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# Microbial psychology: Behavior, associative learning, and relation to antibiotic resistance

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| **ARTICLE INFO** | **ABSTRACT** |
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Single-cell intelligence is a recent terminology suggested since it was clear that "biological intelligence" is deeply rooted in a genetic basis. The possible applications of the term conception are many where noncoding RNAs could be involved as a part to create a specific bacterial behavior through multiple gene regulation networks. Biological intelligence is the origin of the genome unit formation in all organisms, whether unicellular or multicellular. This intelligence is necessary and inevitable for the survival of the being on earth. Microbes are sensitive to some antibiotics, but they quickly acquire resistance against these antibiotics, and this degree of development or adaptation has its genetic factors that may be noncoding RNA or illegible on the genome. Perhaps the noncoding RNA could be transferred into coding RNA or vice versa. Intelligence in beings, in order to survive and/or outlive the earth, is present in its origin if it is a microbe germ, a plant pill, or a human or animal sperm. The current review aims to briefly clarify the genetic basis of classical conditioning and the probability of the connection with the noncoding RNAs and if that concept could be applied to enhance antibiotic sensitivity.

## INTRODUCTION

Today several serious threats afflict humanity worldwide. One of the most severe threats is the rise in antibiotic resistance, where bacterial mutations decrease the efficacy of antibiotics (Ciabuschi *et al.*, 2020). Many bacteria have developed means of resistance to antimicrobials, which can spread to other bacteria reducing the activeness of subsequent antimicrobial treatments. Antibiotic resistance is a growing threat that already causes more than 50,000 deaths per year in the EU and US alone, and several hundreds of thousands of casualties are estimated in the rest of the world. Subsequently, infectious disease experts have called for strategies to minimize the risk of spreading antibiotic resistance. Although the mechanisms which lead to antimicrobial resistance are biological, the motivations behind current levels and methods are determined by a wide range of factors, including individual, psychological, social, cultural, political, and economic forces (Chambers *et al.*, 2020).

The Mine, Model, Manipulation, Measure, and Manufacture (5Ms) strategy is used to overproduce the desired product and gain a deeper knowledge of the intelligence system of microorganisms.

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"Mine" is the initial step toward understanding the internal connections in large datasets, such as omics. The procedure "Model" is used to construct hypotheses from "Mine." "Manipulation" is required to test the aforementioned hypotheses and to point out a viable path to real applications. "Measure" refers to the process of revealing the phenotype of a genome-modified microorganism, while "Manufacture" refers to the process of scaling it up in industrial fermenters. Subsequently, the desired products can be manufactured and scaled up to the industrial level using this 5Ms plan (Gao *et al.*, 2017).

Psychology is the study of the mind and its functions, which considers all possible conditions of the organism and involves the analyses of the acquired information from the surroundings, followed by information processing and finally responding (Baker, 2012). Moreover, behavioral psychology is a branch of psychology that focuses on the connection between the organism's behavior and the mind, which has been shifted through the years between the perspective of nurture and nature. Currently, it is believed that the behavior of any organism has a genetic basis, which could also get influenced somehow by environmental factors. In recent years, a lot of attention has been given to investigating the genetic basis of behavior and intelligence in different higher organisms (Brennan, 2004; Flint, 1999; Plomin and Spinath, 2004), including humans (Hettema *et al.*, 2003).

In this review, the genetic basis of classical conditioning and the probability of the connection with the noncoding RNAs were discussed, and whether that concept could be applied to enhance antibiotic sensitivity was also discussed.

## MOLECULAR PSYCHOLOGY

As a part of behavioral researches in higher and lower organisms, several studies on the genetic background of learning and memory are progressing rapidly in invertebrates (Carew and Sahley, 1986; Giurfa and Sandoz, 2012; Menzel and Benjamin, 2013), especially *Drosophila* (Iliadi, 2009; Malik and Hodge, 2014; Tully and Quinn, 1985). The question was related to the single-celled organism if it has such evidence of biological intelligence. There was no direct relation between behavioral psychology and microbes. In order to conceptionally connect behavioral psychology to the microbial level, the connection between biology and psychology based on the molecular level should be introduced and a brief understanding of the term "molecular psychology" is required.

