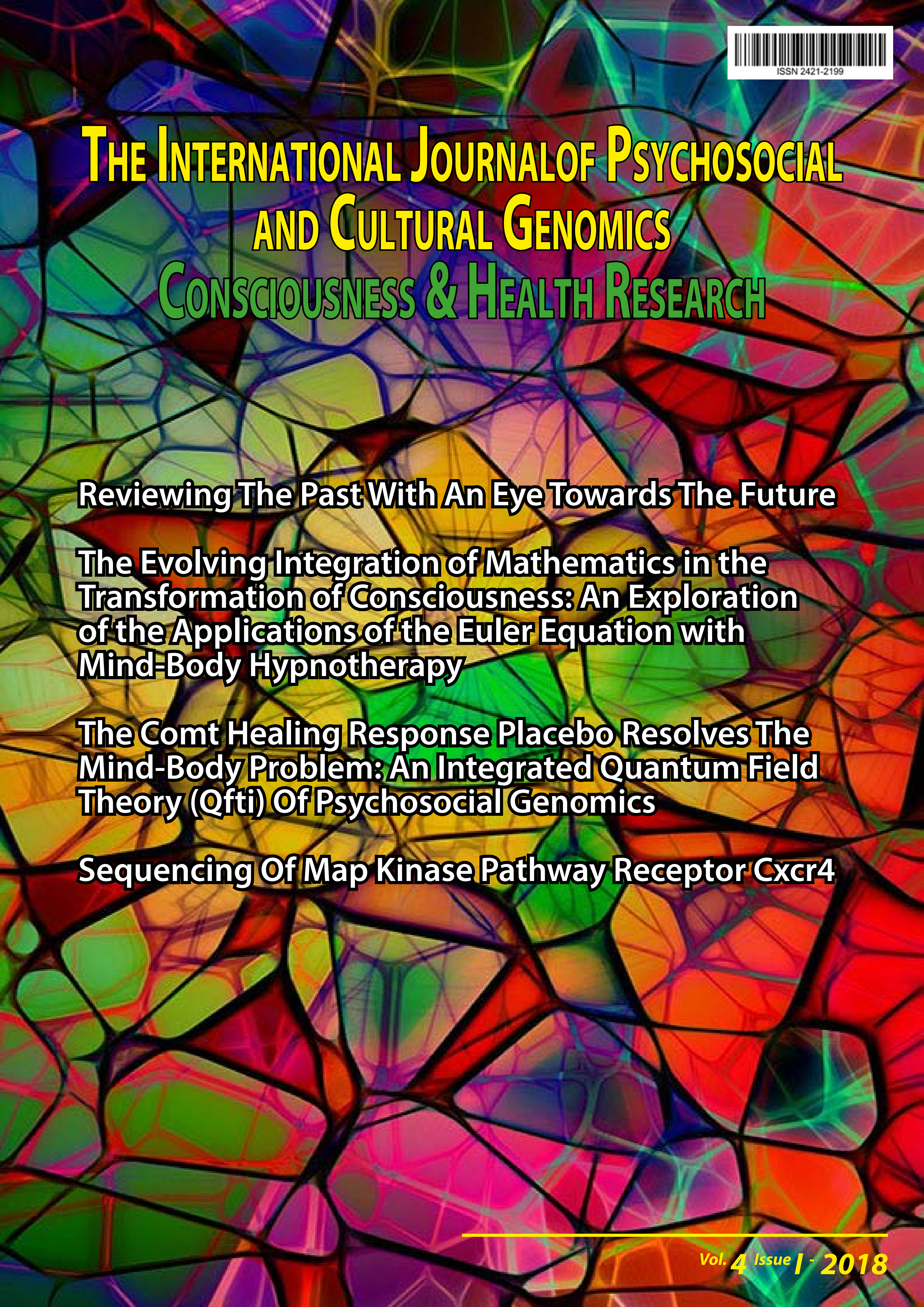

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Consciousness & Health Research

Reviewing The Past With An Eye Towards The Future

The Evolving Integration of Mathematics in the Transformation of Consciousness: An Exploration of the Applications of the Euler Equation with Mind-Body Hypnotherapy

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Editorial

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[...]

Mauro Cozzolino

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EDITORIAL

PSYCHOSOCIAL GENOMICS AND PSYCHOTHERAPY

MATHS, PHYSICS AND MIND-BODY THERAPIES

NEUROSCIENCE AND GENOMIC RESEARCH

REVIEWING THE PAST WITH AN EYE TOWARDS THE FUTURE

MAURO COZZOLINO
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Sometimes we are so involved in expectations for the future and innovation that we forget that there is an important connection between the past and the evolution itself when it takes shape in the novelty. This is the case when we use hypnosis as the only form of anesthesia. Every expert knows very well the power of hypnosis to do that. In fact, Esdale in his book Mesmerism in India, and its Practical Applications in Surgery and Medicine, published in 1846, reported a detailed description of over 300 major surgical operations performed under hypnosis as the only form of anesthesia (Hammond [12]). Hypnosis was later abandoned, following the introduction of general anesthetics (chloroform, ether and nitrous oxide), and only a handful of operations performed under hypnosis or self-hypnosis have been reported since the 1950s [13– 18]. Of course, the past has different functions but often seems to want above all to remind us how things went first and that this way is not correct, not applicable or excessive.

Yet, the past can also be re-read in the light of what we know and can do today. For this reason we can state that past, present and future can be redefined in a new way: remembering and reviewing the past to learn in the present for co-constructing an integrated mind-body dialogue with ourselves and the our world to reach the best possible future scenarios. From my point of view, one possibility to positively redefine the past in the light of Neuroscience and Psychosocial Genomics findings is the case of the utilization of hypnosis as the only form of anesthesia.

To put this into practice, I had the opportunity to use our hypnotic approach - called the Mind-body Transformations Therapy (MBT-T) - as sole anesthesia in dentistry.

The MBT-T is an evidence-based therapeutic approach specifically designed for the treatment of mind-body conditions. It aims at enhancing human resilience and resourcefulness for health and rehabilitation purposes. It makes use of our natural biological rhythms to set the best conditions to activate inner mind-body healing processes, which are capable of treating the stress related dysfunctions in psychiatry, psychology and rehabilitation (Rossi, Iannotti, Cozzolino, Castiglione, Cicatelli, & Rossi, 2008; Rossi, Atkinson, Mortimer, Iannotti, Cozzolino, & Castiglione, 2010; Rossi, Cozzolino, Mortimer, Atkinson, & Rossi, 2011; Cozzolino, et al., 2014).

To meet the specific aspects of this case, the method we used to prepare the patient for surgery and to obtain analgesia was made up of three different hypnotic protocols: (1) Progressive Relaxation (Shone, 1982), (2) the classic Glove Anesthesia protocol (Perussia, 2014; Kroger, 1990) and (3) and the Creative Psychosocial Genomic Healing Experience (CPGHE) protocol (Rossi et al., 2008; Rossi et al., 2010; Rossi et al., 2011; Cozzolino et al., 2014), which is one of the MBT-T clinical interventions.

The hypnotic progressive relaxation protocol includes suggestions aimed at relaxing the nervous system and the mind. The subject is trained to relax the skeletal muscles by focusing on one muscle group at a time and tensing and relaxing these muscles while paying attention to the difference between tension and relaxation (Shone, 1982). Glove Anesthesia (GA) is a hypnotic protocol for anesthesia that addresses pain and anxiety simultaneously. The hypnotist focuses the patient's attention on his/her hand and suggests that an imaginary glove is put on the selected hand. The hypnotic trance is then used to create numbness wherever in the body the "glove" is laid on (Bresler, 1996; Perussia, 2014). The CPGHE (Cozzolino et al., 2014; Rossi et al., 2008; Rossi et al., 2010; Rossi et al., 2011) is one of the MBT-T clinical interventions. It is a protocol which promotes creative psychological experience and a positive change in consciousness (Rossi et al., 2010).

A 32-year-old female patient suffering from a syndrome known as Multiple Chemical Sensitivity, which caused her anaphylactoid reactions to local anesthetics, needed to undergo dental removal. So, her dentist referred her to me for hypnoanesthesia. It only took us three preliminary hypnotic training sessions at my office and a surgery simulation at the dentist's office to ensure that her hypnotizability and the analgesic capability of her hypnotic state were satisfactory for the dentist to proceed with the surgery. On the day of the surgery, which was only the fifth time I had seen the patient, drugs and equipment for pharmacological anesthesia were available in case of failure of hypnosis. As shown in the video available on our site (www.psychosocialgenomics.com), the surgery was successful and the patient confirmed feeling no pain at all, although she was never amnesic and had vivid memories of all stages of the intervention. In line with our studies on clinical hypnosis, not only was full analgesia reached, but the patient also reported a sense of wellbeing, making dental surgery a positive experience that she gladly accepted to repeat for the removal of another tooth a few days on. In this case, the MBT-T therefore allowed us to achieve several important goals at the same time, i.e. a state of calm; a reduction in surgery related stress and anxiety; analgesia and anesthesia; and most importantly, a condition of wellbeing, problem-solving, effective coping and self-empowerment.

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THE EVOLVING INTEGRATION OF MATHEMATICS IN THE TRANSFORMATION OF CONSCIOUSNESS: AN EXPLORATION OF THE APPLICATIONS OF THE EULER EQUATION WITH MIND-BODY HYPNOTHERAPY

BRUCE GREGORY, PH.D.

Key words: implication, derivatives, functions, structure, permission, yes set.

Abstract

Euler's equation is discussed in terms of its relevance and application to the transformation of consciousness with respect to the treatment of resistance. The equation, also called Euler's identity, is considered to be one of the most influential and beautiful equations in all of mathematics in that it integrates the exponential function, the sine and cosine functions, and the imaginary number. The relationship between these three functions and the imaginary number implies connection, and the capacity to connect, as opposed to being alienated and isolated. Emphasis is placed on the mathematical tools utilized to develop the equation, the role of the tools in the enhancement/expansion of trust within the professional providing the treatment, and the inferences contained in the variables of the equation. The equation is compared to the Erickson Resistance Protocol in terms of depth, structure, connection and novelty. Further parallels are drawn with concepts from Tibetan Buddhism and Tai Chi.

Introduction

The transformation of consciousness is often dependent on the focus of attention, and it being shifted in different directions which may include, toward the unconscious, specifics themes, time and space, or areas of the body. (Erickson and Rossi, 1979, Tulku, 1979, Wilbur, Engler and Brown, 1985, Yang, 1996). In mathematical terms this may correspond to vectors, which describe magnitude and direction. Vectors can be thought of as machines or transformers, express rates of change, and infer the roles of space. In psychological terms, vectors can be thought of as frames of reference that focus attention in specific directions in the context of facilitating novelty, unconscious processes and activity dependent gene expression. The appreciation of vectors can be applied to psychological resistance in a number of ways which include; recognizing that avoidance, a subset of resistance, represents a vector pointing in the opposite direction of a goal. In terms of trigonometry this would be 180 degrees from the goal; from the perspective of the appreciation of inferences, recognizing that *yes sets for vectors* can support the creative facilitation of novelty in interrupting rigid patterns of unconscious resistance. The appreciation of vectors can also be applied to uniform or accelerated motion, especially in the context of exponents, which represent something multiplied by itself. (Crease, 2008, Erickson and Rossi, 1979, Gregory, 2016, Isaacson,2006, Merrill-Wolff, 1973, Tulku, 1979, Wilkes, 2016). Processes that support the transformation of consciousness contain a series of inferences, which when appreciated, can facilitate the creative focusing of attention. These inferences include and are not limited to; the appreciation of inferences, opposites, permission, novelty, creativity, momentum, validation, structure and time. These inferences can function as a platform for; the transformation of consciousness, the appreciation of structure that can facilitate connecting to deeper structures, and the connection to deeper structures that facilitate connection to, and comfort from the sources of the creative design of life (Asher and Gross, 2006, Crease, 2008, du Sautoy, 2008, Gregory, 2017, 2018, Merrill Wolff, 1973, Rossi, 2002, Tulku, 1979).

The transformation of consciousness with respect to resistance has been addressed from both eastern and western perspectives at multiple levels of depth which i*nfer* and reflect capacity for transformation at the molecular genetic level that culminates in the KREB cycle and neurogenesis. From a Tibetan Buddhist perspective Tulku (Tulku, 1979) has addressed the resistance factor that is operating when the self is attempting to occupy the position of the center in processing experience. The push hands sequence of Tai Chi addresses resistance through the 'peng-lu-an' sequence that utilizes the appreciation of validation and redirection to transform resistance in accordance with principles of physics (Gregory, 2012, Man Ch'ing, 1985, Yang, 1996). From a western perspective some notable examples of the treatment of resistance to transform consciousness include; Masterson's psychodynamic approach of challenging the efficacy of the defences (Masterson, 1976, 1981); Erickson's Resistance Protocol outlined the steps for utilizing resistance through an appreciation of validation, momentum, opposites and the creative focusing of attention to facilitate receptivity that reflected a transformation of consciousness (Gregory, 2015, 2017, Erickson, 1964); Rossi demonstrated how the appreciation of the transcendent function could be employed with a polarity approach, that included resistance on one pole, and the receptive, resource network for problem solving on the other pole (Rossi, 1996, 2002). Music composition utilizes the appreciation of resistance to creatively resolve chords facilitating harmony and the holding of attention (Gregory, 2010, Levitin, 2006).

The appreciation of the role of structure in the transformation of consciousness has been recognized in a number of areas that utilize and reflect reasoning with respect to set theory, inference, and the appreciation of novelty with respect to the focus of attention, and the utilization of the polarity between the old and the new. A subset that represents the value and application of the appreciation of structure, the philosophy and practice of yoga, utilizes the appreciation of structure to support connection and focus with respect to time, space, and humility. The practice of the asanas or postures supports the transformation of consciousness through the utilization of breathing, and gentle opening which contain multiple inferences that validate and nurture the trust, patience, balance and receiving components of consciousness. (Feuerstein, 1980, 1989, Iyengar, 2003, Lasater, 2000). The practice of Tai Chi supports the transformation of consciousness by complementing harmony of structure around the joints, working the focus of attention from the ground up, which is represented by the term 'rooting', with a harmony of motion that integrates the appreciation of opposites and balance. This is enhanced by an appreciation of both receiving, gathering, and yin aspects of experience. These aspects of experience infer the appreciation of the resource networks for receiving and opening as subsets for comfort, healing and the transformation of consciousness (Gregory, 2012, 2018, Jung, 1916, Man Ch'ing, 1985, Rossi, 2002, Yang, 1996). The theory and practice of Tibetan Buddhist meditation reflects an appreciation of the role of structure with respect to experience, the origins of experience, and the processing of experience as a foundation for transforming consciousness. The logical foundations for this are reflected by the *inferences* utilized in Nagarjuna's *Madhyamikai-karika*. These inferences are encapsulated in Nagarjuna's concept of dependent origination. Dependent origination describes the structure and origins of experience, culminating in the realization of the fundamental role of dependency in the generation of experience. Its primary objective is to support the transformation of consciousness by redirecting the focus of attention away from the ego's delusions and obsessions toward the primary sources of experience, time and space. This approach validates and appreciates structure, and implies that the *appreciation of structure* can be applied in the transformation of consciousness (Garfield, 1995, Gregory, 2015, 2017, Merrill-Wolff, 1973, Tulku, 1979).

