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Research Article

RASER Model of Single-Molecule Enzyme Catalysis and Its Application to the Ribosome Structure and Function

Sungchul Ji*[1]

[1] Department of Pharmacology and Toxicology, Ernest Mario School of Pharmacy, Rutgers University, Piscataway, New Jersey, USA

Introduction

In the article published in 1998 entitled "*The Cell as a Collection of Protein Machines: Preparing the Next Generation of Molecular Biologists*", B. Alberts (1998) [1] made the following remarkable statement which is as true today as when it was printed two decades ago:

"Proteins make up most of the dry mass of a cell. But instead of a cell dominated by randomly colliding individual protein molecules, we now know that nearly every major process in a cell is carried out by assemblies of 10 or more protein molecules. And, as it carries out its biological functions, each of these protein assemblies interacts with several other large complexes of proteins. Indeed, the entire cell can be viewed as a factory that cantains an elaborate network of interlocking assembly lines, each of which is composed of a set of large protein machines."

This statement contains the following key ideas:

(1) The cell is a system of *molecular machines* (also called protein machines).

(2) Every major cell process is carried out by *assemblies* of 10 or more molecular machines.

(3) Cell biological functions are carried out by a *network* of molecular machine assemblies that interact with one another.

In other words, Alberts is distinguishing three levels of organization of protein machines in the cell:

(i) individual molecular *machines* (also called enzymes, protein machines),

(ii) *assemblies of molecular machines*, and

(iii) *networks of molecular machine assemblies*.

For the convenience of discussions, I am suggesting here that we refer to the above conjecture as the Alberts' "molecular machine network doctrine of the cell" or the *AMNDC*.

The AMNDC embodies a hierarchical structure reminiscent of the three linguistic structures indicated in bold letters in the last column of **Table 1.** This is consistent with the hypothesis that cells use a molecular language which is isomorphic (i.e, similar in structure) with the human language [2,3]. As evident in the second column of **Table 1**, there are plethora of terms used to describe the various organizational components of cell metabolism that are largely confined to the first two levels (see the first column of **Table 1**) and do not distinguish between the organizational levels **II** and **III**. But we have recently found a quantitative method referred to as the Planck-Shannon (PS) space that can distinguish molecular sentences (as points in the PS space; see **Table 2 e**) and molecular texts (as lines in the PS space; see **Table 2 e**). Based on these considerations (i.e., the *cell language-human language isomorphism* and the *Planck-Shannon space*), I am recommending here for the first time that cell metabolism be divided into three levels of (i) molecular machines (MM), (ii) metabolic pathways (MP), and (iii) networks of metabolic pathways (NMP). **Table 1**

Table 1. A recommended unification of the terminologies in cell metabolism.

Level of Organization	Common terms now in use	Recommended terms	Cell-linguistic analogs [Evidence] (Ji, 2017c)[18]
I	Molecular machines (MMs)[19] Protein machines[1]	*Molecular machines (MM)* *(Molecular words)*	**Words** (to denote) [long tailed-histograms of turnover times] (see **Figure 1 (g)**)
II	Metabolic pathways (MPs)[c] Assemblies[1] of MMs Metabolons[20] Hyperstructures[21] Metabolic modules[22] Metabolic machines[23] Metabolic fields[24]	*Metabolic pathways (MP)* *(Molecular sentences)*	**Sentences** (to decide) [long-tailed histograms of mRNA levels encoded by genes] (see **Table 2 e**)
III	Assemblies[1] of MPs Metabolons[20] Hyperstructures[21] Metabolic modules[22] Metabolic machines[23] Metabolic fields[24]	*Networks of metabolic pathways (NMP)* *(Molecular texts)*	**Texts** (to reason/ compute) [linear correlations in the Planck-Shannon space] (see **Table 2 e** and **f**)

[19](Ji, 1991).
[1](Alberts, 1998)
[c](Metabolic pathways)
[20](Srere, 1987)
[21](Noris, et al., 1999)
[22](Hartwell, 1999)
[23](Holcombe, 1991)
[24](Welch and Smith, 1990)

Corresponding author: Sungchul Ji, Department of Pharmacology and Toxicology, Ernest Mario School of Pharmacy, Rutgers University, Piscataway, New Jersey, USA, Tel: 609-240-4833; Fax: 609-240-4833; E-mail: sji.conformon@gmail.com

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Isomorphism between cell and human languages

There may be two complementary aspects to the isomorphism between cell language (*cellese*) and human language (*humanese*) [4] (Ji, 1999) -- the qualitative and the quantitaive. References [2,4,5] discuss the qualitative similarity (or qualitative *functor*, to borrow the category-theoretic idiom) and **Table 2** below lists the quantitative similarities (or quantitative *functor* [6,7]. It is surprising to find that both cellese and humanese obey the same pair mathematical equations: Planckian Distribution Equation (PDE) was derived from physics [8,9] and the Menzerath-Altmann law (https://en.wikipedia.org/wiki/Menzerath%27s_law) was derived from linguistics but they are indistinguishable as far as their ability to fit long-tailed histograms generated from biology (not shown) or linguistics (see the right column in **Table 2**). Therefore, it seems reasonable to conclude that these observations provide both the *qualitative* and *quantiative* evidence supporting the validity of the isomorphism postulate between cellese and humanese [2-5]. Once a long-tailed histogram is fitted into PDE, two numbers can be generated from the PDE – (i) the *Planckain information* of the second kind, I_{PS}, and (ii) the *Shannon entropy* (H). I_{PS} is defined by Eq. (1):

$$I_{PS} = -\log_2((\mu - mode)/\sigma) \quad (1)$$

where μ and σ are the mean and the standard deviation of the long-tailed histogram under consideration. The Plankian information of the first kind, I_{PF}, was defined as the binary logarithm of the ratio of the Area Under the Curve (AUC) of PDE over the AUC of the associated Gaussian –like equation (GLE) [10]. The Shannon entropy is calculated based on Eqs. (2) and (3):

$$H = -\Sigma p_i \log_2 p_i \quad (2)$$

where p_i is the probability of observing the i^{th} event or entity calculated as

$$p_i = y_i / \Sigma y_i \quad (3)$$

where y_i is the frequency of the i^{th} event of entity and the index I runs from 1 to n, the total number of events or entities.