Psychology in term is rooted in biology, since not so long ago the field was greatly transformed by the development and breakthroughs of molecular biology tools. Those tools of molecular biology and genetics were applied successfully in uncountable studies to investigate the organism's behavior and the brain system, which raised the term "molecular psychology" as the study of behavior and its underlying brain systems using the tools of molecular biology (Craddock and Owen, 1996; Demkow and Wolańczyk, 2017; Plomin, 1995).

Jennings (1906) argued that one of the relevant mechanisms underlying protozoan behavior was learning. He observed that repeated aversive stimulation of the ciliate *Stentor roeselii* resulted in a characteristic sequence of distinct adaptive behaviors, which may be interpreted as an elementary form of learning which is considered a key feature of learning in "higher" organisms. Single cells have the ability to carry out a form of information processing that neuroscientists have traditionally attributed to networks of cells. For example, Table 1 illustrates molecules/pathways suggested to be involved in learning and memory, with homologs in ciliates (Gershman *et al.*, 2021).

The question remains, to what extent do molecular biology and genomics affect the psychological concepts in higher organisms? Five breakthrough discoveries made during the past two decades were suggested to be the main pillars of genomic psychology (Canli, 2007). The previous findings linked genetic variations to personality and to brain function and also suggested such interaction with environmental factors affecting mental health, leading to identifying the neural and molecular correlates of these gene–environment interactions. However, none of the findings showed evidence in regards to the behavioral psychology of the single cell organisms. Lack of information in such scope was the main authors' motivation in the current review to align the evidences and previous art in context to hint something related to a perspective about the philosophical term "microbial psychology" or better known as "bacterial intelligence", with special regard to

**Table 1.** Molecules/pathways suggested involved in learning and memory, with homologs in ciliates.

| Molecules/pathways | Ciliates with reported homologues |
| --- | --- |
| N-methyl-D-aspartate receptor | *Paramecium primaurelia* (partial sequences) |
| Glutamate receptor | *Paramecium tetraurelia* |
| Calmodulin | *Paramecium tetraurelia* |
| *cAMP* | *Paramecium tetraurelia* |
| *cAMP*-dependent protein kinase | *Paramecium tetraurelia* |
| Mitogen activated protein kinase | *Paramecium caudatum* |
| Protein kinase C | *Tetrahymena thermophila* |
| Calcineurin | *Paramecium tetraurelia* |
| DNA methyltransferases | *Tetrahymena thermophila* |
| Histone acetyltransferases | *Tetrahymena thermophila* |
| Histone deacetylases | *Tetrahymena thermophila* |

Gershman *et al.* (2021) Table 1.

the classical conditioning phenomena and its connection with the non-coded RNAs.

## CLASSICAL CONDITIONING THEORY

There is a theory for the learning process in higher organisms which has been well studied through the years in psychology called "classical conditioning theory," which involves learning a new behavior via the process of association. In simple terms, two stimuli are linked together to produce a newly learned response in a person or animal (Andersson, 2016; Bitterman, 2006; Lorenzetti *et al.*, 2011). Classical conditioning is the process where the combination of stimuli produces a specific response in an organism. The response of the conditioned organism can occur positively or negatively according to the connotation of the stimuli. The interest in studying this association process helped largely in deciphering critical problems in clinical psychiatry (Follette and Dalto, 2015). Classical conditioning was and still is under extensive studies to clarify the genetic basis of the association. However, a direct connection between stress and classical conditioning has been reported (Schreurs and Burhans, 2015).