The novelty components in the above orientations are reflected by the creative focusing of attention on parts of the body, and the connections between different parts of the body, in conjunction with breathing, focus, and visualization to access comfort, and connect with spiritual aspects of experience, which facilitates the transformation of consciousness in the process. From the perspective of set theory, the parts of the body, which are expressions of *structur*e, and the connections between them can be seen and understood as resource subsets/sources for comfort and the transformation of consciousness. (Ash and Gross, 2006, du Sautoy, 2008, Matthews and Butler, 2011, Rossi, 2002, Yang, 1996).

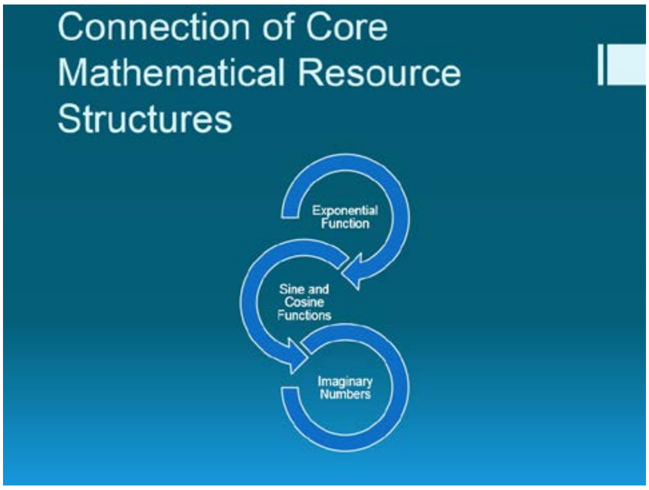
In the contexts of set theory and inference, research in neuroscience has supported the appreciation and value of structure from a variety of directions and levels. At the organ level the structure and processes of the hippocampus that are so fundamental to activity dependent gene expression and the resulting transformation of consciousness were identified in detail by Squire and Kandel (Rossi, 2002, Squire and Kandel, 1999). At the molecular level Loewenstein (Loewenstein, 1999) illustrated how the structure of adenylyl cyclase was critical to the sharing of information. Penrose and Hameroff highlighted the role of structure in relation to the role of microtubules in consciousness processes (Penrose and Hameroff, 2011). Rossi's discussion of the different types of genes, and their temporal parameters inferred the value of structure and its potential application through an appreciation of set theory (Dunham, 1991, Gregory, 2015, Rossi, 2002).

Euler Equation

The Euler Equation, developed by Leonard Euler, was presented in Euler's *Introduction to Infinite Analysis*, published in 1748 (Euler, 1748). For any real number x the formula states:

e^{ix}=cosx + isinx.

When x = pi, then the equation becomes $e^{i\cdot fl'}$ + 1= 0. 'e' is the abbreviation for the exponential function, the only function whose derivative is itself. The exponential function describes a special accelerated rate of change. From a set theory and opposites perspective this could be either a positive or negative accelerated rate of change with respect to the accomplishment of a goal. 'i' is the imaginary unit which represents the square root of -1, which does not lie on the number line. 'cos' and 'sin' are abbreviations for the trigonometric functions sine and cosine. The sine and cosine functions relate to distances and directions with respect to the exploration of properties of circles and their radii. When plotted on a graph, they become waves, describing rate of change that are only different in their initial positions. The sine and cosine functions are descriptions of subsets of the entire set of rates of change, and infer like other subsets of the rates of change general set the *value of derivatives* as tools and opportunities for facilitating novelty once a yes set for rates of change has been established. The equation expressed the deep, fundamental connection between the exponential function, the trigonometric functions, and imaginary numbers (Crease, 2008, Nahin, 2006, Transnational College of LEX, 1995). The connection between these core mathematical resources/tools is represented in Figure 1 below.



Connection of Core Mathematical Resource Structures

Figure 1 Connection of Core Mathematical Resource Structure © 2018 Bruce Gregory, Ph.D.

Richard Feynman, Nobel Prize winning physicist, called the equation 'our jewel' and 'the most remarkable formula in mathematics'. The basis for this assessment comes predominantly from the equation describing one of the most fundamental structures of life, and its implications being applied consistently to help formulate many of the wave equations of quantum mechanics. The equations of quantum mechanics provided the mathematical and scientific experimental validation of the *capacity for connection* at fundamental levels through the process of quantum entanglement. Examples of some of the wave equations and processes that incorporate the connection between the exponential function, the sine and cosine functions, and imaginary numbers include; the amplitude of harmonic oscillation, multiplication in quantum mechanics, transitions of electrons from one energy level to another, and Heisenberg's equation of motion (TCL, 1995). When this is reasoned and factored in with some of the primary variables in the transformation of consciousness listed below, there are a number of significant implications involving the variables below that can be applied to creatively focus attention.

- Set theory
- Implied directive
- Novelty
- Resources/tools
- Empowerment
- Trust
- Focus of attention

The inferences of the equation represent the potential value of the equation. They point like vectors in the direction of continuing the expansion of trust within professionals to creatively focus attention, facilitate novelty, activate unconscious healing processes and facilitate gene expression. These vectors can be utilized upon the establishment of *yes sets* for the inferences within the professional (Erickson and Rossi, 1979, Gregory 2015, 2018). Some of the main implications include;

- Variables of the equation are subsets of the sources of connection.
- When set theory is applied to the functions, they can be seen as resources themselves.
- The variables of the equation can function as bridges to the *sources* of their value.
- Structure can be utilized as a theme for focusing attention once a yes set is established.
- Processes that supported the derivation of the equation can be seen and utilized as resources or tools.

The primary inference of the equation is that the variables of the equation are subsets of the *sources of connection*, which identify them as potential bridges to new forms of comfort, healing and gene expression. The variables of the equation reflect *connection* on the deepest level of creative design, and as such function as bridges to depth and safety. In addition, within this inference lies another, more powerful *inference*, which is that these variables, which represent aspects of *structure*, have *sources*, which include both content and process sources. Accompanying this inference is that having a *yes set for structure* can expand a professional's ability to creatively focus attention, facilitate novelty, and unconscious healing processes. Content examples include; hippocampus, KREB molecules, serotonin, electrons, mitochondria, lipid membrane, microtubules (Loewenstein, 1999, Penrose and Hameroff, 2011). Examples of simple vectors, or basic accessing questions that can activate an exploration of these sources include;

I wonder what internal structures within the unconscious have supported the discovery of this equation and the resources represented by it?

I wonder what process tools have been utilized in the process of discovering this equation?

The *process resources* are a reflection of the *appreciation* of Poincare's four stage creative process (data collection, incubation, insight, integration) (Poincare, 1905, Rossi, 1996, 2002). These process resources function as subsets of the set of all resources for learning, discovery and healing. They provide the substructure for exploration, stage 1 of Poincare's four stage creative process, which can enhance feelings of capacity and trust, thereby reducing anxiety and pressure. They are the answer to how the exploration is engaged on the conscious level of stage 1, laying the groundwork for stage 2, incubation, wherein unconscious exploration is engaged. Further, these resources *open up* the process of exploration itself, which also reduces anxiety and pressure. The process resources include; experimentation, visualization, substitution, waiting, implicit trust of unconscious processes, permission to work with small steps, make mistakes, adopt a mind set of play, repeat, and fail (Crease, 2008, Dunham, 1991, Transnational College of LEX, 1995, Wilkes, 2016). These process resources can be understood as tools/ resources that reflect capacity, and highlight the *appreciation of permission* in the process of transforming consciousness. Further, these process resources function as subsets of the set of all permission, and imply how permission can be expressed creatively, and that permission is a *bridge connecting* to opening, waiting, appreciation of time, and receiving from the unconscious. In doing so they function as the tools for exploring, which supports the nurturing of capacity and the utilization of the polarity between pressure and permission to activate unconscious processes. When permission is then factored with the dynamics of exponentiation, the possibilities for the utilization of permission receive a boost. Rather than it simply being 'how many doses of permission'? Or, instead of 2 times permission or even seven times permission, it can be permission x permission x permission which is permission cubed. Processing can shift from linear and nonlinear to exponential, while simultaneously reinforcing the nurturing of needs and curiosity. Figure 2 below represents a collection of the process resources.

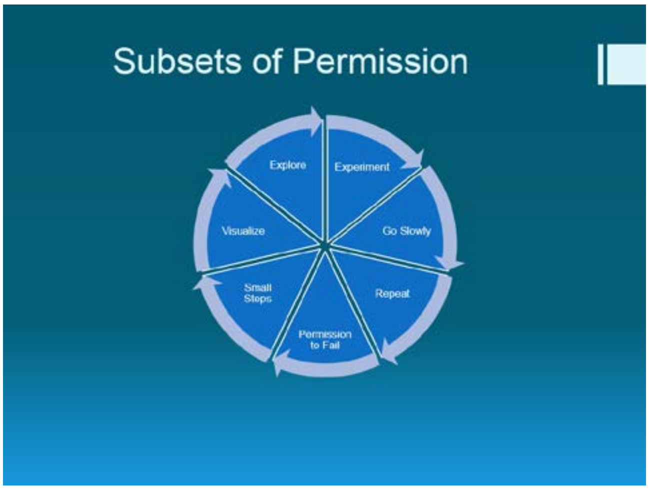

Subsets of Permission

Figure 2. Mathematical Resource Tools © 2018 Bruce Gregory, Ph.D.

The fourth implication is that *structure*, connection with structure, and yes sets for structure can be utilized to facilitate comfort, creative problem solving and unconscious healing processes. This may reflect a deeper appreciation of structure than the one exemplified by group theory. Group theory was developed by Evariste Galois and later developed by Lie, Klein and others. Group theory involves hidden patterns of structure, that generally applies more to geometric structures, and an appreciation of opposites. It is a language that describes the interactions of symmetries, actions between elements that preserve its structure. Group theory was instrumental in the development of quantum physics, the solving of complex mathematical equations, and the Lorentz transformation, which was an essential ingredient in the formulation of Einstein's equation of special relativity. By thinking in terms of group theory, Galois' core realization that the interactions between the symmetries of a group determines and reflects its essential structure can be creatively applied to orient consciousness toward the core of the healthy side of the polarity within the patient. This is done by an appreciation of the permutations, which is what Erickson creatively utilized in his resistance protocol. This is in contrast to the structures that are implied by the function analysis available in the relationship between the exponential functions, the trigonometric functions of sine and cosine, and the imaginary number. In the former the emphasis is on the trust and utilization of the permutations and in the latter the emphasis is on the utilization of visualization, substitution, and multiple levels of permission (Asher & Gross, 2006, du Sautoy, 2008, Erickson, 1964, Gregory, 2015, Livio, 2005).

An example of Erickson's utilization of permutations is below;

"In other words, I will ask a question to which only your unconscious mind can give the answer, and concerning which your unconscious mind can only guess if it does at all; maybe correctly, maybe wrongly, or maybe have only some kind of opinion, but if so, only an opinion, not an answer.

Before I ask that question, I would like to suggest two possibilities. (1) Your conscious mind might want to know the answer. (2) Your unconscious mind might not want you to know the answer. My feeling, and I think you will agree, is that you came here for therapy for reasons out of the reach of your conscious mind. Therefore, I think that we should approach this matter of the question I am going to put to your unconscious mind for its own answer in such a way that your own deep unconscious wishes to withhold the answer or to share the answer with your conscious mind are adequately protected and respected.

Now, to meet your needs, I am going to ask that yes or no question, and be prepared to be pleased to let your unconscious mind answer, and in doing so either to share the answer with your conscious mind or to withhold it, whatever your unconscious mind thinks to be the better course. The essential thing, of course, is the answer, not the sharing nor the withholding. This is because any withholding will actually be only for the immediate present, since the therapeutic gains you will make will eventually disclose the answer to you at the time your unconscious mind regards most suitable and most helpful to you. Thus you can look forward to knowing the answer sooner or later, and your conscious desires, as well as your unconscious desires, are the seeking of therapy and the meeting of your needs in the right way at the right time." (Erickson, 1964, p. 304).

In the quotes above Erickson was permuting the themes of the polarities of the conscious vs the unconscious, and knowing and not knowing. Resources/tools he employed in the process included; pacing, the creative focusing of attention, the appreciation of possibilities, and the appreciation of timing.

The discovery of the Euler equation was part of Euler's extensive exploration and analysis of functions, which eventually became a major component of the mathematical landscape known as function analysis (Crease, 2008). Functions are descriptions of relationships. From a psychological perspective, they are abbreviated descriptions of relationships, how one thing is affected by another. Or, how one thing affects, or transforms another, and in what direction and what speed. In interpersonal communication terms, this would translate to how person B's response is affected by person A's delivery or presentation. In intrapersonal terms this would translate to how one's experience is affected by the direction or theme of focus, and the amounts of time allocated for this focus. When plotted on graphs, functions provide a visual picture of how relationships change, in what direction, and what speed. As such, functions can be understood as a subset of the set of all relationships, and contain a *series of implications* that can be applied to the treatment of resistance in either working with couples or individuals. These implications include; 1) that the exploration of functions/relationships can be done in a variety of ways which opens up different angles or frame of reference for the focusing of attention, facilitating novelty and substantial possibilities for unconscious processing. 2) that there are different types of functions, some of which are continuous, smooth, or analytic, and these functions can correlate to different kinds of conversations involving resistance or a variety of internal processes which reflect resistance that can be organized in terms of opposites that can be explored to activate the hippocampus, transcendent function and facilitate activity dependent gene expression (Jung, 1916, Rossi, 1996, 2002, Squire and Kandel, 1999). 3) that the functions that describe machines, transformations, and vectors can be seen as doors, resources, tools, and sources of comfort and transformation; 4) that rates of change, which are expressed as derivatives, can be utilized as themes for facilitating novelty; 5) the derivatives themselves, and the processes for computing them can be seen as tools that can enhance trust in both professionals and patients (TCL, 1995, Wilkes, 2016).

For example, in terms of distinctions between types of functions, some functions describe transformations, and can be of the form $f(x) = 2x$, or $f(x) =3x + 3$, while analytic functions are functions that can be expressed in terms of an infinite series. Analytic functions utilize the taking of derivatives, and include the exponential, sine and cosine functions. When functions are put on graphs, and represented visually, the implications of the directional component in terms of conversations (interpersonal) and internal processing experiences (intrapersonal) like blocking, obsessing, avoiding or exploring, receiving, or opening become significant, and opportunities for focusing attention creatively expand exponentially (Crease, 2008, Gregory, 2018 in press, TCL, 1995).