The information encoded in PDE parameter values of a long-tailed histogram can be visualized as a point in what is referred to as the *Planck-Shannon space* (see **Table 2 e** and **f**). When two groups of 10 sets each of the mRNA levels are chosen from the budding yeast transcriptome measured by Garcia-Martinez et al [11], one group having metabolic functions and the other not, the Planck-Shannon plots produced a linear correlation for the former (see **Table 2 e**) but not for the latter (see **Table 2 f**). Since each point in **Table 2 e** represents a long-tailed histogram of a metabolic pathway, the ten points forming a correlated line indicates that the *Planck-Shannon space* can recognize the third level of metabolic organizations as predicted in the last row of **Table 1.** That is, the Planck-Shannon space can distinguish molecular sentences (or metabolic pathways) as individual points, regardless of whether or not correlated with one another and molecular texts as linearly correlated points three or more in number.

Table 2

Planckian Distribution Equation (PDE): Role of Standing (or Resonance) Waves in Material Organizations in the Universe.

In 2008, the author noticed the similarity between the blackbody radiation spectrum at 5000 °K (see **Figure 1 (c)**) and the histograms of single-molecule enzyme turnover times reported by Lu, Xun and Xie [12] (see the blue curve in **Figure 1 (g)**). This motivated the author to 'generalized' the Planck's blackbody radiation formula, Eq. (4) in **Figure 1**, by replacing the universal constants and temperature with 4 or later 3 free parameters as shown in Eqs. (5) and (6), respectively, resulting in the so-called Planckian Distribution Equation (PDE), Eq. (5) or (6). PDE was also referred to as BRE (Blackbody Radiation-like Equation) before the term PDE was coined in analogy to the Gaussian Distribution Equation (GDE) [10]. These two equations are equivalent and can be mutually transformed using the equalities, (7), (8) and (9). As evident in **Figures 1 (f)** and **(g)**, PDE (or BRE) fits both the blackbody radiation spectrum and the single-molecule enzyme kinetic histogram**.** PDE has been found to fit many other long tailed histograms generated in the fields of protein folding (**Figure 1 (h)),** whole-cell RNA metabolism (**Figure 1 (i)**), T-cell receptor diversity [10], 7-mer DNA frequency distribution (**Table 2 a**), protein length frequency distribution (**Table 2 c**), word length frequency distribution in a speech (**Table 2 b**), sentence length frequency distribution in private letters (**Table 2 d**), decision time histogram [10], US annual income distributions in 1996 and 2013 [10], and the polarized microwave background radiations [10].

Figure 1

In order to account for the unexpected universality of PDE fitting almost all long tailed histograms examined so far (over 100), it was postulated, based on the physical interpretations of the two terms in PDE (see **Figure 1 (d)**), that all the observed regularities (or organizations) in the Universe that produce long-tailed histograms are the results of the standing (or resonance) waves generated by the input of energy into the system of oscillators under consideration (see **Figure 2**), just as an input to the Chladni plate generates *energy-dependent patterns* of particle distributions on its surface, the patterns being the visible examples of material organizations driven by standing (or resonance) waves of the vibrating plate.

