μM-G and 1 mM-A.C.U.

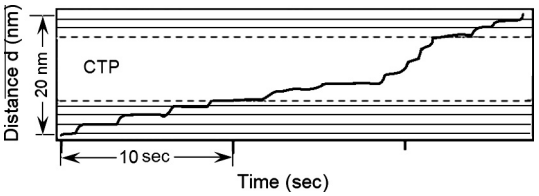

Fig. 3. CTP molecule for 2.5 μM-C and 1 mM-A.G.U.

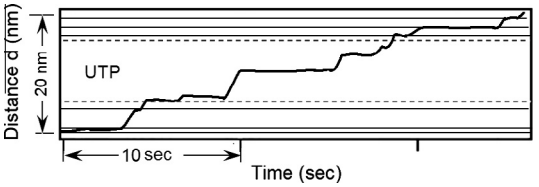

Fig. 4. UTP molecule for 2.5 μM-U and 1 mM-A.C.U.

alignment are denoted by solid horizontal lines. The extreme limits are spaced 20 nm apart. The corresponding time intervals are shown in seconds. The regions to be sequenced are indicated by dotted horizontal lines. Note that mM and μM in the figures stand for the "molecular units" of the DNA sequencing.

Fig. 5 displays the normalized and smoothed position histograms for the data in Figs. 1–4 inclusive. The DNA sequence is shown with 30 of 32 (arrows). Boldface letters refer to the correct bases.

2.2. Curve fitting of single molecules of Escherichia coli RNA polymerase [9]

The distance versus time data in Figs. 1–4 inclusive are approximated by the polynomials in Eqs. (1)–(4), respectively. Table 1 gives the numerical values of the 17 time segments of ATP for the total time span of 80 s. The time span of 22.5 s

$$d(t) = 2.38299 + 0.23116t - 0.0119094t^2 + 0.000539538t^3 - 0.0000107277t^4 + 1.05319\times10^{-7}t^5 - 4.06216\times10^{-10}t^6 \quad (1)$$

$$d(t) = 1.10322 + 0.213523t + 0.0524242t^2 - 0.0105201t^3 + 0.000776802t^4 - 0.0000158851t^5 \quad (2)$$

$$d(t) = 1.63283 - 0.0771415t + 0.0892223t^2 - 0.00806697t^3 + 0.000367787t^4 - 5.65726\times10^{-6}t^5 \quad (3)$$

$$d(t) = 1.06528 + 0.050611t + 0.300358t^2 - 0.0309534t^3 + 0.00122151t^4 - 0.000016964t^5 \quad (4)$$

for GTP in Table 2 is divided into 10 segments. Summarized in Tables 3 and 4 are the 12 time segments for CTP and UTP with the same time span of 27 s.