Euler's explorations of functions, specifically those that led to the Euler equation that described the connection between the exponential function, the sine and cosine functions, and the imaginary number can be understood as a series of steps that involved the utilization of a variety of tools, and corresponded to some of the processes of Tai Chi, neurogenesis, the electron transport chain in 'atp' processes, Tibetan Buddhist meditation theory, classical music composition theory, and the Erickson Resistance Protocol. The correspondences imply fundamental, central organizing themes and processes. The steps validate the role of the *appreciation of permission* as a fundamental variable in the transformation of consciousness. They imply the need for an appreciation of containment and structure in transformation of consciousness processes. Thinking in terms of steps implies the need and value of structure, the need for containment, and the need for permission.

Euler's first step was to trust his intuition and explore the exponential function, which is similar to exploring the flow of conversations or internal processing dynamics in the hopes of discovering hidden patterns that can be utilized to facilitate novelty and transformation. This exploration included taking the time to identify its properties, and experiment with alternative ways that the exponential function could be represented. Taking the time to do this supported the development of yes sets that could be later utilized by the unconscious in stage 2, the incubation stage, of the four stage creative process. By taking its derivative, a description of its rate of change, multiple times, which can be considered a tool or resource for exploration, Euler was able to represent the exponential function as an infinite series. This implied three important aspects that are relevant in transformation of consciousness processes, and are also components of Tibetan Buddhist meditation theory and practice, the Erickson Resistance Protocol, classical music composition theory, and Tai Chi;

- The appreciation of the rate of change can be a tool in transforming consciousness. (Rossi, 2002, Yang, 1996).
- The application of set theory could be useful in exploring the possibilities of different types of exponential functions.
- The appreciation of the role of possibilities can be a tool in the transformation of consciousness (Dunham, 1991, Erickson and Rossi, 1979, Gregory, 2015, 2017).

This property of being able of being expressed as an infinite series made the exponential function an analytic function, opening up the opportunity to employ set theory to expand possibilities of exploration, and the facilitation of novelty. In addition, it implied the wide applications of the utilization of substitution as a tool in exploration and the discovery of hidden patterns.

In step two Euler turned to an examination and exploration of the trigonometric functions of sine and cosine, which was an additional example of the opportunity to utilize set theory. The utilization of set theory can be utilized in mathematical explorations and problem solving, the exploration of the dynamics of conversations, resistances, or internal processing problems. The functions of sine and cosine are also analytic functions that can be expressed by an infinite series. The sine and cosine functions relate to distances and directions with respect to the exploration of properties of circles, and their radius'. Euler's exploration of the properties of circles and the truisms/axioms available may correspond to Erickson's utilization of learning sets and Tulku's utilization of truisms regarding the roles of time and space in both the structure and processing of experience. Circles can represent wholeness, can represent the self, and the dual parts of the self, healthy or unhealthy, or as Jung conceptualized, the hero vs. the shadow (Crease, 2008, Jung, 1960, Rossi, 1996). In terms of other approaches; from a mind-body healing perspective the circle can represent the polarities of resistance vs. receptivity; from Tai Chi, active vs. passive/receiving, retreating, gathering; from a Tibetan Buddhist perspective, the polarities between lower space and Great Space, and lower time vs. Great Time; from a classical music composition framework, the polarity between the one and five chords. Taoism and Tai Chi expand the possibilities for exploring polarities even further when they represent the yin/yang polarity as a curved line as opposed to a straight line, implying that smoothness and flow can also be doorways and yes sets for facilitating the transformation of consciousness (Erickson and Rossi, 1979, Gregory, 2012, Levitin, 2006, Man Ch'ing, 1985, Tulku, 1979).

When the sine and cosine functions are plotted on a graph they reveal patterns of waves that are out of phase with each other, as cosine starts at 1, and sine at 0. These wave functions that move between -1 and 1, depending on where in the rotation of the angle of the circle is, in situations when the radius of the circle is 1. Euler continued his exploration, looking for patterns. When he took the derivatives of sine and cosine he identified two infinite series having alternating positive and negative values in the terms. This was because every other term became zero depending on the position of sine or cosine, and every fourth term, the positive or negative changed because of the repeating wave going from 1 to -1. Euler followed his intuition by exploring *subsets* of the exponential function, specifically, e^{ix}. When he took the derivative of this function he noticed a pattern that resembled aspects of both sine and cosine functions. When he factored out the 'I' component, the equation appeared (Crease, 2008, TCL, 1995). The discovery of the equation validated the *value of derivatives*, which are expressions of rate of change and the fundamental nature of time (Gregory, 2017, Merrill-Wolff, 1973, Tulku, 1979) as tools/resources in the exploration process that mirrored stage 1, data collection, of Poincare's four stage creative process.

Questions for facilitating yes sets and unconscious exploration of rate of change issues include;

- Have you ever considered that the speed of the conversation would affect its rate of change in either a positive or negative direction?
- Have you ever considered how you may slow down or speed up thoughts?
- Have you ever visualized slowing down or speeding up thoughts?
- Can you imagine the part of you that can accelerate the unfolding of a conversation in your left hand, and imagine the part of you that can slow down a conversation in your right hand?

The *appreciation* and application of structure can be executed in a variety of ways which include: the conversational approach, story-telling about structures, multi-embedded metaphor, the polarity approach, and permutations around the theme of structure (Asher and Gross, 2006, Gregory, 2015, Lankton and Lankton, 1983, Rosen, 1982, Rossi, 1996, 2002). The foundation, or substructure for these processes is the professional having a deeply integrated *yes set* for structure, which can be understood as a cousin to the professional's having a yes set for clarity of thinking, feelings, opposites, the unconscious, or a variety of other resource networks or tools (Erickson and Rossi, 1979). This *yes set for structure* within a professional *implies* that structure, the set of all structures, and the accompanying subsets of structure are sources for comfort and activity dependent gene expression. An additional implication is that a connection to structure enhances capacity, which simultaneously reduces anxiety. Integrating set theory with a yes set for structure can support the exploration of different perspectives, types and depths of structure. Structures can be museums, doorways, valleys or caves. Or, they can be bridges, houses, planes, cars, utensils, tools, books, music or movies. These can be considered types of external structures, as contrasted with the internal structures of the human body which add the dimension of depth and include; bones, organs, cells, complex molecules like hemoglobin or adenyl cyclase, amino acids, dna base molecules, and the nucleus of the atom. From a completely different frame of reference there are geometric structures like points, lines, planes, triangles, spheres, polygons, etc., whose applicability to the transformation of consciousness are represented in Abbott's *Flatland*. *Flatland* described the consciousness of geometric structures of different dimensions that highlighted the power of frame of reference in both consciousness and the transformation of consciousness. *Flatland* foreshadowed the discovery of the Lorentz Transformation and Einstein's Special Theory of Relativity (Abbott, 1885, Gregory, 2015, 2017, Isaacson, 2006). The variables of Euler's equation point like vectors to deeper levels of structure.

Additional examples of the utilization of the appreciation of structure to transform consciousness include Erickson's use of the 'foot bone being connected to the ankle bone' (Rosen, 1982) and Tulku's truisms about the role of space in the body, described in the 'giant body' exercise, the role of space in the structure of experience, and the understanding of space as intervening distance (Tulku, 1979). A yes set for structure can be utilized to introduce novelty in the dynamics of couples through the creative exploration of the structure of conversations.

Examples for the utilization of structure for creatively focusing attention and facilitating novelty include;

- Have you ever visualized or drawn a picture, or a flow chart of how you wanted the conversation to go?
- Have you ever visualized or drawn possible pathways for you to either explore or avoid your experience?
- If you were to imagine building a house for yourself, or someone you cared deeply about, what psychological resources would you put in the foundation? What resources would you use for the floors or walls?
- Do you have any favorite bridges?
- Have you ever made a list evaluating the effectiveness of plans you have made?
- Are there any specific structures of the body you focus on when you need comfort?
- When you walk or run, how does structure support you?
- Do any specific levels of structure/ muscles, bones, cells, organs resonate with you more than others?

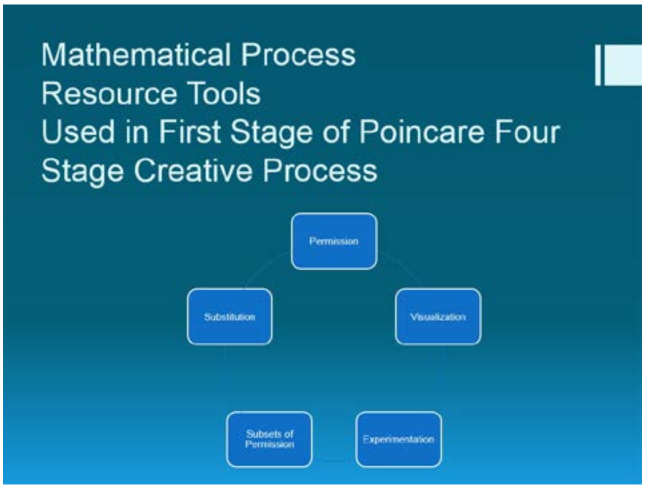
Examples of utilizing visualization, substitution, and permission include;

- Have you visualized the problem, or possible solutions?
- Have you drawn a picture of the problem, the sources of the problem, resources for solving the problem, or strategies for the solution?
- Have you drawn a picture expressing how reactivity, defensiveness, deflection, and avoidance affect the direction of efforts toward a solution?
- Have you considered or experimented with other ways of representing the problem?

Both sets of examples above can be utilized to enhance the professional's trust in focusing attention creatively, setting up opposites, introducing novelty, and facilitating unconscious healing processes.

Euler's *appreciation* and utilization of permission as a resource and tool to nurture, support and sustain the exploration of his intuition about the significance and connection between the different functions was highly evolved. This demonstrated a yes set for *permission* at a deeply integrated level. It may correspond to, and reflect Erickson's utilization of permissive, indirect suggestions (Erickson and Rossi, 1979). This appreciation of permission carried with it a number of significant, applicable *implication*s. On a foundational level, there is the implication that the appreciation of permission is but a subset of the larger set of the *consciousness of appreciation*. Following this, the appreciation of permission as a tool or resource implies that there are subsets of permission and degrees of permission. The types of permission are represented in Figure 3 below.

When Abbott's metaphors about dimensions are considered and factored, permission itself can be explored from the frame of reference of how much permission, which opens up possibilities that include; is it whole units of permission, fractional or exponential units of permission. This further opens up the possibilities of whether permission is utilized independently, or in combination with other tools, like validation, curiosity, patience, enjoyment, etc.



Mathematical Process
Resource Tools
Used in First Stage of Poincare Four
Stage Creative Process

Figure 3. Subsets of Permission © 2018 Bruce Gregory, Ph.D.

Each unit of permission can support the patient opening, which signifies receiving and safety, and implies capacity, needs for time, and worthiness. These are all dynamic metaphors for addressing narcissistic and developmental wounds, and can facilitate unconscious processes, neurogenesis, and the transformation of consciousness. More importantly, permission implicitly reduces pressure about time, reducing anxiety. Yes sets for exponentiation and vectors within the professional can further expand possibilities for creatively focusing attention, as exponentiation and vectors are subsets of the range of possibilities available to the professional for focusing attention. Just the distinction between two doses of permission and permission times permission times permission, which is permission cubed, can facilitate novelty within the patient as it often is a possibility that the patient has not considered previously.

An additional Implication is that the variables of the Euler equation (exponential, sine, and cosine functions, pi, imaginary number) have value, are sources of comfort, and contain their own series of applicable implications that can be translated into expanded trust within the professional.

Summary

The Euler equation has been discussed in terms of its implications, tools, and applications in the transformation of consciousness. The variables of the equation, the exponential function, the sine and cosine function, and the imaginary number are recognized as subsets for comfort when the professional performing the treatment has an established, integrated yes set for their value. These variables can be utilized to introduce novelty in a variety of ways, one of which is the incorporation of the theme of structure. The equation reflects a deeper connection to structure, which complements the structures of quantum entanglement, and the geometric structures of group theory. The value and application of the appreciation of functions and derivatives is explored in terms of set theory and facilitation of novelty. The implications of the equation are discussed in terms of their overlaps with Tai Chi, Tibetan Buddhist Meditation theory and practice, and Erickson's work with resistance. The ideas and process resources utilized to develop the equation by Euler are integrated to support the expansion of the professional's trust in facilitating stage 1 of Poincare's four stage creative process, creatively focusing attention by adding a variety of new vectors/frame of references, and reducing anxiety and pressure within the professional and the patient.

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THE COMT HEALING RESPONSE PLACEBO RESOLVES THE MIND-BODY PROBLEM: AN INTEGRATED QUANTUM FIELD THEORY (QFT$_i$) OF PSYCHOSOCIAL GENOMICS

ERNEST LAWRENCE ROSSI & KATHRYN ROSSI

Abstract

We explore the profound implications of recent research on the Quantum Mind/Body COMT Healing Response Placebo. Catechol-O-Methyl-Transferase (COMT) is an enzyme that metabolizes major human brain neurotransmitters for mind-brain-body consciousness, cognition and communication. These neurotransmitters are catecholamines such as dopamine and epinephrine, which have pleiotropic epigenetic effects on a broad set of stress-related psychosomatic problems and medical treatments. The quantum dynamics of the COMT Healing Response Placebo are not psychological tricks or mere suggestions for hopeful people. We review scientific evidence that quantum mechanical-molecular mechanisms (QM-MM) are an appropriate model the COMT psychophysiological and pleiotropic dynamics of an Integrated Quantum Field Theory (QFTi) of psychosocial genomics, health and well-being. We evaluate scientific evidence supporting the hypothesis that the COMT Healing Response Placebo could resolve the so-called cartesian mind-body gap problem or paradox in the history of medicine, psychology and philosophy.

Introduction: What is the COMT Healing Response Placebo?

The COMT Healing Response Placebo integrates the mind-brain-body COMT dynamics of normal behavior, consciousness and therapeutic cognition in medicine, psychology and psychosocial genomics. We propose that the COMT Healing Response Placebo resolves the so-called mind-body problem in the history of medicine, psychology and philosophy. The U.S Nation Library of Medicine (NIH) describes the COMT gene, which we abbreviate here as follows.

The Normal Functions of the COMT Gene and Enzyme Dynamics

The *COMT* gene provides instructions for making an enzyme called catechol-O-methyltransferase. Two versions of this enzyme are made from the gene. The longer form, called membrane-bound catechol-O-methyltransferase (MB-COMT), is chiefly produced by nerve cells in the brain. Other tissues, including the liver, kidneys, and blood, produce a shorter form of the enzyme called soluble catechol-O-methyltransferase (S-COMT). This form of the enzyme helps control the levels of certain hormones. In the brain, catechol-O-methyltransferase helps break down certain chemical messengers called neurotransmitters.

These chemicals conduct signals from one nerve cell to another. *Catechol-O-methyltransferase is particularly important in an area at the front of the brain called the prefrontal cortex, which organizes and coordinates information from other parts of the brain.* This region is involved with personality, planning, inhibition of behaviors, abstract thinking, emotion, and working (short-term) memory. To function efficiently, the prefrontal cortex requires signaling by neurotransmitters such as dopamine and norepinephrine. Catechol-O-methyltransferase helps maintain appropriate levels of these neurotransmitters in this part of the brain. (COMT gene - Genetics Home Reference – NIH. Italics added here.).