Figure 2

RASER Model of Single-Molecule Enzyme Catalysis

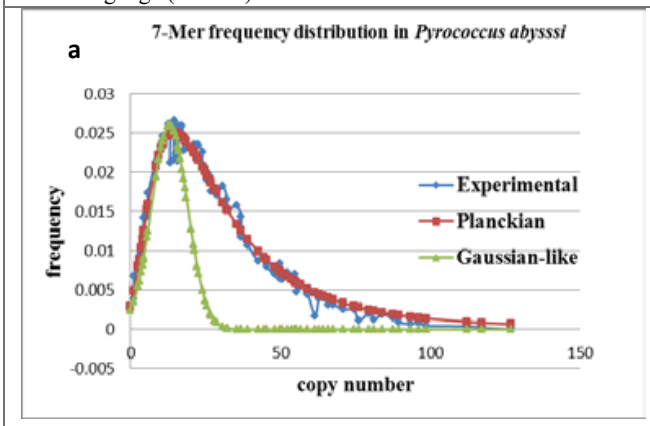
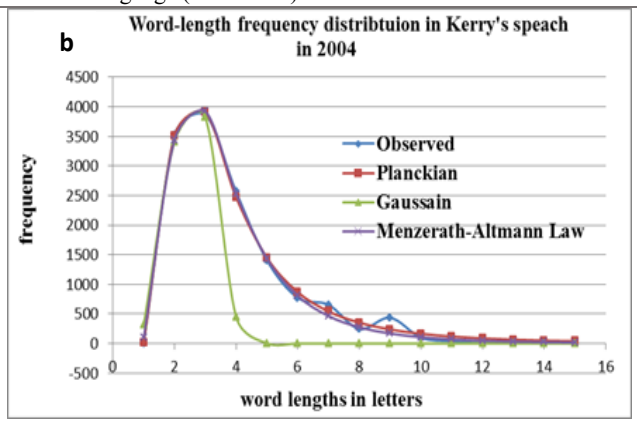
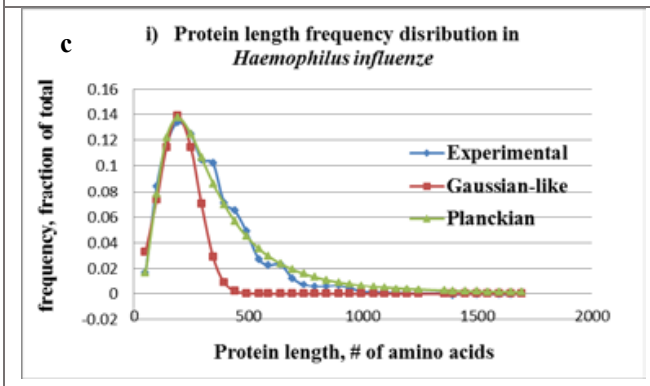
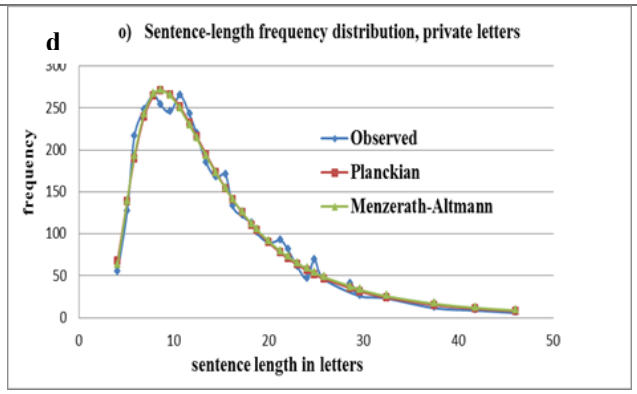
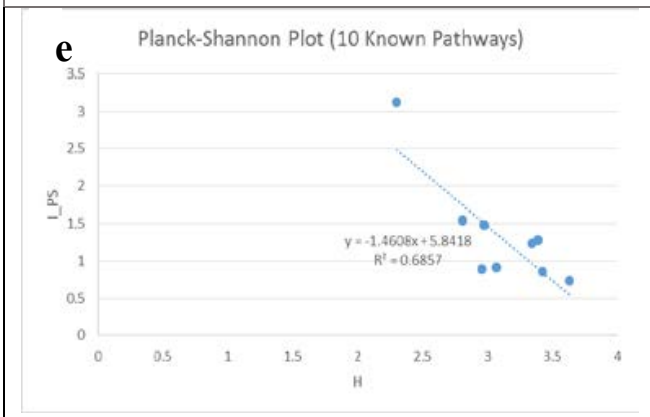
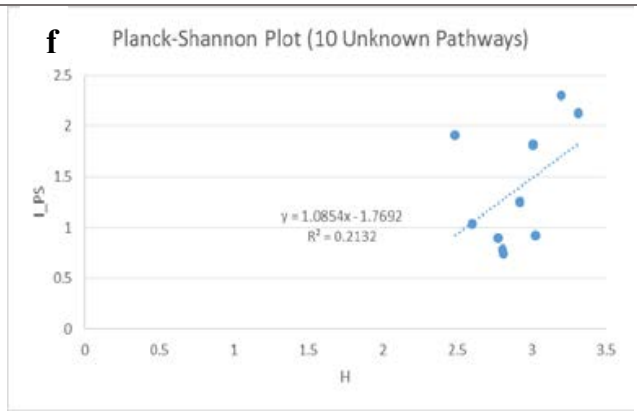
The fitting of the single-molecule enzyme turnover histogram into PDE, **Figure 1 (g)**, indicates that the free energy content of an enzyme molecule may be quantized (see **Figure 3** below), just as the fitting of the blackbody radiation spectra of atoms into the Planck's radiation equation implied the quantization of the electronic energy of atoms Figure 3.

Once it is accepted that the free energy content of an enzyme molecule is quantized (**Figure 3**) as evidenced by the PDE fitting of the single-molecule enzyme kinetic data (see **Figure 1 (g)),** it is relatively easy to find similarities between laser and enzymic catalysis as depicted in **Figure 4**.

RASER is an acronym derived from **R**ate **A**mplification based on the **S**ubstrate-**E**nhanced reaction **R**ates, in analogy to **laser**, or **L**ight **A**mplification based on **S**timulated **E**mission of **R**adiation. There is the possibility that, just as the blackbody radiation equation of Planck was found to apply to the single-molecule enzyme turnover times of cholesterol oxidase [5], so the subatomic mechanisms underlying the phenomenon of laser may apply (analogically) to the molecular mechanism of enzyme action, as proposed in **Figure 4 (b)**.

In the mechanism of laser (**Figure 4 (a)**), the input of "pumping" photons, $h\nu_1$, causes the electrons of the atoms constituting the laser medium (e.g., ruby crystal) to undergo the transition from the ground state energy level to the excited state energy level (see the 1 to 2 arrow). The excited state is short-lived and loses some of its energy as heat and undergo a transition to a lower energy level called "metastable" state (see the 2 to 3 arrow, **Figure 4 (a)**). Sate 3 is more stable than State 2 but still much more unstable than the ground state (see 1). When there are enough number of electrons in the metastable/excited state (thus creating the so-called "population inversion"), the arrival of triggering photons, $h\nu_2$, induces the de-excitation of electrons from

Table 2. The Planckian Distribution Equation (PDE) and the Menzerath-Altmann Law (MAL) connect the *cell* and *human languages*. Adopted from (Ji, 2017a) [10].

Cell Language (*Cellese*)	Human Langauge (*Humanese*)
	
	
	

the metastable excited state to the ground state (see the 3 to 1 arrow), accompanied by the emission of photons identical to the triggering photons, $h\nu_2$, but larger in number than the original triggering photons leading to light amplification. The emitted photons are "coherent" in that they are identical with respect to (i) amplitude, (ii) frequency, and (iii) phase.

Unlike electrons in atoms that are all in the lowest-energy ground state before absorbing photons, enzymes appear to exist in *different ground states* to begin with, before thermal excitation (i.e., before absorbing thermal energy), as indicated by the four solid bars in Figure 4 (b), which is enabled by the quantization of the Gibbs free energy levels of enzymes indicated by the observation that the single-molecule enzyme turnover times of cholesterol oxidase fit PDE as demonstrated in Figure 1 (g).