Very limited studies provide a possible connection between classical conditioning and microbial level. However, there are plenty of researches reporting varied bacterial behavior such as symbiosis, mutualism, commensalism, and parasitism, including the mechanisms of biofilm formation, swimming, swarming, cell-to-cell communication, and stress response (Niu and Wang, 2012). All those studies came together to point out that bacteria are adaptive microorganisms. Just like other living organisms, the latter have the genetic material that enables them to receive the surrounding signals (sensing), process them, and then respond. Since bacteria already have different abilities of sensing the environmental signals, processing them, and responding, obviously that is the reason why some bacterial species are considered more adaptable and on an industrial scale valuable than others. The size of the genetic material in bacteria is also an advantage over higher organisms in regard to behavioral studies. Several reports showed that the bacterial ability to adapt to the environment is a result of multiple and complex genetic regulation networks (Brooks *et al.*, 2011; Lozada-Chávez *et al.*, 2006; McAdams *et al.*, 2004). Gandhi *et al.* (2007) suggested that the presence of polycistronic RNA in bacteria and its involvement in the complex regulation process of biochemical networks are already evidence of a direct relation between genomic adaptation and applied classical conditioning. However, the complexity of those mechanisms in bacteria will never reach the same level as gene regulatory networks in higher organisms, as simply genetic complexity can be measured by genome size and the number of the Open Reading Frames (ORFs) included (Davidson and Peter, 2015; Huang and Kauffman, 2013; Somogyi and Sniegoski, 1996; Walhout, 2011).

If microorganisms could be considered as a useful candidate for behavioral studies, then why should not psychological concepts like classical conditioning be considered to explain bacteria and microorganisms' behavior and therefore applied to the microbial level?

## NONCODING RNAS (lncRNAs)

Long noncoding RNAs (lncRNAs) are a group of non-protein-coding RNAs with a length exceeding 200 nucleotides. They will not be translated into proteins but affect the binding of DNA, mRNA, microRNA, and proteins and regulate gene expression at the transcriptional, posttranscriptional, translational, and posttranslational levels (Karakas and Ozpolat, 2021). lncRNAs, potential RNA polymerase II transcription byproducts, have been reported to regulate cellular processes, such as chromosome and genome modification, transcription activation and interference, and nuclear transport. lncRNAs functions are dependent on their position, so they are categorized in terms of position in the genome to protein-coding genes: they can be classified as sense, antisense, bidirectional, intronic, intergenic, and enhancer lncRNAs. They also may be classified according to length, function, location, and targeting mechanism. An unveiled value of lncRNAs was reported which encodes small peptides to fine-tune general biological processes in a tissue-specific manner (Chen *et al.*, 2021).

The recent two decades have revealed that lncRNAs pervasively exist in the eukaryotic system. lncRNA (i) might indirectly affect controlling the expression or subcellular localization of the key protein factors, (ii) might act as a molecular platform, bringing diverse proteins together into an ribonucleoprotein (RNP) complex, or a decoy by sponging and prevent them from associating with their targets, and (iii) might be organizers of nuclear architecture. More efforts are required to provide insights into how these special transcripts are controlled and function, especially in the nucleus (Song *et al.*, 2021).

## BACTERIAL GENETIC COMPOSITION

Most bacteria have single, covalent closed, circular chromosomes, as opposed to the linear chromosomes found in eukaryotic cells. Many have circular chromosomes and linear plasmids, while some have linear chromosomes and linear plasmids. In several cases, multiple chromosomes have been discovered, including *Brucella*, *Leptospira interrogans*, *Burkholderia*, and *Vibrio cholera* (The Desk Encyclopedia of Microbiology, 2004). *Borrelia* and *Streptomyces* have linear chromosomes, and most strains contain both linear and circular plasmids (Miller *et al.*, 2013). The *Escherichia coli* chromosome is around 1.35 mm long, which is longer than the bacterial cell a hundred times, but the circular DNA is looped and supercoiled to fit the chromosome into the limited space inside the cell (Guentzel, 1996). The bacterial genome is considered as the first level of the genome composition. However, the second level is considered as the transcribed genes, which are categorized into two main groups: protein-coding and noncoding RNA. The third level in the bacterial genome composition is the translated proteins, which involve structure and functional proteins.