This introductory statement is certainly consistent with our initial hypothesis: The COMT Healing Response Placebo integrates the mind-brain-body dynamics of health and illness. The U.S Nation Library of Medicine (NIH) also outlines many of the malfunctions of the COMT Gene/Enzyme system throughout the mind-brain-body that confirm our hypothesis in this way.

Mental Health Conditions Related to COMT Gene/Enzyme Malfunctions

The characteristic signs and symptoms of 22q11.2 deletion syndrome result from a deletion of a small piece of chromosome 22. The chromosomal region that is typically deleted contains 30 to 40 genes, including the *COMT* gene. As a result of the deletion, people with this disorder have only one copy of the *COMT* gene in each cell instead of the usual two copies.

A loss of one copy of the *COMT* gene in each cell leads to abnormal regulation of catechol-O-methyltransferase levels in the brain. Researchers believe that changes involving this enzyme in the prefrontal cortex may help explain the increased risk of behavioral problems and mental illness associated with 22q11.2 deletion syndrome. Little is known, however, about the relationship between catechol-O-methyltransferase activity and the specific mental and emotional problems characteristic of this condition. People with 22q11.2 deletion syndrome are much more likely than people without the condition to develop schizophrenia, depression, anxiety, and bipolar disorder [as well as] Alcohol use disorder, Fibromyalgia and Opioid addiction.

Variations in the COMT gene also may be associated with mental illness in people without 22q11.2 deletion syndrome. Researchers have looked extensively at the potential connection between changes in the *COMT* gene and the risk of developing schizophrenia. Most studies have focused on the effects of a particular common variation (polymorphism) in catechol-O-methyltransferase. This variation alters as ingle protein building block (amino acid) in the enzyme, replacing the amino acid valine with the amino acid methionine. In the longer form of the enzyme, this variation occurs at position 158 (written as Val158Met). In the shorter form of the enzyme, it occurs at position 108 (written as Val108Met). Researchers often shorten this notation to Val108/158Met. The change affects the stability and activity of catechol-O-methyltransferase, which alters the enzyme's ability to break down neurotransmitters in the prefrontal cortex.

Studies of the Val108/158Met polymorphism in people with schizophrenia have had mixed results. While most studies report no evidence of heightened risk with either methionine or valine at this position, some studies have found a slightly increased risk of schizophrenia in people with valine at position 108/158. Having valine at this position is associated with differences in thought processes that are common in people with schizophrenia, including problems with working memory, inhibition of behavior and attention. Other changes in the COMT gene may also contribute to these differences. Variations in the COMT gene are among many factors under study to help explain the causes of schizophrenia. A large number of genetic and life style factors, most of which remain unknown, likely determine the risk of developing this condition.

The Val108/158Met polymorphism has also been associated with other disorders that affect thought (cognition) and emotion. For example, researchers have studied this variation as a possible risk factor for bipolar disorder, panic disorder, anxiety, obsessive-compulsive disorder (OCD), eating disorders, and attention deficit hyperactivity disorder (ADHD). Studies suggest that these conditions may be related to inefficient processing of information in the prefrontal cortex. As with schizophrenia, however, many factors play a part in determining the risk of these complex disorders. (COMT gene - Genetics Home Reference – NIH).

Figure 1 outlines the 4-Stage Creative Quantum Mind-Body Field Therapy (QFT_i), which we propose as a model of the quantum communication cycle that underpins the conscious/unconscious transition experiences that bridge the cartesian mind/body gap (Rossi & Rossi, 2016).

Quantum Mechanical-Molecular Mechanical (QM/MM) of the COMT Gene/Enzyme

In an extensive paper Yang et al. (2018) provide exquisitely detailed theory, research and practical details of the so-called quantum microscope that enabled us (Rossi & Rossi, 2016) to conceptualize COMT Gene/Enzyme dynamics at the Planck scale (10^{-33}) that are too tiny to see with an ordinary light microscope. Yang et al. (2018) begin their paper as follows.

> Enzymes have evolved to facilitate challenging reactions at ambient conditions with specificity seldom matched by other catalysts. Computational modeling provides valuable insight into catalytic mechanism, and the large size of enzymes mandates multi-scale, quantum mechanical-molecular mechanical (QM/MM) simulations. Although QM/MM plays an essential role in balancing simulation cost to enable sampling with full QM treatment needed to understand electronic structure in enzyme active sites, the relative importance of these two strategies for understanding enzyme mechanism is not well known. We explore challenges in QM/MM for studying the reactivity and stability of three diverse enzymes: i) Mg2+-dependent catechol O-methyltransferase (COMT), ii) radical enzyme choline trimethylamine lyase (CutC), and iii) DNA methyltransferase (DNMT1), which has structural Zn2+ binding sites. In COMT, strong

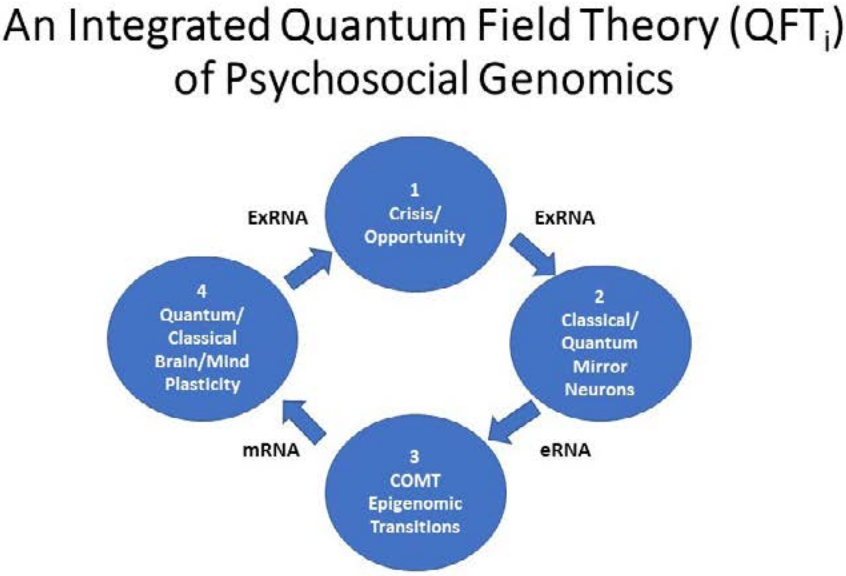

Figure 1: The 4-Stages of an Integrated Quantum Field Theory (QFTi) of Psychosocial Genomics. An overview of the quantum communication cycle that underpins conscious/unconscious transition experiences in 4-stages that bridge the cartesian mind/body gap. 1. The crisis/opportunity that people typically experience as a stress. 2. The Classical to Quantum Transitions within mirror neurons. 3. Epigenomic Transitions of the COMT Healing Response Placebo, which integrates the mind-brain-body. 4. The Quantum to Classical Transitions of Brain/Mind Plasticity that integrates the new insights of therapeutic consciousness and cognition that converts a Crisis into an Opportunity. (Hill & Rossi, 2017)

> non-covalent interactions lead to long range coupling of electronic structure properties across the active site, but the more isolated nature of the metallocofactor in DNMT1 leads to faster convergence of some properties. We quantify these effects in COMT by computing covariance matrices of by-residue electronic structure properties during dynamics and along the reaction coordinate. In CutC, we observe spontaneous bond cleavage following initiation events, highlighting the importance of sampling and dynamics. We use electronic structure analysis to quantify the relative importance of CHO and OHO non-covalent interactions in imparting reactivity. These three diverse cases enable us to provide some general recommendations regarding QM/MM simulation of enzymes. (Yang et al. 2018, p. 30).

Figure 2 is an updated image of our Integrated Quantum Field Theory (QFT$_i$) of consciousness and therapeutic cognition as a pyramid that now includes the Yang et al. equation QM/MM simulation of the COMT gene/enzyme energy dynamics in stage 4 of the creative cycle.

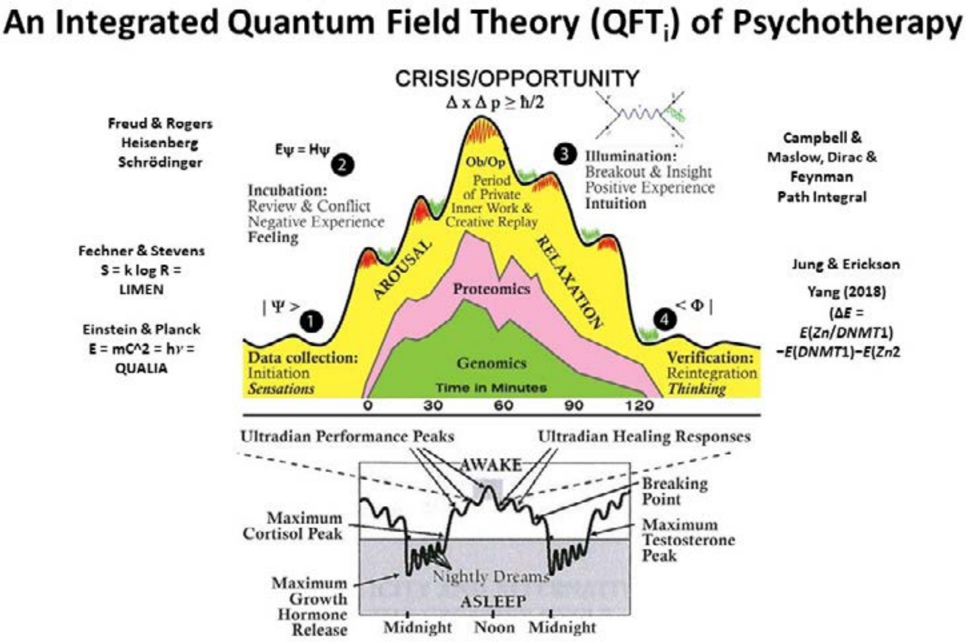

Figure 2a: An update of our Integrated Quantum Field Theory (QFT$_i$) of consciousness and therapeutic cognition as a pyramid illustrating some of the math, physics, chemistry, biology and psychology of the 90-120-minute basic rest-activity cycle (BRAC) and the 4-stage creative cycle of problem solving in everyday life along with some of the key scientists who conceptualized it with their math equations over the last century (Rossi & Rossi, 2016).

A fundamental quantum insight into our Integrated Quantum Field Theory (QFTi) of consciousness and therapeutic cognition of figure 2a is the Schrödinger cat animation presented in figure 2b.

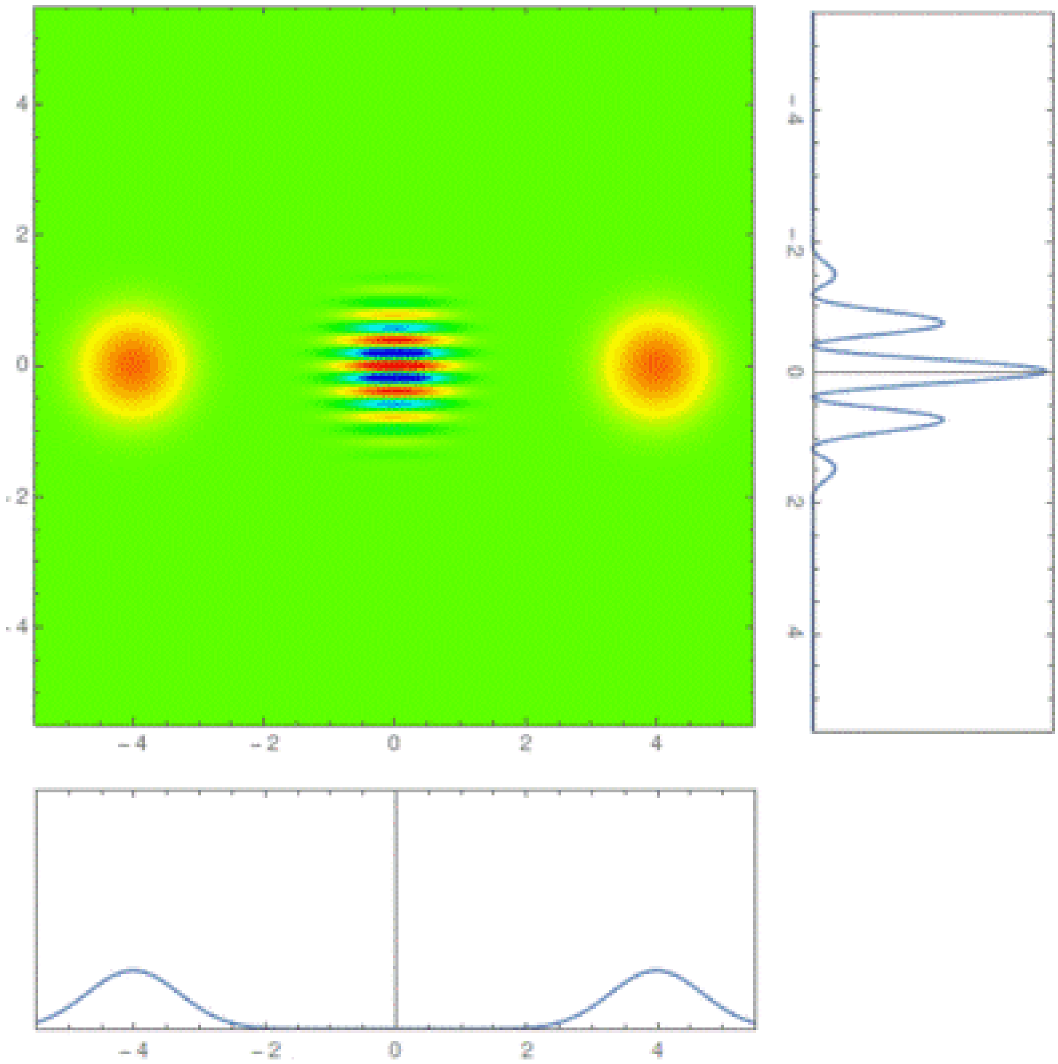

Figure 2b: An animation of the quantum wave function of a "Schrödinger cat state" in the Quantum Harmonic Oscillator. The probability distribution is drawn along the ordinate, while the phase is encoded by color. The two coherent contributions interfere in the center which is characteristic for a cat-state. (This animation was created with Matplotlib by Geek3 - Own work, which is available on Wikipedia Creative Commons https://en.wikipedia.org/wiki/Cat_state). Notice the similarity in the fluctuating triangle of the 90-120-Minute Basic Rest-Activity Cycle (BRAC) and the superimposed 4-Stage creative cycle of figure 2a and this proposed animation of our Quantum Field Theory (QFT$_i$). We conceptualize the Quantum Engine Fluctuations that powers the acceleration of our expanding cosmos, as well as the evolution of life, consciousness and therapeutic cognition in psychosocial genomics (QM-MM). (Bucke, 1901, 2010; Cockell, 2018; Rossi & Rossi, 2016]

In quantum computing, the "cat state," refers to Schrödinger's cat paradox, which is a quantum superposition of two macroscopically distinct states in figure 2b. The individual states being superposed could be classical or quantum, but their macroscopic (the ordinary perspective of everyday life) is an important criterion for the face validity and value of any scientific theory. Physicists may view the cat state as composed of two diametrically opposed conditions such that a cat could be alive and dead at the same time. Schrödinger's cat paradox, however, can be resolved by our Integrative Quantum Field Theory (QFT$_i$) of Life, Consciousness and Cognition, which proposes that the cat is alive when the quantum engine that energizes the molecules of life (DNA, ATP etc.) is functioning in an optimal manner by bridging cartesian mind/body gap. The cat is dead when the quantum/classical transitions fail because of the accumulation of gene malfunctions. Figure 3 illustrates the quantum mechanical core of the COMT gene/enzyme in green that modulates the structure and function of the molecules of life in more detail.