It is possible that, when an enzyme molecule absorbs enough thermal energy through Brownian motions, it is excited to the transition state lasting only for a short period of time, probably 10^{-14} to 10^{-12} seconds, the periods of chemical bond vibrations. The thermally excited enzyme is thought to undergo a transition to a more stable state called the "metastable" or "activated" state probably lasting up to 10^{-9} seconds. It appears that the metastable/activated state can be deactivated in two ways – (i) spontaneously (as in "spontaneous emission" in laser), and (ii) induced by substrate binding (as in "induced emission"). It is possible that during spontaneous deactivation of the active/metastable state of an enzyme, the excess energy is released as uncoordinated and random infrared photons

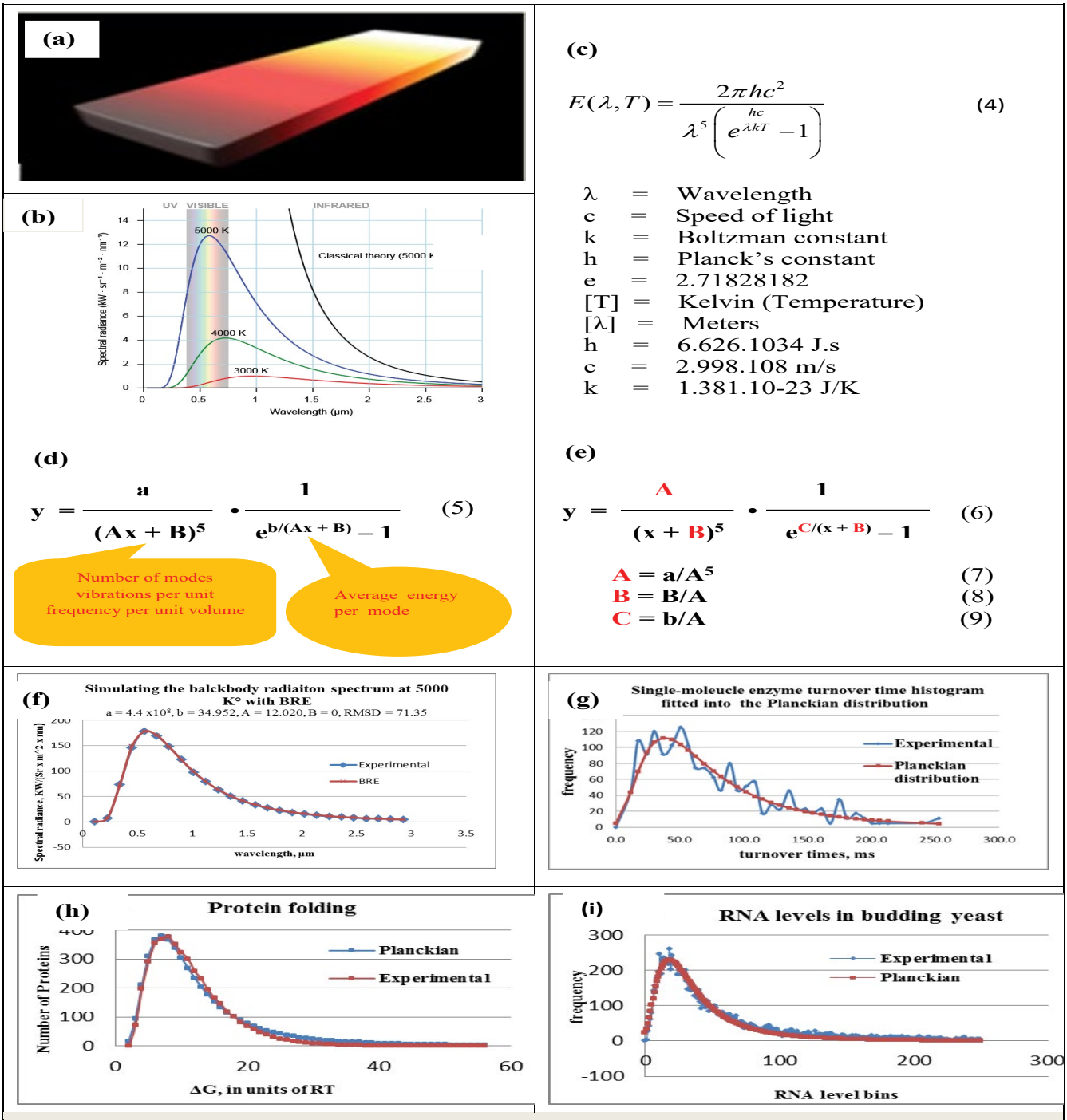


Figure 1. **(a)** Blackbody radiation. A heated iron bar emits light at different wavelengths depending on local temperature. Retrieved from an online source. **(b)** The blackbody radiation spectra. Retrieved from https://en.wikipedia.org/wiki/Black-body_radiation on 01/05/2016. **(c)** The Planck radiation equation. Reproduced from *Blackbody radiation*. http://hyperphysics.phy-astr.gsu.edu/hbase/mod6.html. **(d)** The blackbody radiation-like equation or BRE [5], also called the generalized Planck equation (GPE) or the Planckian Distribution equation (PDE). The interpretations of the two terms in PDE (shown in balloons) were reproduced from http://hyperphysics.phy-astr.gsu.edu/hbase/mod6.html. **(e)** The 3-parameter (colored red) version of BRE/GPE/PDE. The relations between the 4- and 3-parameter versions of BRE/GPE/PDE are given in Eqs. (4), (5), and (6). **(f)** PDE fits the blackbody radiation spectrum at 5000 5000 °K. **(g)** PDE fits the histogram of the single-molecule enzyme kinetic data of cholesterol oxidase reported by Lu et al [12]. (h) PDE fits the histogram of the protein folding Gibbs free energies of 4,300 proteins isolated from E. coli [25]. **(i)** PDE fits the histogram of mRNA levels measured at 6 time points over a 850 minute period from budding yeast after switching the nutrient from glucose to galactose [11].