An example to give about dynamic interaction in bacterial genetic levels is that of transmembrane proteins and sensors, which are involved in the reception of transduction signals emitted by other cells in the surrounding environment. It has been thought for a long time that the acquisition model of these signals is a single-component one before admitting that the complexity and simultaneity of the induced intracellular phenomena are far from responding to this hypothesis. The double-component model was then introduced with the implication of different levels of the genome, from gene to protein-coding RNA (Hellingwerf, 2005). This said, the question arises more about the role of noncoding RNAs in bacterial signal acquisition and social intelligence. Nucleotide sequence differences are in the form of

single nucleotide polymorphism, insertion–deletion mutations, and simple sequence repeats. These individual single and/or multi nucleotide differences can lead to different observable or hidden traits, in addition to other ones that could possibly be silent on the genotypic level (Ismail and Essawi, 2012).

## BACTERIAL INTELLIGENCE CONCEPT

The definition of "bacterial intelligence" is likely to have emerged from observations of the rudimentary cooperation of single cells (Ben-Jacob, 2009; Ben Jacob *et al.*, 2004; Ben-Jacob and Shapira, 2005) and then was further developed by other authors (Ford, 2009, 2006; Hellingwerf, 2005). The study of biology focused on a generic vision of the large biological systems, and it gradually progressed towards the study of minutiae. This therefore led to a loss of the real contextual scale, and the unit cell was no longer considered as a whole organism. Ford (2009, 2006) and others (Hellingwerf, 2005; Ben Jacob *et al.*, 2004) questioned this by initiating the first observations of a rudimentary form of cooperation and "social intelligence" in bacteria. British Psychologist Richardson (2012) concluded in his study that unicellular intelligence might provide the key to understanding intelligence in complex vertebrates, including humans (Lyon, 2015).

Due to its existence, bacteria have been able to convert the complex matter into easy matter to metabolize molecules to ensure its survival. This ability is not only at the service of the individual cell, but also for a structured hierarchical organization in the colony and communication as with coordination (Ben Jacob *et al.*, 2004). Beyond a basic signal transfer in the form of physical interactions and biochemical exchange, the bacterial cell communicates its internal physiological state in a global context of cooperation and decision-making. The involvement of the dynamic and self-conscious genome in the biochemical regulation of this synchronized process between cells is a form of "pragmatic intelligence," in which the experience of the bacterial community is exchanged and the core's "wisdom" is the only determinant of the response. This "smart" process transforms the colony into a super brain and deserves a categorization of bacterial species according to their intelligence quotient (Pinto and Mascher, 2016). It is important to note that the understanding of these forms of communication and intelligence in bacteria was an inspiration for other studies, especially those on the cooperation and resistance mechanism in cancer cells (Ben-Jacob *et al.*, 2012).

## BACTERIAL NONCODING RNAs AND STRESS RESPONSE

Several reports studied small regulatory RNAs in bacteria (Dutta and Srivastava, 2018; Wagner and Romby, 2015; Waters and Storz, 2009). It all started with the genomewide studies of bacterial gene expression, which has shifted from microarray technology to second-generation sequencing platforms. Transcriptome analysis via RNA-seq has a number of advantages, such as annotation-independent detection of transcription, improved sensitivity, and increased dynamic range. Early studies have uncovered the novelty of several coding sequences and noncoding RNA in microorganisms. That reveals the similarity of a transcriptional landscape with a eukaryote. The basic RNA-seq protocols have been improved to fit the rapid progress of the studies of RNA biology, with special regard to the noncoding RNAs. Our understanding of gene expression and genome content depends mainly on the further refinements and improvement of the current techniques (Croucher and Thomson, 2010).