Yang et al. (2018) present an equation of the binding energy of the Quantum- Mechanical core of Molecular Mechanics (QM/MM) of DNA, which documents how quantum dynamics can energize and modulate the movement of many foundational molecules of life such as DNMT1 as follows.

The COMT Healing Placebo QM-MM of Mind-BodyTherapy

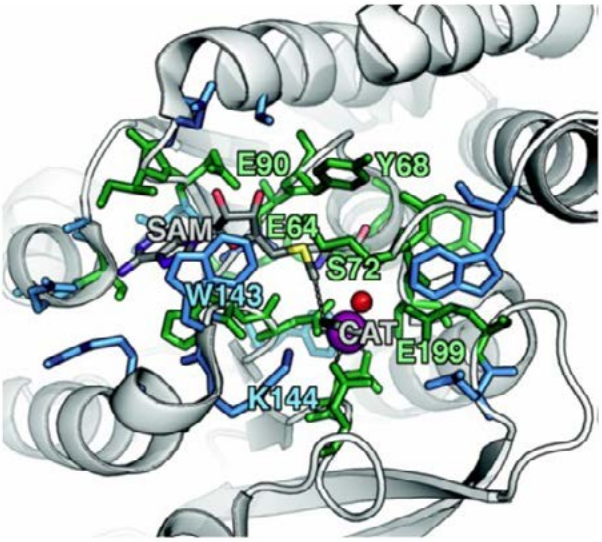

Figure 3: The COMT Healing Placebo structure with SAM and catecholate (CAT) substrates shown in gray along with Mg2+ as a magenta sphere and a water coordinating the Mg2+ as a red sphere. The 28 protein residues (518 atoms with H atoms) included in a large quantum mechanical (QM) region are shown as sticks. A subset that was identified by systematic analysis of QM regions is shown in green, whereas the remainder is shown in blue. Specific residues of interest are labeled by their single letter residue code and number (Adapted from Yang et al. 2018, p. 8). We now propose that this image is an example of the quantum engine whose fluctuating dynamics energizes the accelerating expansion of the cosmos as well life, consciousness and cognition via (QM-MM) evolution.

> We evaluate key electronic structure and energetic properties with seven QM regions to determine QM/MM QM region dependence for DNMT1. As a measure of the electronic structure, we evaluate the Mulliken partial charge of Zn2+ in the holoenzyme and focus on its variation with QM region size rather than absolute charges that will be more sensitive to the partial charge scheme. Next, we evaluate a rigid binding energy of Zn2+, which provides an upper bound estimate of the binding strength of Zn2+ to the active site residues and thus how easily it can be displaced by other metals. We evaluate the Zn2+ rigid binding energy, ΔE, as:
>
> $\Delta E = E(Zn/DNMT1) - E(DNMT1) - E(Zn2+)$
>
> where each energy corresponds to the QM/MM single point energies of DNMT1 with Zn bound, DNMT1 without Zn2+, and the energy of isolated Zn2+, respectively. (Yang et al. 2018, p. 30)

DNMT1 is a major gene/enzyme responsible for maintaining methylation which is important for epigenetic gene regulation; faulty methylation is found in human tumors and developmental abnormalities. Dysfunctions of this gene/enzyme system are associated with cerebellar ataxia, deafness, and narcolepsy and neuropathy of many psychiatric problems. Yang et al. (2018) now summarize the quantum dynamics of the COMT system, which is consistent with our hypothesis that quantum mechanical-molecular mechanisms (QM-MM) are an appropriate model for the COMT psychophysiological and pleiotropic dynamics of health and well-being.

> In COMT, a system with a catalytic metal ion and a bulky SAM cofactor, we noted large differences in predictions depending on the means by which QM regions were constructed, ranging from minimal regions, to radially enlarged regions, and finally systematic construction methods, due to the numerous non-covalent substrate-protein interactions in the active site. To explain why techniques to reduce the sizes of QM regions for 0 K reaction coordinates were less successful when applied to QM/MM free energy simulations, we analyzed covariance matrices of the by-residue-summed partial charges. We observed long-range coupling between active site residue charges and distant residues and found that the pattern of couplings varied dynamically along the reaction coordinate.
>
> *Here, we noted the important role of sampling and averaging over configurations through a robust MM force field.* We also observed rapid convergence in small QM regions of some properties (i.e., Mulliken charge of Zn) dictated by nearest neighbor interactions, whereas others that involve significant perturbations to the electrostatic environment (i.e., rigid Zn binding

energy) had slower convergence in line with observations on COMT. . .*Thus, when studying new proteins, researchers will always benefit from QM region sensitivity analysis of properties being studied, and systematic tools should make this analysis straightforward*. Beyond these considerations, outstanding challenges remain for computational enzyme modeling, including: accelerating sampling, improving QM methods along with MM embedding, and improved sampling considerations in systematic QM/MM partitioning, which are underway in our MIT Research Group (Yang et al., 2018; Italics added here).

The Quantum Psychosocial Genomics (QFTi) of the COMT Healing Response Placebo

Tsao et al. (2011) have illustrated quantum models of epigenomic transitions of the COMT healing placebo that integrates mind-brain-body dynamics COMT Healing Response Placebo documented here in figure 4.

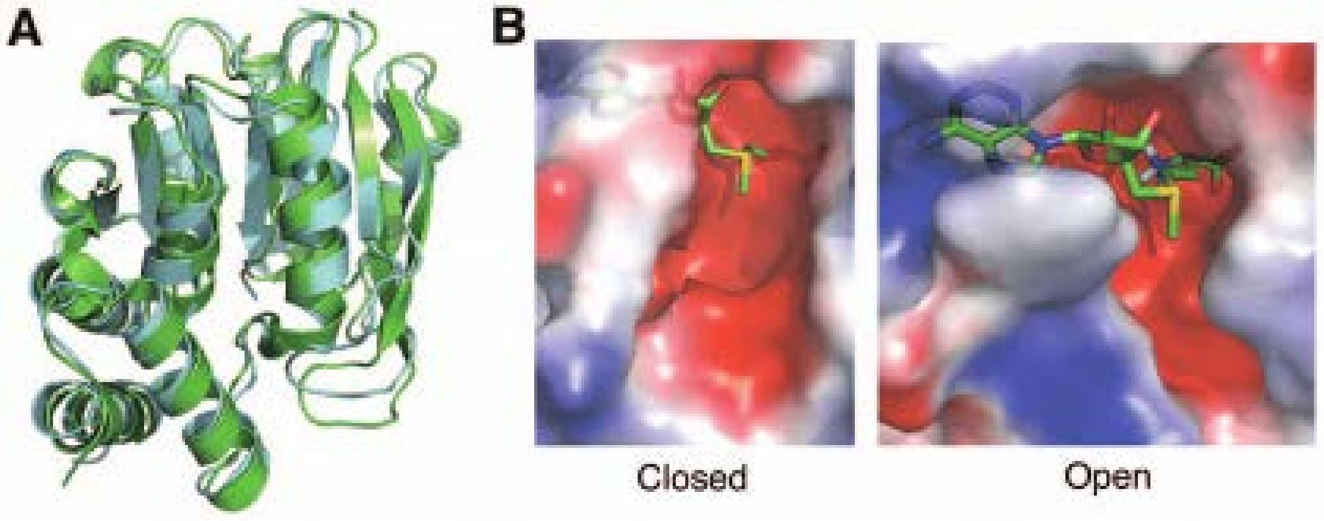

Figure 4a & 4b: Quantum Structural Mechanism of S-Adenosyl Methionine Binding to Catechol O-Methyltransferase (Tsao et al., 2011), which we propose is a model of the quantum psychosocial genomic (QFTi) transitions of the COMT Healing Response Placebo that integrates mind-brain-body dynamics of consciousness and therapeutic cognition).

Tsao et al. (2011) point out the focal significance of the COMT Healing Response Placebo for medicine, psychology and psychotherapy.

Catechol O-methyltransferase (COMT) is a metalloenzyme that metabolizes biologically active catechol-containing structures by methylation of a single hydroxyl group. A number of neurotransmitters contain a catecholamine moiety and are deactivated by COMT. Activity of COMT is thus correlated with many critical biological functions including cognition, stress response and pain sensitivity (Tsao et al., 2011).

Although the overall structure of COMT remains identical in the absence of ligands, the solvent accessibility of the active site changes (Figure 4a & 4b). In the crystal structure, COMT forms two pockets that accommodate the adenosine and methionine sidechains of SAM. The adenosine pocket partially collapses, and the methionine-binding motif completely closes in the absence of SAM. *Comparison of the two active sites shows two main conformations of COMT: an open and a closed state.* Within the closed state of COMT, SAM cannot bind inside the active site and therefore methylation cannot occur. To accommodate SAM, the COMT must initially open so that SAM can access the active site. Since only the adenosine-binding motif is partially open in the closed COMT structure, this region of the SAM cofactor may be responsible for initial binding and perhaps induces the open state. Because the closed COMT state makes the active site inaccessible, all docking simulations are performed with the open state of COMT under an assumption of induced fit. Within the open state, we refer to the absence of ligands as apo-COMT and the presence of all ligands as holo-COMT. (Tsao et al., 2011. Italics added here).

We now propose that precisely this quantum shift between the opened and closed state of COMT is scientific evidence supporting our hypothesis that the COMT Healing Response Placebo could resolve the so-called cartesian mind-body gap (problem or paradox) in the history of medicine, psychology and philosophy. The practical significance of our hypothesis profound in current experimental design for research on placebos, which are indispensable controls in randomized clinical trials (RCTs) and "the placebome" conceptualized by Hall, Loscalzo and Kaptchuk (2018).

> Placebos are indispensable controls in randomized clinical trials (RCTs), and placebo responses significantly contribute to routine clinical outcomes. Recent neurophysiological studies reveal neurotransmitter pathways that mediate placebo effects. Evidence that genetic variations in these pathways can modify placebo effects raises the possibility of using genetic screening to identify placebo responders and thereby increase RCT efficacy and improve therapeutic care. Furthermore, the possibility of interaction between placebo and drug molecular pathways warrants consideration in RCT design. The study of genomic effects on placebo response, "the placebome", is in its infancy. Here, we review evidence from placebo studies and RCTs to identify putative genes in the placebome, examine evidence for placebo-drug interactions, and discuss implications for RCTs and clinical care. (Hall et al. 2018)

Crum et al. (2018) confirm such research on the psychosocial genomics of altering the debilitating stress mindset of the human condition in this way.

> There is evidence that altering stress mindset—the belief that stress is enhancing vs. debilitating—can change cognitive, affective and physiological responses to stress. However individual differences in responsiveness to stress mindset manipulations have not been explored. Given the previously established role of catecholamines in both placebo effects and stress, we hypothesized that genetic variation in catechol-O-methyltransferase (COMT), an enzyme that metabolizes catecholamines, would moderate responses to an intervention intended to alter participants' mindsets about stress. . . The associations of the COMT rs4680 polymorphism with the effect of stress mindset video manipulations on cognitive and affective responses were examined. Genetic variation at rs4680 modified the effects of stress mindset on affective and cognitive responses to stress. Individuals homozygous for rs4680 low-activity allele (met/met) were responsive to the stress-is-enhancing mindset manipulation as indicated by greater increases in positive affect, improved cognitive functioning, and happiness bias in response to stress. Conversely, individuals homozygous for the high-activity allele (val/val) were not as responsive to the stress mindset manipulation. These results suggest that responses to stress mindset intervention may vary with COMT genotype. These findings contribute to the understanding of gene by environment interactions for mindset interventions and stress reactivity and therefore warrant further investigations. . . Cognitive, emotional, and physiological responses to stress are not solely determined by the amount of stress one experiences but also by one's beliefs about stress. *Research on stress mindset the belief that stress has enhancing versus debilitating properties has demonstrated that higher indices of health, performance, and well-being can ensue from holding a stress-is enhancing relative to a stress-is-debilitating mindset and placebo response have implicated genetic variation at COMT rs4680 as a broader potential neurogenetic link between social and interpersonal environmental cues and cognitive, emotional, and physiological responses.* (Crum et al., 2018. Italics added here.).

Such COMT quantum research paradigms now are required to correct the cartesian misconceptions of mind-body dualism in order to resolve our problems of accelerating stress, uncertainty and conflict in the human condition.

Summary

We review scientific evidence supporting the hypothesis that the COMT Healing Response Placebo could resolve the so-called cartesian mind-body gap problem or paradox in the history of philosophy.

The Quantum Molecular - Molecular Mechanisms (QM-MM) of the COMT Healing Response Placebo are a new foundational reality of the Integrated Quantum Field Theory (QFTi) of medicine, psychology and psychosocial genomics.

COMT (Catechol-O-Methyl-Transferase) is an enzyme that metabolizes major human brain neurotransmitters for mind-brain-body consciousness, cognition and therapeutic communication.

The mind/body dynamics of the COMT Healing Response Placebo is powered by the quantum engine fluctuations of cosmos, consciousness and cognition of medicine and psychosocial genomics.

SAMe is a component of the COMT Healing Response Placebo that available to the general public in pharmacies (over the counter) for facilitating positive, healthy mood regulation and well-being.

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SEQUENCING OF MAP KINASE PATHWAY RECEPTOR CXCR4

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Abstract

Mitogen-activated protein kinases (MAPK) proteins are serine/ threonine specific kinases which are activated by a wide range of stimuli including proinflammatory cytokines, growth factors, mitogens, osmotic stress, heat shock etc. These proteins function in signaling cascades which are activated upon ligand binding to a cell surface receptor activating several MAP/ER kinases, which in turn phosphorylate their respective substrates; these events thereby regulate various cellular activities, such as gene expression, mitosis, differentiation, proliferation, and cell survival/apoptosis. Then, upon the extracellular mitogen binding to the ligand, Ras a GTPase exchanges GDP for GTP, in turn initializes a cascade activating MAP3K (Raf), which in turn activates MAP2K that activates MAPK. This MAPK can then activate a number of transcription factors which control key cellular processes Chemokine receptors are essential for triggering chemotaxis to immune cells and a number of them can also mediate death when engaged by nonchemokine ligands; when the chemokine receptor CXCR4 (gene involved in MAP KINASE pathway) is engaged by stromal cell-derived factor (SDF1), it triggers cells to chemotax and in some cells, it causes cell death. In this work, the CXCR4 receptor was modeled using homology modeling. Further the mRNA sequence the receptor was folded using sFold and silenced with siRNA technique. The sequence‘s statistical analysis was done using PRINSEQ and annotated usingRAST.