Figure 1

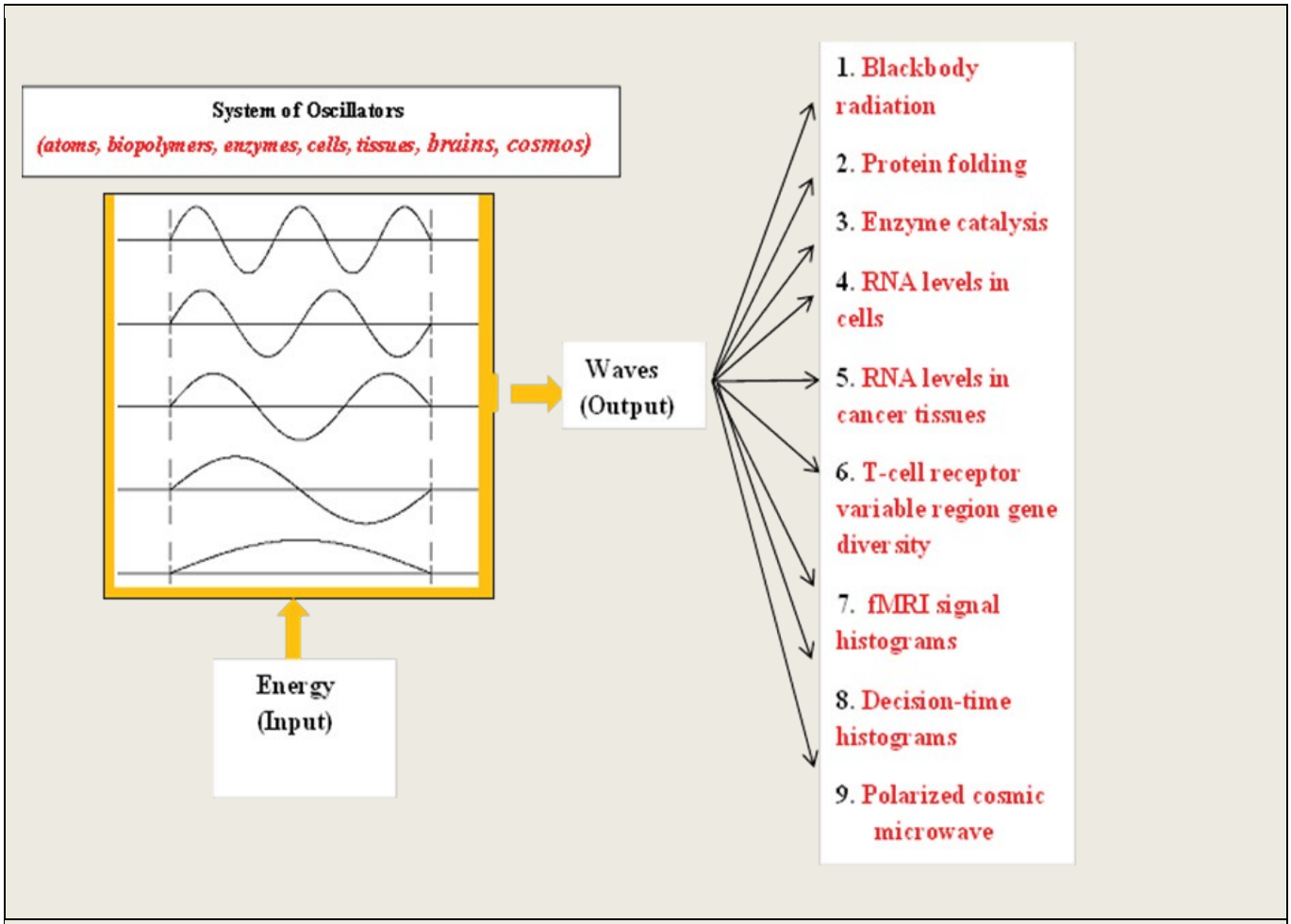


Figure 2. A possible explanation for the universality of the Planckian Distribution Equation based on the postulate that resonance (or standing) waves are the immediate causes underlying all material organizations in the Universe**.** Reproduced from [10] (Ji, 2017a, Figure 8.8).

Figure 2

(i.e., as heat), whereas, *during the substrate-induced deactivation*, the excess energy of the enzyme-substrate complex is released in a *coordinated manner* via, e.g., the synchronization of local enzyme processes [5], resulting in catalysis, just as the triggering photon-induced de-activation of population-inverted electrons in atoms results in the amplification of emitted photons as laser.

Figure 4

The enzyme catalytic mechanism proposed in Figure 8.5 (b) is referred to as the SID-TEM-TOF mechanism because it embodies the following three key processes [8,9]:

(i) Substrate- or Stimuli-Induced Deactivation in Step 4,

(ii) Thermally Excited Metastable state in the 1 to 2 and 2 to 3 steps

(iii) leading TO Function i.e., catalysis, in the 3 to 1 Step.

It is here postulated that the SID-TEM-TOF mechanism described here underlies many so-called Planckian processes defined as the physicochemical or social processes generating long-tailed histograms that fit PDE) [8,9] (and their records/results) that obey the Planckian distribution equation, Eqs. (5) or (6).

A Resonance Model of the Structure and function of Ribosomes.

Unlike in the transcriptional steps in gene expression where the same kinds of molecules, i.e., the nucleic acids, DNA and RNA, directly interact (or contact or touch each other) via the Watson-Crick base-paring mechanism, in the translational step, there is no direct interaction between mRNA and amino acids, but rather their interactions are mediated by tRNA which recognizes mRNA at its *anti-codon arm* and amino acids at its 3'-*acceptor stem*, about 60 Å away (see the blue region in the mechanism of translation. The universality of the wave-particle duality demonstrated in [10] suggests that the tripartite coupling among codon, anticodon, and amino acid in the ribosome-mRNA-tRNA complex may be mediated by *resonant vibrations* or *standing waves* (also called *resonance* or *resonant waves*) (see **Figure 5 (c), (d)** and **(e)**) generated within the complex, just as the vibrational patterns located at distant regions on the Chladni (1756-1827) plate are coordinated via resonance **Figure 5.**

The Chladni plate is an ideal model for illustrating the role of resonance in molecular biology. At a given resonance frequency, the particles on remote regions of the Chaldni plate are coordinated without any direct interactions between them and yet form ordered patterns. This is similar to what happens in the ribosome system when