Expression of the small RNA, which is tightly regulated at the level of transcription, can help the cell cope with environmental stress by redirecting cellular metabolism (Table 2,) (Azhikina *et al.*, 2015; De Bruijn, 2016; De La Fuente and Martínez-Guitarte, 2016; Fröhlich *et al.*, 2013; Gottesman *et al.*, 2006; Michaux *et al.*, 2014; Sonnleitner *et al.*, 2011). A large number of these small RNAs act by pairing to their target mRNAs. The outcome of pairing can be either stimulation or inhibition of translation. Many of the well-studied stress response regulons have now been found to include regulatory RNAs (Gottesman *et al.*, 2006; Plomin and Spinath, 2004; Wagner and Romby, 2015).

## STRESS RESPONSE AND CLASSICAL CONDITIONING

Classical conditioning (or respondent conditioning) refers to acquiring a new behavior via the process of association. In that regard, stresses are considered as a valuable classical conditioning tool (Li, 2012; Moreira and Volpato, 2004; Shors *et al.*, 1992; Wood and Shors, 1998). It has been studied well enough in higher animal models though there is still limited available literature on the nonneural organisms (Clark *et al.*, 2002; Dayan *et al.*, 2000; Hesslow and Yeo, 2002).

This curiosity about the presence of a direct link between stress and classical conditioning is in fact induced by the abovementioned "social" behavior of bacteria. Under limiting conditions, the adaptive mutagenesis induced in the cell is not necessarily in favor of its own survival but rather of the general framework of the entire colony. Morphotypes observed during stress are characteristic and involve social resistance (Crespi, 2001; Ben Jacob *et al.*, 2004; Tarnita, 2017; West *et al.*, 2007). These facts have shifted the standard definition of the bacterial genome from a static unit of storage of genetic information to a cybernetic, self-conscious, and dynamic agent. Figure 1 illustrates a diagram of the model for general stress response in *E. coli* that shows that under stress conditions microorganisms may develop signal transduction systems to sense environmental stresses and to control the coordinated expression of genes involved in cellular defense mechanisms. These evolved protective or adaptive networks assist microorganisms in modifying their environments and/or surviving the stress condition (Chung *et al.*, 2006).

## CLASSICAL CONDITIONING AND NONCODING RNA

Classical conditioning showed an impact on the noncoding RNA's expression in *Drosophila* (Maniatis, 2015). There are few other reports that showed the same principle of the involvement of noncoding RNA in higher cognitive processes and classical conditioning in other animal models (Salta and De Strooper, 2012; Schmidt *et al.*, 2015). One report showed clear evidence of the impact of the classical conditioning on the noncoding RNA's expression in *Lymnaea*, where antiNOS-2 RNA is axonally trafficked and regulated by classical conditioning (Korneev *et al.*, 2013) and critically a single conditioning trial changes the amount of antiNOS-2 RNA transported along the axon. The previous study concluded that gene regulation networks get altered by conditioning; a specific behavior therefore comes out from the organism. Thus, such data might summarize the fact that the specific behavior is regulated while the noncoding RNA is involved as a part of the regulatory system in the specific organism.

The core difference between neural and nonneural organisms in acquiring a new behavior is briefed in Figure 2. As