Keywords: MAP KINASE pathway, CXCR4 receptor, homology modeling, gene statistical analysis, gene annotation, psychosocial genomics

INTRODUCTION

The MAPK/ERK pathway also known as the Ras-Raf-MEK-ERK pathway (Fig. 1) is a chain of proteins in the cell that communicates a signal from a receptor on the surface of the cell to the DNA in the nucleus of the cell. This pathway includes many proteins, like MAPK (mitogen- activated protein kinases), originally called ERK, extracellular signal-regulated kinases which communicate by adding phosphate groups to a neighboring protein, that acts as an on or off switch and when one of the proteins in the pathway is mutated, it can become stuck in the “on” or “off” position, which is a necessary step in the development of many cancers [1-4]. Components of the MAPK/ERK pathway were discovered in cancer cells. Cervical cancer is one of the most preventable cancers. It is a cancer found in the cells of the cervix. The cervix is the lower part or neck‘ of the uterus where it joins the inner end of the vagina. The protein encoded by this gene (Fig. 2) is a member of the MAP kinase family and MAP kinases act as an integration point for multiple biochemical signals, and are involved in a wide variety of cellular processes such as proliferation, differentiation, transcription regulation and development [5, 6]. It targets specific transcription factors, and thus mediates immediate-early gene expression in response to various cell stimuli [7-10]. Drugs those reverse the ―on― or off switch are currently being investigated as Cervical cancer treatments. Psychological barriers are significant impediments to preventive healthcare behaviors and treatments seeking behaviors. [11].

METHODOLOGY

Step 1: *Homology Modeling using MODELLER:*

Modeller is used for homology or comparative modeling of protein three dimensional structures. Users provide an alignment of a sequence to be modeled with known related structures and modeller automatically calculates the model containing all non-hydrogen atoms [12].

Step 2: Protein Structural validation using RAMACHANDRAN PLOT

Ramachandran diagram or plot was originally developed by G. N. Ramachandran, C. Ramakrishnan, and V. Sasisekharan in 1963. Ramachandran Plot is a way to visualize energetically allowed regions for backbone dihedral angles ψ against φ of amino acid residues in protein structure [13].

Step 3: RNA Folding using SFOLD

Sfold is developed based on algorithms by Ding and Lawrence for RNA folds and prediction of target accessibility including rational design of RNA-targeting nucleic acids. RNA folding is a molecular process by which a linear ribonucleic acid (RNA) molecule attains secondary structure through intra-molecular interactions; the folded areas of RNA molecules are often the locations of specific interactions with proteins in forming RNA- protein (ribonucleoprotein) multiplexes [14].

Step 4*: *Nucleotide sequence statistics using PRINSEQ

PRINSEQ is a tool that generates summary statistics of sequence and quality data and that is used to filter, reformat and trim next-generation sequence data and it is available through a user-friendly web interface (Fig. 3) [15].

Step 5*: *Nucleotide sequence annotation using RAST

RAST (Rapid Annotation using Subsystem Technology) is a fully-automated service for annotating bacterial and archaeal genomes and provides high quality genome annotations for the genomes across the whole phylogenetic tree (Fig. 4) [16, 17, 18].

RESULTS

Homology Modeling and model verification:

Modeller generated 5 models. These models were verified using Ramachandran Plot. The 1st model had 291 amino acid residues (89.0%) in most favored regions, 30 residues (9.2%) in additional allowed regions, 3 residues (0.9%) in generously allowed regions and 3 residues (0.9%) in disallowed regions.

The 2nd model had 287 amino acid residues (87.80%) in most favored regions, 34 residues (10.4%) in additional allowed regions, 5 residues (1.5%) in generously allowed regions and 1 residue (0.3%) in disallowed regions.

The 3rd model had 288 amino acid residues (88.1%) in most favored regions, 32 residues (9.8%) in additional allowed regions, 7 residues (2.1%) in generously allowed regions and no residue in disallowed regions.

The 4th model had 295 amino acid residues (87.8%) in most favored regions, 26 residues (7.78%) in additional allowed regions, 10 residues (3.0%) in generously allowed regions and 5 residues (1.5%) in disallowed regions.

The 5th model had 289 amino acid residues (88.4%) in most favored regions, 30 residues (9.2%) in additional allowed regions, 6 residues (1.8%) in generously allowed regions and 2 residues (0.6%) in disallowed regions.

It is seen that model 1 and 2 has 6 residues in the generously allowed and disallowed region in combination but model 1 is seen to have highest number of residues in the favored region, i.e., 291 amino acid residues and hence it is selected as the best model (Fig. 5).

SFOLD Analysis

From a statistical mechanics perspective, an RNA molecule can have a population of structures distributed according to a Boltzmann distribution, giving the probability of a secondary structure I at equilibrium as (1/U) exp [-E (I)/RT], where E (I) is the free energy of the structure, R is the gas constant, T is the absolute temperature, and U is the partition function for all admissible secondary structures of the RNA sequence. A focus of Sfold is on applications of prediction of target accessibility, and rational design of RNA-targeting nucleic acids. SFOLD generated Minimum Free Energy (MFE) Structure at ΔG= -56.30 (stable structure) among the 10 generated structures of energy between -56.20 and 33.90 (Fig. 6). Its Essemble Centriod (EC) structure had energy of -28.00.

The Sfold siRNA design method works by integrating target accessibility evaluation, thermodynamic properties and sequence features for siRNA duplexes and Sfold computes a total score of predicted siRNA potency where the total score is the sum of target accessibility score, duplex sequence feature score and duplex thermodynamics score. The starting (ending) position of the target sequence corresponds to position 19 (1) of the antisense siRNA (i.e., dinucleotide leader and nucleotide sequence (nt) 22 and nt 23 in Tuschl patterns are not considered by us to be part of the target sequence); sense siRNA=target sequence +3 prime dTdT overhang; dTdT for both sense and antisense siRNAs can be replaced by UU; GC %= GC count in siRNA (excluding overhangs)/19 x100%; total siRNA duplex score is the sum of target accessibility score, duplex feature score and duplex thermodynamics score, with a maximum of 20 points; the accessibility score is based on antisense siRNA binding energy and has a range of [0, 8] the duplex feature score is computed with the algorithm with contribution of 1 point for DSSE > 0, and 1 point for AIS > -8.6 kcal/mol. The RNA sequence of the CXCR4 receptor gene was spliced. This technique is finding application in cancer therapeutics and research (Table 1).

Nucleotide sequence annotation and analysis

As per PRINSEQ results the mean GC content is 47%, minimum DUST score of 2, and maximum entropy at 83 J/K (Fig. 7).

As per RAST results we identify the locations of genes and all of the coding regions in the CXCR4 genome and determining its function including the conserved domains (Fig. 8).

DISCUSSION

Effective clinical translation of genomic information in cancer research from low- penetrance genes into meaningful health improvements remains elusive since research to date indicates that genomic information from single nucleotide polymorphisms (SNPs) could have a limited impact on long-term behavior change [19]. In similar manner, the evidence for other types of health behavior alters following provision of genomic risk information is equivocal. Large scale genetic studies such as those conducted by The Coriell Personalized Medicine Collaborative (CPMC) and the NIH suggest that although participants understood the genomic information and did not report negative emotional responses, minimal behavior change was noticed [19]. Behavioral research has enhanced the translation of genetic discoveries into clinical practice. Currently, the —vision—for behavioral research in genomics includes use of genomic information to facilitate health behavior change efforts but till date, more than 95% of funded cancer genomic research has focused on the early stages of genomic discovery [19]. The potential for genomic advances to influence population health will not be realized until and unless we engage in translational research on implementation and outcomes of behavioral research in genomic testing. Recent studies have examined multiple health behavior change consequences within the context of pre- and post-test cancer genomics education and testing [19].

Psychosocial Genomics Research Program in Cancer or Oncology (PSGPO) aims to integrate psychological, bioinformatics and medical knowledge at the ground level of neuro- informatic-scientific findings, genome-informatics research and mind-gene-body medicine. Research in the psychosocial genomics of cancer is achieving a quiet but significant breakthrough in understanding the fundamentals of the etiology and proliferation of a variety of women ailments including cervical cancer [20]. A counseling process which takes into consideration an individual's demographic, psychological, and cultural profile is necessary to facilitate informed decision making and maximize patient satisfaction with potentially irreversible conclusions [21]. The findings also elevate an issue for health care policy makers. As genetic testing becomes more and more incorporated into clinical practice, it will be even more important to understand the characteristics of those who seek and those who do not seek cancer genetic counseling and testing and the impact of testing on subsequent preventive health behaviors like cancer screening [21]. By understanding more about those who do and do not wish to acquire genetic knowledge, researchers can ensure that programs of mandatory testing that minimize psychological distress. Better the knowledge of cultural biases and the role of psychological factors such as resistance will enable researchers to develop educational materials and programs that speak to patients literally and figuratively in the languages they understand. As a consequence of this enhanced understanding, our ability to provide truly informed consent may improve [21].

Functional genomics studies show interesting connections between mind-body therapies and immune system of cancer. Psychosocial and behavioral outcomes of genetic testing in oncology are well known, though it is not known how these findings generalize to more complex genomic testing. Advances in genomics and psychosocial genomics offer promise for earlier detection or prevention of cancer, by personalization of medical care tailored to an individual's genomic risk status but however genome sequencing can generate an unprecedented volume of results for the patient to process with potential implications for their families and reproductive choices [20]. Also, no studies assessed the outcomes of Whole genome sequencing (WGS) or Whole-exome sequencing (WES) and there is limited evidence of adverse psychosocial outcomes and changes in health behavior following genomic testing to assess cancer risk [22].

CONCLUSION

The nucleotide sequence was successfully analyzed & annotated. As per Fig. 5 we get best modeled protein of gene CXCR4. As per SFOLD analysis, RNA structure was successfully folded (Fig. 6). The mRNA sequence of the genes where successfully silenced using siRNA technique. This siRNA technique can be explored in cancer therapy including cervical cancer. Using PRINTSEQ, we analyze the nucleotide sequence viz. sequence contents, ploy A/T tails, TAG sequence, sequence complexity, dinucleotide ratio, and gene annotation. These next generation methods provide information for novel computational pipeline development for the therapeutics.

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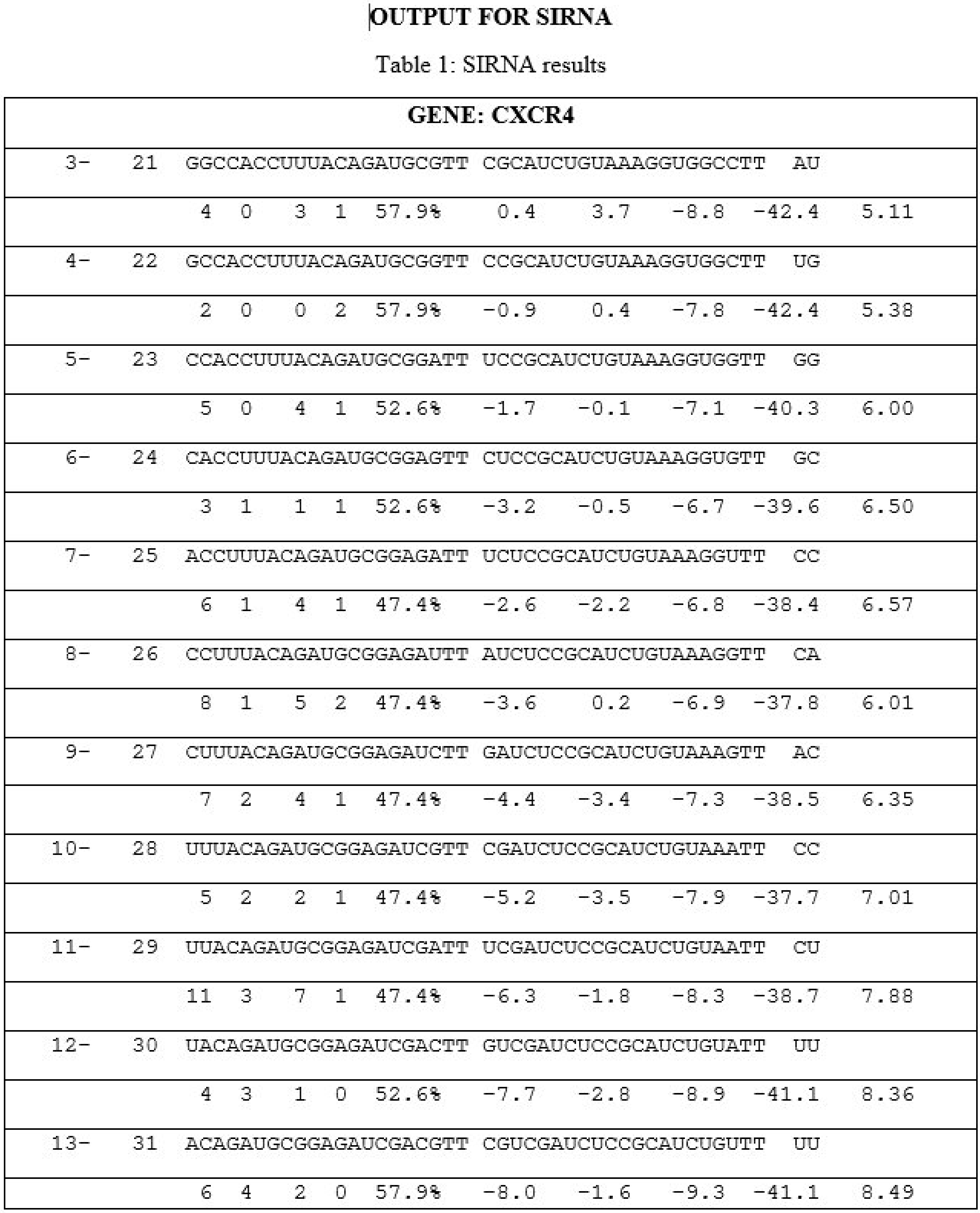