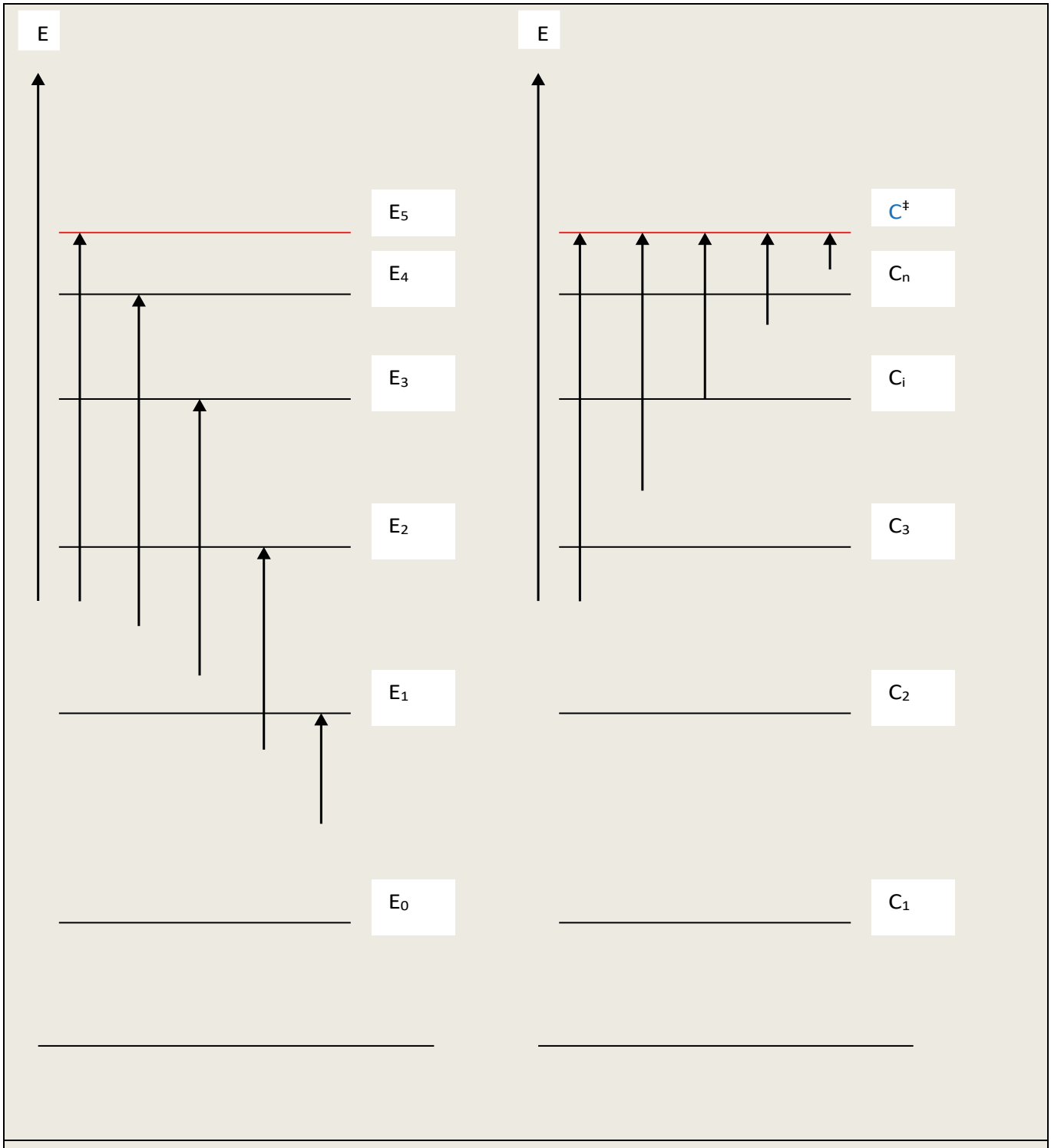


Figure 3. A comparison between *blackbody radiation* and *enzyme catalysis*.

(**Left**) Blackbody radiation involves promoting the energy levels (vibrational, electronic, or vibronic, i.e., both vibrational and electronic) of oscillators from their ground state E_0 to higher energy levels, E_1 through E_5. The wavelength of the radiation (or quantum) absorbed or emitted is given by $\Delta E = E_i - E_0 = hf$, where E_i is the i^{th} excited-state energy level, h is the Planck constant, f is the frequency, and ΔE is the energy absorbed when an oscillator is excited from its ground state to the i^{th} energy level. Alternatively, blackbody radiation can be thought of as resulting from the transitions of electrons from one energy level to another within matter, e.g.,