OUTPUT FOR SIRNA

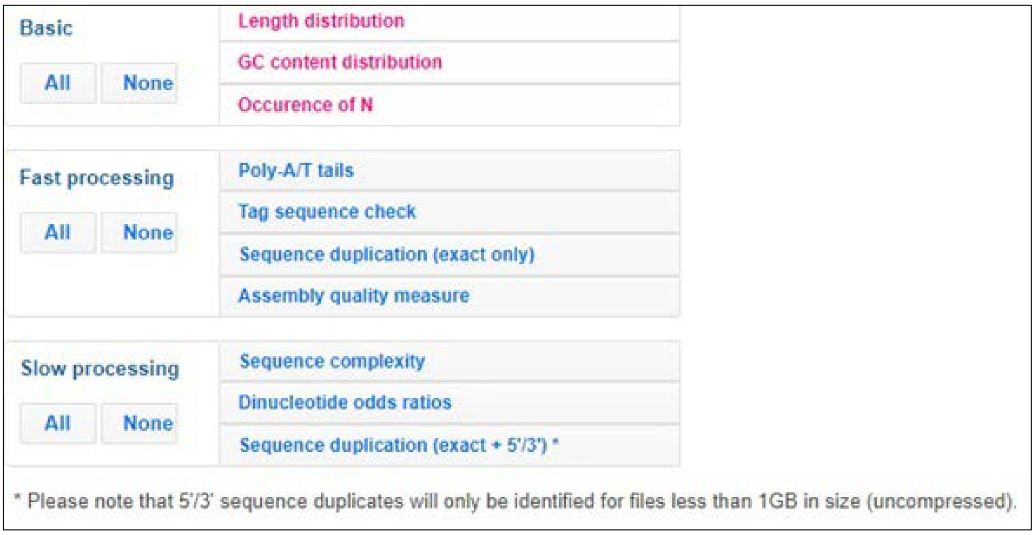
Table 1: SIRNA results

GENE: CXCR4											
3-	21	GGCCACCUUUACAGAUGCGTT	CGCAUCUGUAAAGGUGGCCTT	AU							
		4	0	3	1	57.9%	0.4	3.7	-8.8	-42.4	5.11
4-	22	GCCACCUUUACAGAUGCGGTT	CCGCAUCUGUAAAGGUGGCTT	UG							
		2	0	0	2	57.9%	-0.9	0.4	-7.8	-42.4	5.38
5-	23	CCACCUUUACAGAUGCGGATT	UCCGCAUCUGUAAAGGUGGTT	GG							
		5	0	4	1	52.6%	-1.7	-0.1	-7.1	-40.3	6.00
6-	24	CACCUUUACAGAUGCGGAGTT	CUCCGCAUCUGUAAAGGUGTT	GC							
		3	1	1	1	52.6%	-3.2	-0.5	-6.7	-39.6	6.50
7-	25	ACCUUUACAGAUGCGGAGATT	UCUCCGCAUCUGUAAAGGUTT	CC							
		6	1	4	1	47.4%	-2.6	-2.2	-6.8	-38.4	6.57
8-	26	CCUUUACAGAUGCGGAGAUTT	AUCUCCGCAUCUGUAAAGGTT	CA							
		8	1	5	2	47.4%	-3.6	0.2	-6.9	-37.8	6.01
9-	27	CUUUACAGAUGCGGAGAUCTT	GAUCUCCGCAUCUGUAAAGTT	AC							
		7	2	4	1	47.4%	-4.4	-3.4	-7.3	-38.5	6.35
10-	28	UUUACAGAUGCGGAGAUCGTT	CGAUCUCCGCAUCUGUAAATT	CC							
		5	2	2	1	47.4%	-5.2	-3.5	-7.9	-37.7	7.01
11-	29	UUACAGAUGCGGAGAUCGATT	UCGAUCUCCGCAUCUGUAATT	CU							
		11	3	7	1	47.4%	-6.3	-1.8	-8.3	-38.7	7.88
12-	30	UACAGAUGCGGAGAUCGACTT	GUCGAUCUCCGCAUCUGUATT	UU							
		4	3	1	0	52.6%	-7.7	-2.8	-8.9	-41.1	8.36
13-	31	ACAGAUGCGGAGAUCGACGTT	CGUCGAUCUCCGCAUCUGUTT	UU							
		6	4	2	0	57.9%	-8.0	-1.6	-9.3	-41.1	8.49

Table 1: SIRNA results of CXCR4 showing the regions of splicing

Fig. 1 MAP pathway (source: https://en.wikipedia.org/wiki/MAPK/ERK_pathway#/media/File:MAPKpathway_diagram.svg)

Fig. 2: MAPK gene



Basic

All None

- Length distribution
- GC content distribution
- Occurence of N

Fast processing

All None

- Poly-A/T tails
- Tag sequence check
- Sequence duplication (exact only)
- Assembly quality measure

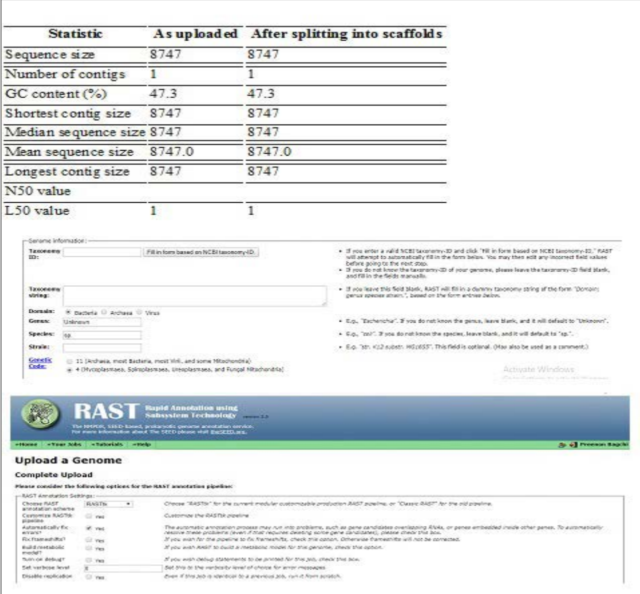
Slow processing

All None

- Sequence complexity
- Dinucleotide odds ratios
- Sequence duplication (exact + 5'/3') *

* Please note that 5'/3' sequence duplicates will only be identified for files less than 1GB in size (uncompressed).

Fig. 3: PRINSEQ input page



Statistic	As uploaded	After splitting into scaffolds
Sequence size	8747	8747
Number of contigs	1	1
GC content (%)	47.3	47.3
Shortest contig size	8747	8747
Median sequence size	8747	8747
Mean sequence size	8747.0	8747.0
Longest contig size	8747	8747
N50 value		
L50 value	1	1

Genome Information:

Taxonomy ID: Fill in form based on NCBI taxonomy-ID

- If you enter a valid NCBI taxonomy-ID and click "Fill in form based on NCBI taxonomy-ID," RAST will attempt to automatically fill in the form below. You may then edit any incorrect field values before going to the next step.
- If you do not know the taxonomy-ID of your genome, please leave the taxonomy-ID field blank, and fill in the fields manually.

Taxonomy string:

- If you leave this field blank, RAST will fill in a dummy taxonomy string of the form "Domain; genus species strain.", based on the form entries below.

Domain: ● Bacteria ○ Archaea ○ Virus

Genus: Unknown

- E.g., "Escherichia". If you do not know the genus, leave blank, and it will default to "Unknown".

Species: sp.

- E.g., "coli". If you do not know the species, leave blank, and it will default to "sp.".

Strain:

- E.g. "str. K12 substr. MG1655". This field is optional. (Has also be used as a comment.)

Genetic Code:
○ 11 (Archaea, most Bacteria, most Virii, and some Mitochondria)
● 4 (Mycoplasmaea, Spiroplasmaea, Ureoplasmaea, and Fungal Mitochondria)

RAST Rapid Annotation using Subsystem Technology

The NMPDR, SEED-based, prokaryotic genome annotation service.
For more information about The SEED please visit theSEED.org.

Upload a Genome

Complete Upload

Please consider the following options for the RAST annotation pipeline:

RAST Annotation Settings:

Choose RAST annotation scheme	RASTtk	Choose "RASTtk" for the current modular customizable production RAST pipeline, or "Classic RAST" for the old pipeline.
Customize RASTtk pipeline	☐ Yes	Customize the RASTtk pipeline
Automatically fix errors?	☑ Yes	The automatic annotation process may run into problems, such as gene candidates overlapping RNAs, or genes embedded inside other genes. To automatically resolve these problems (even if that requires deleting some gene candidates), please check this box.
Fix frameshifts?	☐ Yes	If you wish for the pipeline to fix frameshifts, check this option. Otherwise frameshifts will not be corrected.
Build metabolic model?	☐ Yes	If you wish RAST to build a metabolic model for this genome, check this option.
Turn on debug?	☐ Yes	If you wish debug statements to be printed for this job, check this box.
Set verbose level	0	Set this to the verbosity level of choice for error messages.
Disable replication	☐ Yes	Even if this job is identical to a previous job, run it from scratch.

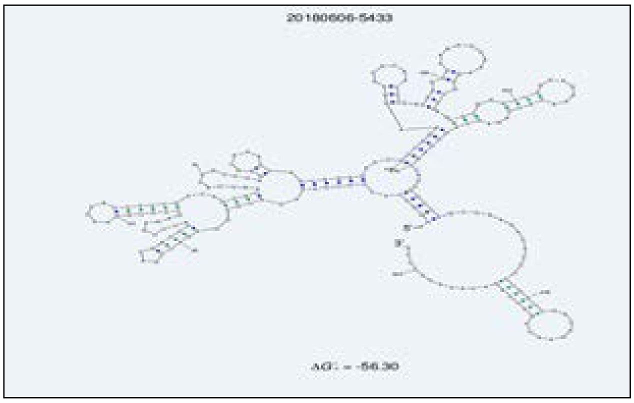


Fig. 4: RAST input Data

Fig.6: SFOLD Result of CXCR4

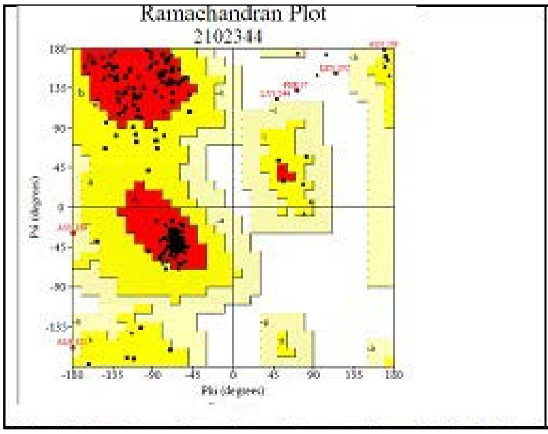


Fig. 5(a): Ramachandran plot results of CXCR4

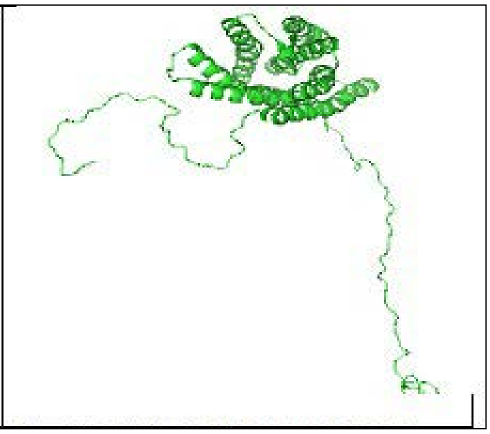
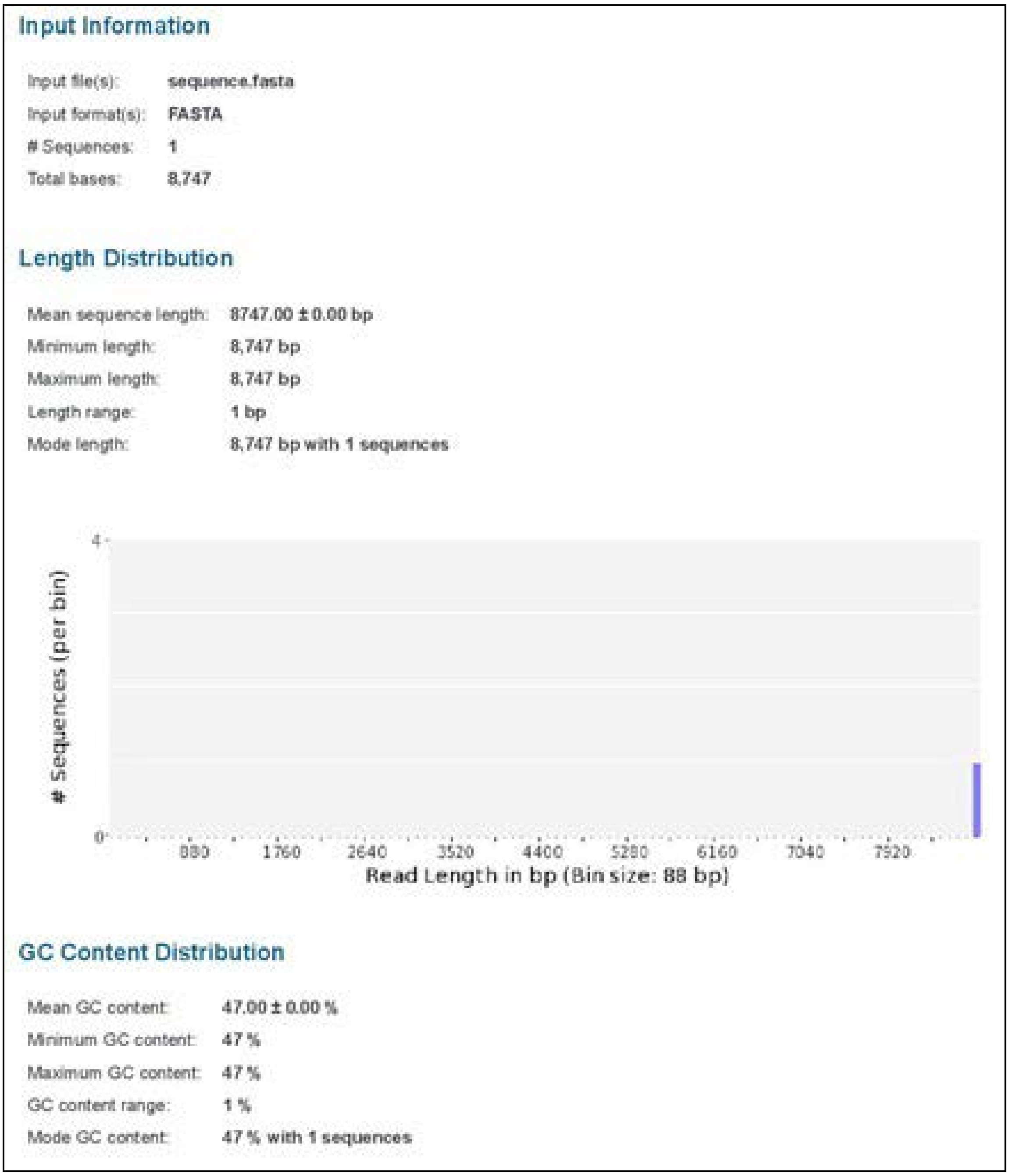


Fig. 5(b): GENE: CXCR4 (MODEL 5)



Input Information

Input file(s):	sequence.fasta
Input format(s):	FASTA
# Sequences:	1
Total bases:	8,747

Length Distribution

Mean sequence length:	8747.00 ± 0.00 bp
Minimum length:	8,747 bp
Maximum length:	8,747 bp
Length range:	1 bp
Mode length:	8,747 bp with 1 sequences

GC Content Distribution

Mean GC content:	47.00 ± 0.00 %
Minimum GC content:	47 %
Maximum GC content:	47 %
GC content range:	1 %
Mode GC content:	47 % with 1 sequences