Figure 3

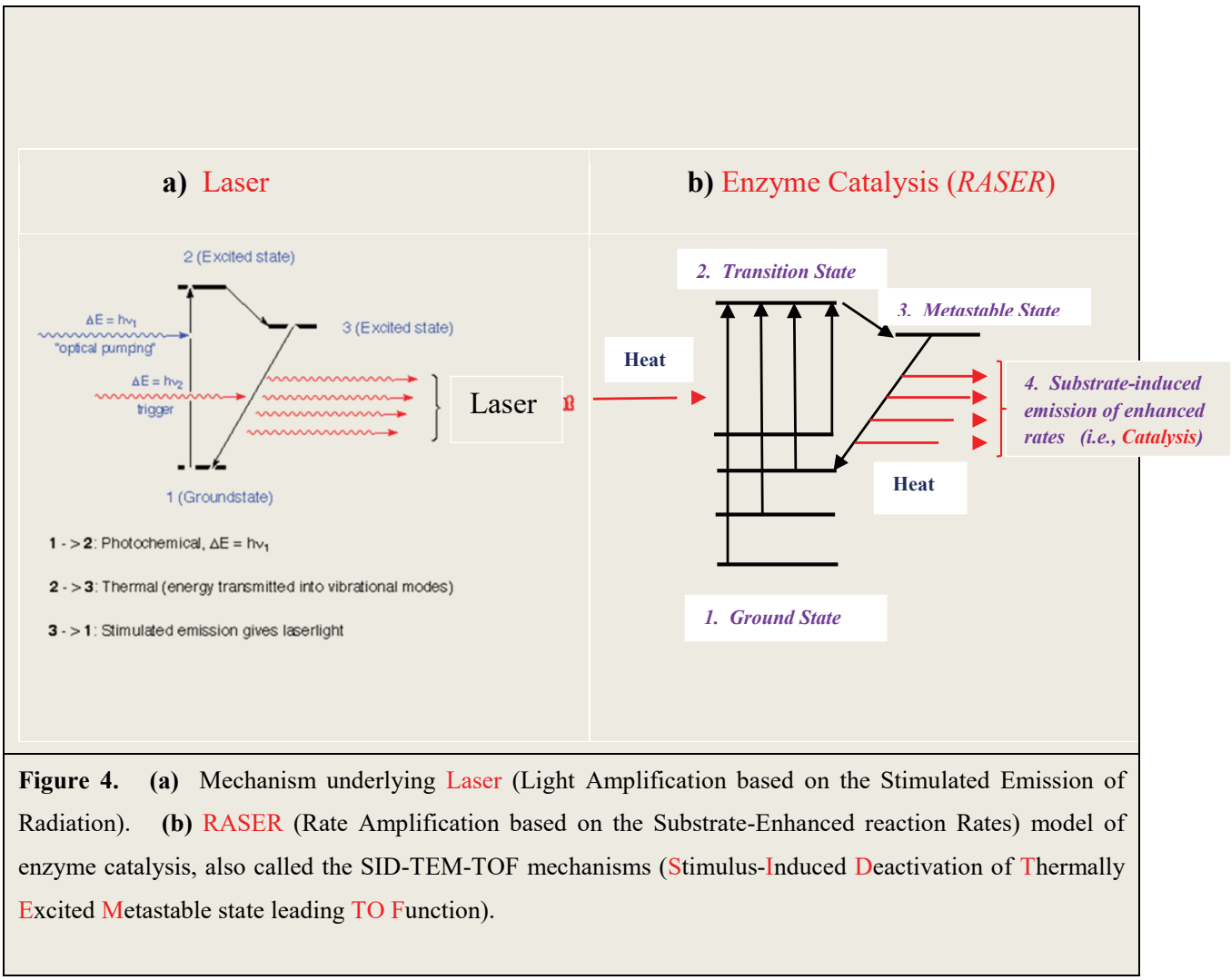


Figure 4. **(a)** Mechanism underlying Laser (Light Amplification based on the Stimulated Emission of Radiation). **(b)** RASER (Rate Amplification based on the Substrate-Enhanced reaction Rates) model of enzyme catalysis, also called the SID-TEM-TOF mechanisms (Stimulus-Induced Deactivation of Thermally Excited Metastable state leading TO Function).

Figure 4

a peptide molecule is synthesized; i.e, different components of the ribosome-mRNA-tRNA complex execute their motions that are so coordinated as to achieve the peptide synthesis. The ribosome and the Chladni plate are compared at several levels in **Table 1**.

Table 3

Table 3: The ribosome-Chladni plate comparison.

	Chladni plate	Ribosome
1. Vibrating system	metal plate	ribosome + mRNA + tRNA complex
2. Objects being organized	sand particles	codons, anticodons, aminoacyl residues
3. Scale	macroscopic	microscopic (also called molecular)
4. Source of energy driving the organization	electricity/sound waves	thermal energy paid back by the free energy of chemical reactions without violating the Second Law [7]
5. Common principle obeyed	Fourier theorem	Fourier theorem

The idea of using the Chladni plate (see **Figure 5 (e)**) as a molecular model of the protein synthesis in the ribosome occurred to this author while preparing for the keynote lecture, "RASER model of single-molecule enzyme catalysis", that I presented at the **8th International Conference on Proteomics and Bioinformatics**, held in Osaka, Japan, in May, 2017 (see **Figure 5 (g)**). I formulated this idea before I realized that J. Franck and his group was working on the mechanism of protein synthesis in the ribosome along based on a similar approach [13] (i.e., the wave approach to molecular biology [10], for which he shared the Nobel Prize in Chemistry this year. There are several components in what is here referred to as the "resonance model of the ribosome structure and function' (RMRSF):

(**i**) The ribosome and its associated RNA's and proteins are a system of molecular oscillators that obey the Fourier theorem (see **Figure 5 (a)**), i.e., all the wave patterns, both traveling and standing (see **Figure 5 (b)**) of the system can be constructed from the linear combinations of the vibrational motions of all the chemical bonds [14],

(**ii**) the standing waves in the ribosome system are determined by the geometrical (or conformational) shape (or topology) and the energy content of the system, and

(**iii**) the chemical (i.e., peptide bond formaton) and mechanical events (i.e., translocation of the tRNA from the A site to the P site, etc.) taking place at the anti-codon arm and the 3'-acceptor stem (see **Figure 5 (f)**) are 'coupled' or 'coordinated' through the resonance mechanism, just as are the motions of the sand particles located in distant regions on the Chladni plate, or just as the vibrational motions of the tuning forks (see **Figure 5 (c)**) are coupled to the vibrational motions of the water column by resonance thereby exchanging both energy and information between them. The resonance model of the *ribosome structure and function* depicted in **Figure 5** is based on the simiarilties and differences between the ribosome and the Chaladni plate summarized in **Table 3**.

It may be noted that my vibrational approach to enzymology/molecular biology dates back to 1974 [15] when I concluded as follows:

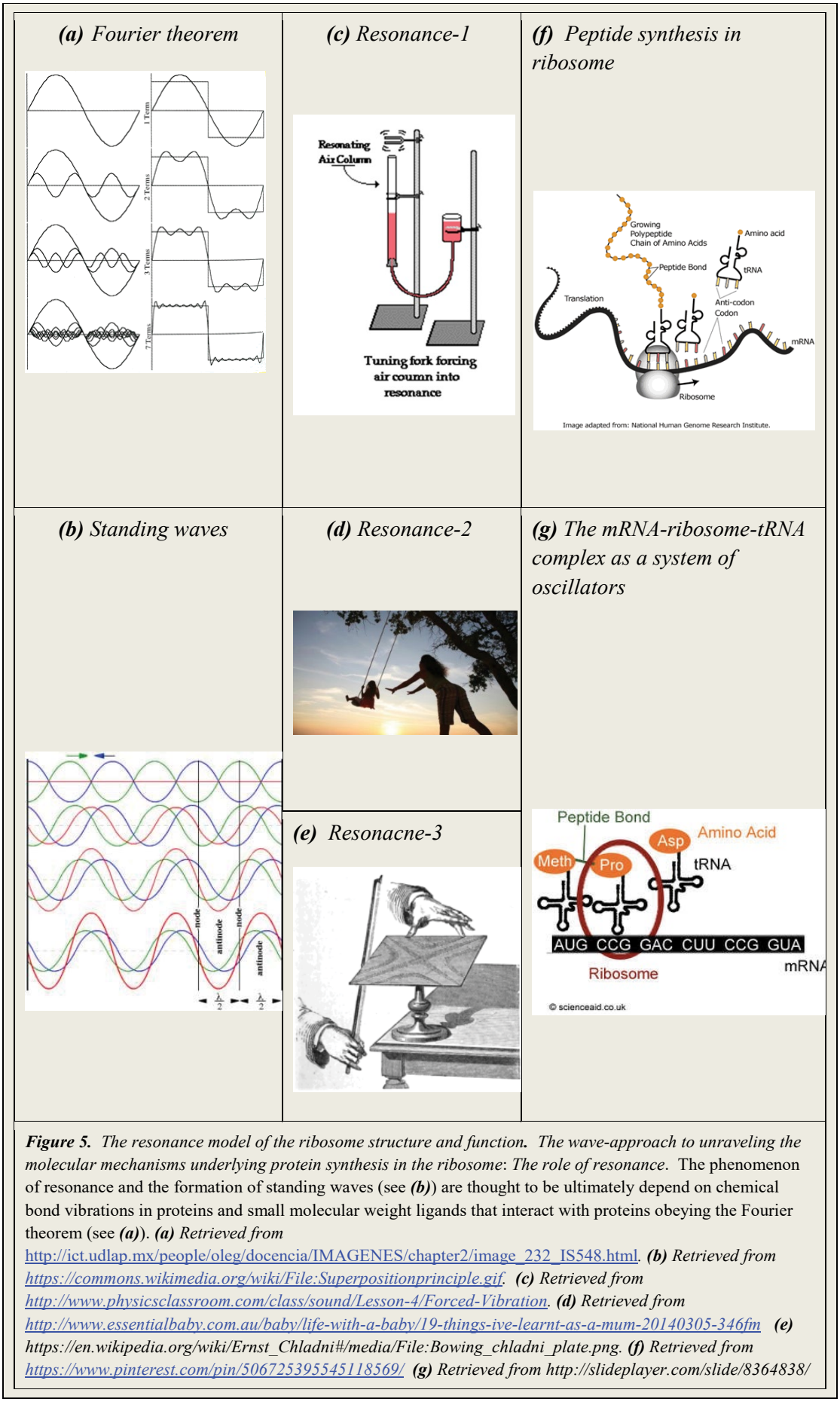


Figure 5. *The resonance model of the ribosome structure and function. The wave-approach to unraveling the molecular mechanisms underlying protein synthesis in the ribosome*: *The role of resonance*. The phenomenon of resonance and the formation of standing waves (see ***(b)***) are thought to be ultimately depend on chemical bond vibrations in proteins and small molecular weight ligands that interact with proteins obeying the Fourier theorem (see ***(a)***). ***(a)*** *Retrieved from* http://ict.udlap.mx/people/oleg/docencia/IMAGENES/chapter2/image_232_IS548.html. ***(b)*** *Retrieved from* https://commons.wikimedia.org/wiki/File:Superpositionprinciple.gif. ***(c)*** *Retrieved from* http://www.physicsclassroom.com/class/sound/Lesson-4/Forced-Vibration. ***(d)*** *Retrieved from* http://www.essentialbaby.com.au/baby/life-with-a-baby/19-things-ive-learnt-as-a-mum-20140305-346fm ***(e)*** *https://en.wikipedia.org/wiki/Ernst_Chladni#/media/File:Bowing_chladni_plate.png.* ***(f)*** *Retrieved from* https://www.pinterest.com/pin/506725395545118569/ ***(g)*** *Retrieved from http://slideplayer.com/slide/8364838/*

Figure 5

" *An ordinary enzyme possesses 10^3 to 10^4 vibrational degress of freedom, as compared to 3 each for the translational and rotational degrees of freedom. It is therefore reasonalble to assume that the vibrational motions of individual bonds in the enzyme will be far more important in enzyme catalysis than the translational or rotatioal motions of the enzyme as a whole. Given all the vibrational frequencies of the individual bonds in an enzyme, as well as their three-dimensional arrangements, we can in principle deduce the thermodynamic and catalytic properties of the enzyme under any conditions.*"

The resonance mechanism of coupling proposed in **Figure 5** between the aminoacyl group at the 3' acceptor stem and the anticodon at the opposite side of the ribosome about 60 Å away is consistent with the conclusion reached by Petoukhov that *genes in DNA can be viewed as oscillators* that couple to one another via resonance [16]. One of the reasons that Petoukhov came to invoke the *resonance mechanism* is that many of the regularities found in the genetic codes and DNA sequences (e.g., Chargaff's parity rules [17] obey the *tensor multiplication rules of matrices* widely used in engineering and physics to analyze vibrational mechanics. Thus, it is clear that Petoukhov's resonance approach to modeling genetic structures [16,17] indirectly supports the resonance coupling mechanism postulated for the transfer of genetic information from the codons of mRNA to the amino acyl residues of tRNA as briefly summarized in **Figure 5** above [26-28].

Conclusions

The fitting of the single-molecule enzyme turnover histograms to the Planckian Distribution Equation (PDE) derived in 2008 from the blackbody radiation equation discovered by M. Planck in 1900 opened up an unprecedented avenue of research concerning the molecular mechanism of enzyme catalysis, i.e., the possible role of standing waves or resonance and the possible analogy between laser and enzyme catalysis. This in turn led to the possible role of resonance in the coupling between the anti-codons and the amino acyl groups on the opposite sites of tRNA molecule about 60 Å apart, thus removing the mystery behind the coupling between genes and amino acids during protein synthesis. The resonance-based mechanism of information transfer from genes on DNA to proteins mediated by t-RNA is consistent with by the recent findings of [16,17] who was able to generate the 64 genetic codons staring from the four letters of the gentic alphabet using the mathematical techniwu of tensor multiplicaitons of matrices of the genetic alphabet, the same method widely used in studying resonance phenomena in physics and engineering.

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