Fig. 7-1: PRINTSEQ output (CXCR4 gene analysis)

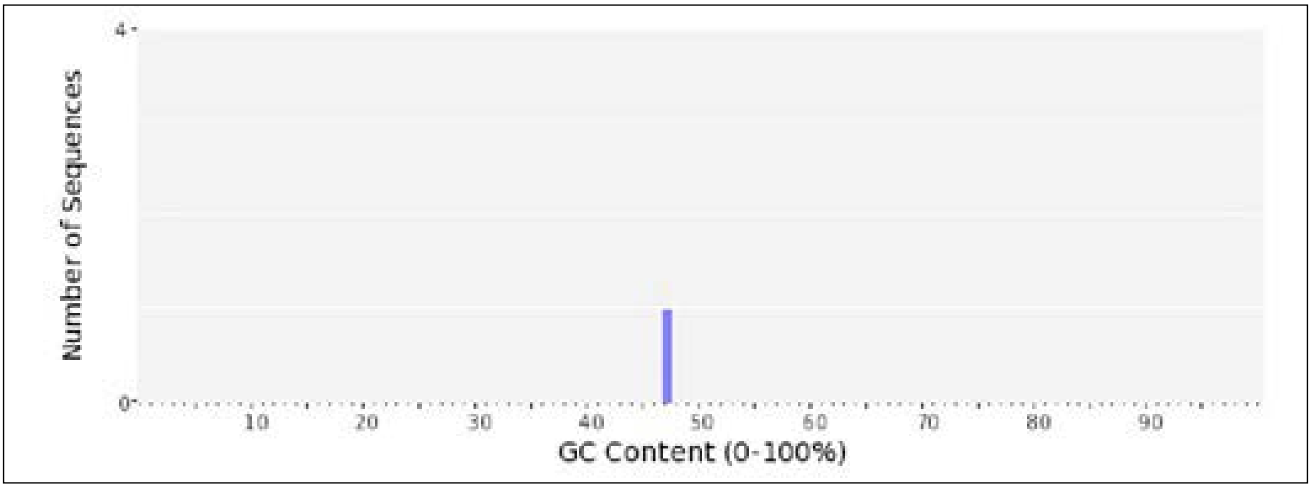
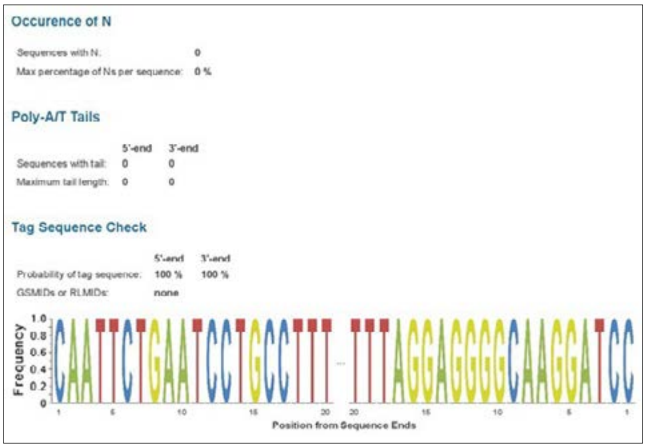


Fig. 7-2



Occurence of N

Sequences with N:	0
Max percentage of Ns per sequence:	0 %

Poly-A/T Tails

	5'-end	3'-end
Sequences with tail:	0	0
Maximum tail length:	0	0

Tag Sequence Check

	5'-end	3'-end
Probability of tag sequence:	100 %	100 %
GSMIDs or RLMIDs:	none	

Fig. 7-3

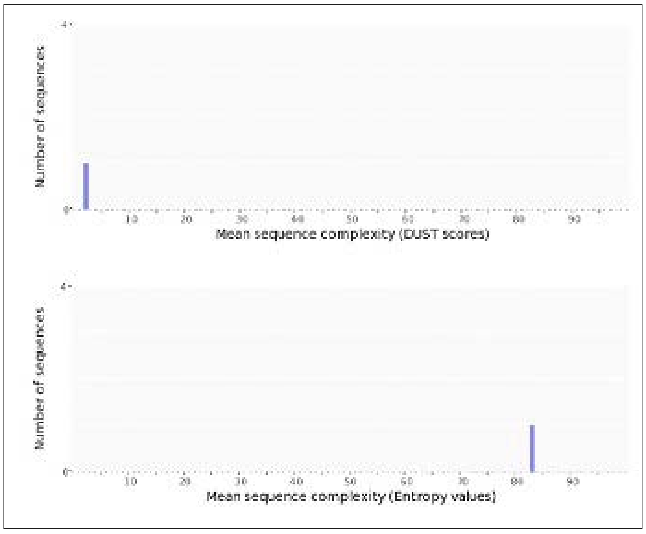
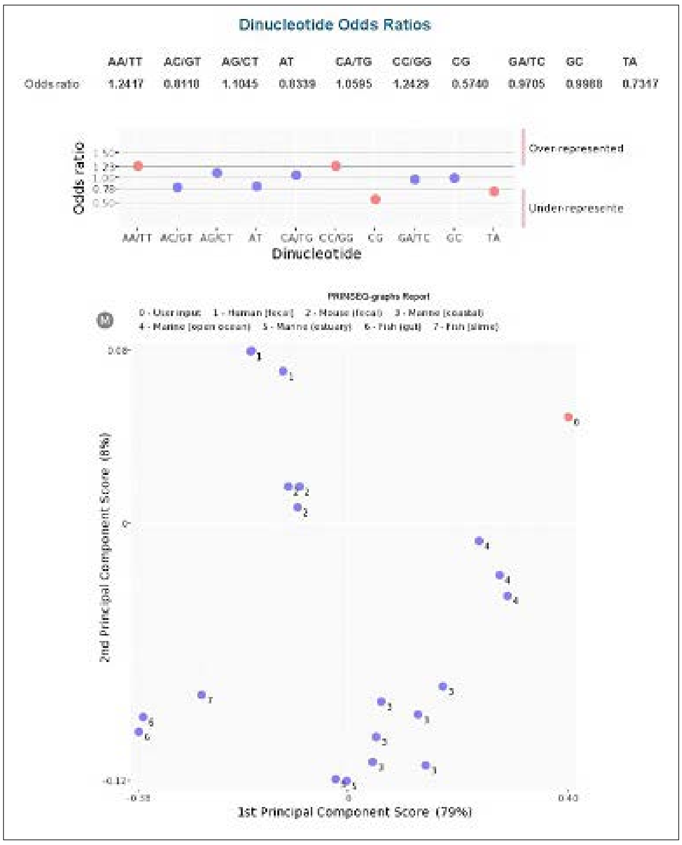


Fig. 7-4



Dinucleotide Odds Ratios

	AA/TT	AC/GT	AG/CT	AT	CA/TG	CC/GG	CG	GA/TC	GC	TA
Odds ratio	1.2417	0.8110	1.1045	0.8339	1.0595	1.2429	0.5740	0.9705	0.9988	0.7317

Fig. 7-5

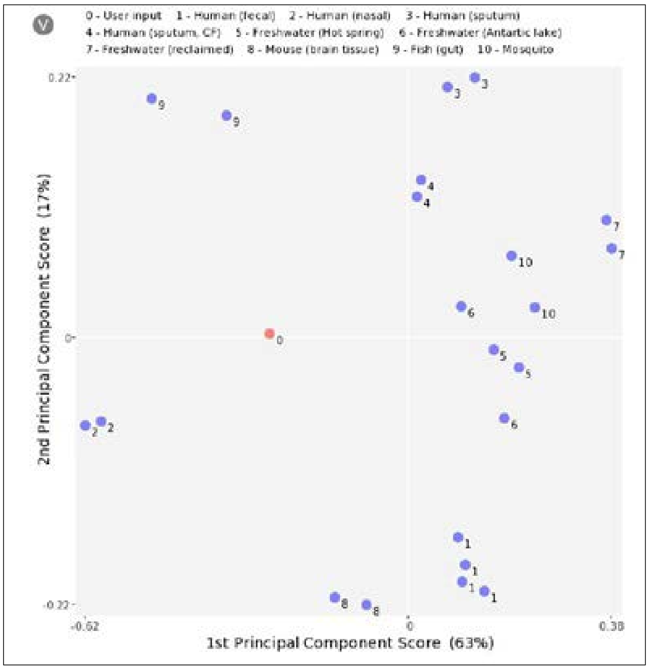
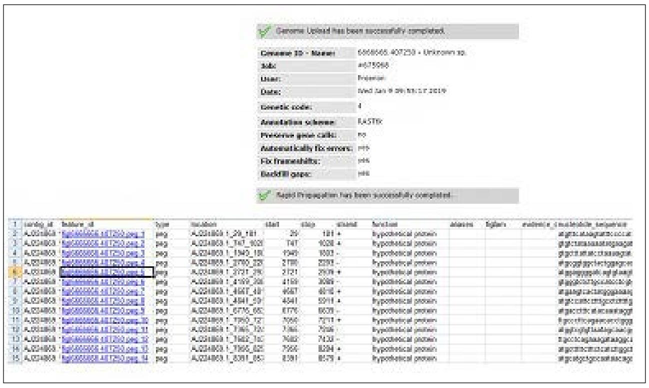


Fig. 7-6



Genome Upload has been successfully completed.

Genome ID - Name: 6666666.407250 - Unknown sp.

Job: [illegible]

User: [illegible]

Date: Wed Jan 9 09:55:17 2019

Genetic code: 4

Annotation scheme: RASTtk

Preserve gene calls: no

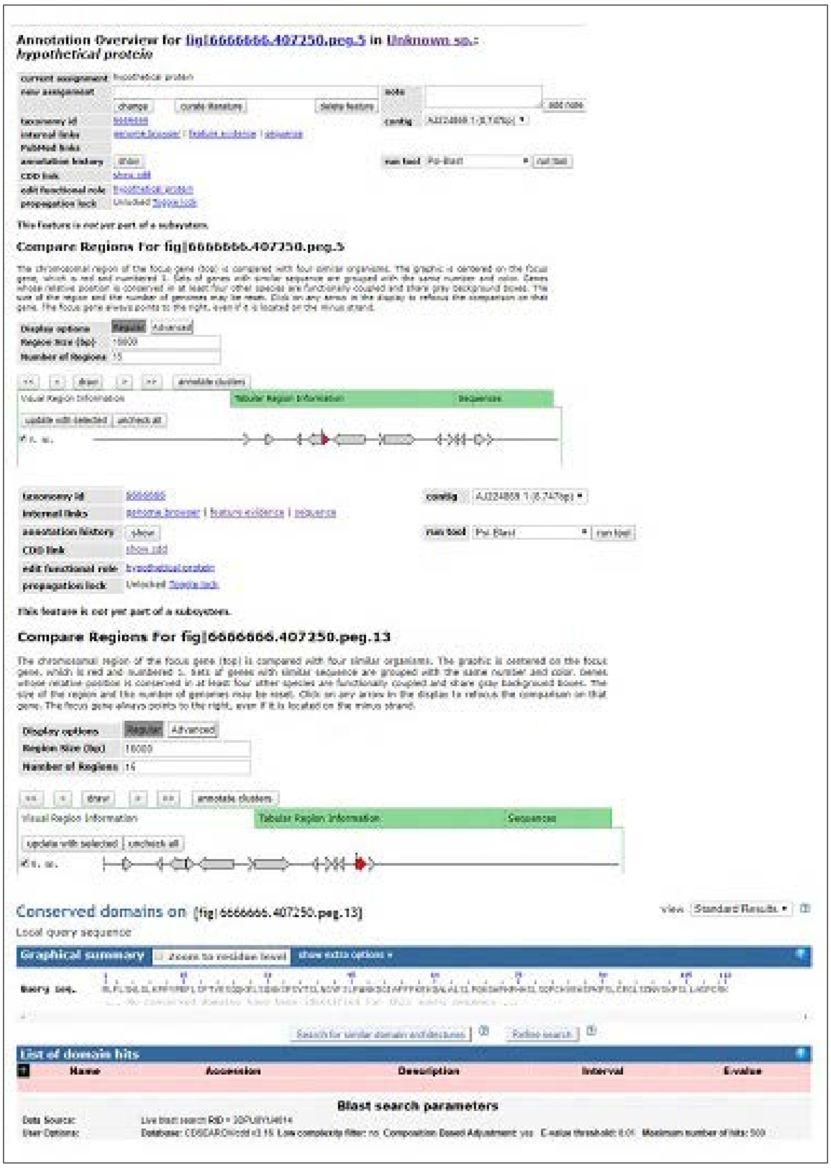
Automatically fix errors: yes

Fix frameshifts: yes

Backfill gaps: yes

Rapid Propagation has been successfully completed.

Fig. 8-1: RAST Output (CXCR4 gene annotation)



Annotation Overview for fig|6666666.407250.peg.5 in Unknown sp.: *hypothetical protein*

current assignment hypothetical protein

new assignment

taxonomy id 6666666

internal links genome browser | feature evidence | sequence

PubMed links

annotation history show

CDD link show cdd

edit functional role hypothetical protein

propagation lock Unlocked Toggle lock

contig AJ224869.1 (8,747bp)

run tool Psi-Blast

This feature is not yet part of a subsystem.

Compare Regions For fig|6666666.407250.peg.5

The chromosomal region of the focus gene (top) is compared with four similar organisms. The graphic is centered on the focus gene, which is red and numbered 1. Sets of genes with similar sequence are grouped with the same number and color. Genes whose relative position is conserved in at least four other species are functionally coupled and share gray background boxes. The size of the region and the number of genomes may be reset. Click on any arrow in the display to refocus the comparison on that gene. The focus gene always points to the right, even if it is located on the minus strand.

Display options Regular Advanced

Region Size (bp) 16000

Number of Regions 15

taxonomy id 6666666

internal links genome browser | feature evidence | sequence

annotation history show

CDD link show cdd

edit functional role hypothetical protein

propagation lock Unlocked Toggle lock

contig AJ224869.1 (8,747bp)

run tool Psi-Blast

This feature is not yet part of a subsystem.

Compare Regions For fig|6666666.407250.peg.13

The chromosomal region of the focus gene (top) is compared with four similar organisms. The graphic is centered on the focus gene, which is red and numbered 1. Sets of genes with similar sequence are grouped with the same number and color. Genes whose relative position is conserved in at least four other species are functionally coupled and share gray background boxes. The size of the region and the number of genomes may be reset. Click on any arrow in the display to refocus the comparison on that gene. The focus gene always points to the right, even if it is located on the minus strand.

Display options Regular Advanced

Region Size (bp) 16000

Number of Regions 15

Conserved domains on [fig|6666666.407250.peg.13]

Local query sequence

Name	Accession	Description	Interval	E-value

Blast search parameters

Data Source: Live blast search RID = [illegible]

User Options: Database: CDSEARCH/cdd v3.16 Low complexity filter: no Composition Based Adjustment: yes E-value threshold: 0.01 Maximum number of hits: 500

Fig. 8-2