**Table 2.** Examples of bacterial noncoding RNA involved in stress response regulation.

| Role of sRNA/species | sRNA | Target | Remarks | References |
|---|---|---|---|---|
| **Acid stress response** | | | | |
| *E. coli* | *GadY* | gadXW | Acts as a positive regulator of the gadXW operon where gadX encodes the major acid tolerance regulator. | Opdyke *et al.* (2011) |
| **Oxidative stress response** | | | | |
| *E. coli* | *OxyS* | rpoS, fhlA | Acts as an antimutator, inhibits rpoS translation, regulates fhlA, activator of the hyp operon and contributes to cell protection against oxidative DNA damage. | Johnson *et al.* (2006) |
| **Osmotic stress** | | | | |
| *E. coli* | *FnrS* | sodB, maeA, gpmA, folEX | Expressed under anaerobic conditions; under the control of two $O_2$-dependent FNR and ArcA regulators, downregulates mRNAs encoding enzymes of energy metabolism. | Durand and Storz (2010) |
| **Aerobic or anaerobic growth conditions** | | | | |
| *E. coli* | *MicF* | ompF | Regulates the expression of the major outer membrane porinOmpF. | Andersen and Delihas (1990) |
| *Pseudomonas aeruginosa* | *PhrS* | PqsR | Activates the synthesis of PqsR, a key regulator in quorum-sensing communication under oxygen dependent conditions. | |
| **Phospho-sugar stress** | | | | |
| *E. coli* | *SgrS* | ptsG, manXYZ, yigL | Decreases phosphosugar accumulation by repressing translation of sugar transporter mRNA and enhancing translation of sugar phosphatase mRNA. | Papenfort *et al.* (2013) |
| **Nitrogen fixation or sorbitol stress conditions** | | | | |
| *Pseudomonas stutzeri* A1501 | *NfiS* | *nifK* mRNA | The *nfiS*-deficient mutant displayed reduced nitrogenase activity, as well as increased sensitivity to multiple stresses, such as osmotic and oxidative stresses. | Zhan *et al.* (2016) |
| **Membrane stability** | | | | |
| *Salmonella enterica* | *RydC* | *cfa* mRNA | Selectively activates two isoforms of *cfa* mRNA which are encoding cyclopropane fatty acid synthase. | |
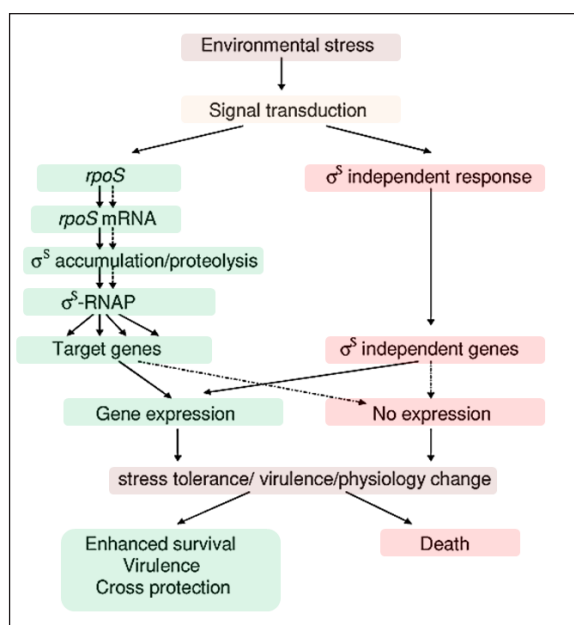


**Figure 1.** A diagram of the model for general stress response in *E. coli*. Solid line: positive control, dotted line: negative control (Chung *et al.*, 2006).

in animal models, the new behavior is acquired by associative learning via creating or modifying a neural network (Veit *et al.*, 2015). This is different in plants since a recent report showed that they could learn also by association, as the plant behavior is acquired via regulating the metabolic pathways, which are subsequently regulated by gene regulation networks (Gagliano *et al.*, 2016). However, evidence for learning in nonneural organisms is scant, and only a few unequivocal reports of learning have been described in single-cell organisms (Andersson, 2016; Ginsburg and Jablonka, 2009). Several studies showed that the nonneural organism *Physarum polycephalum* could be classically conditioned (Boisseau *et al.*, 2016; Nakagaki *et al.*, 2000, 2004; Saigusa *et al.*, 2008), although *P. polycephalum* is considered a multicellular organism.

## FUTURE RESEARCH AND APPLICATIONS

### Ability to predict

Serial studies since 2009 have been showing the ability of the bacterial cells to memorize and plan for the future events by developing a biochemical-based timer (Brunke and Hube, 2014; Mandli and Modak, 2014; Mitchell *et al.*, 2009; Mitchell and Pilpel, 2011). The predictive behavior of the bacterial cells
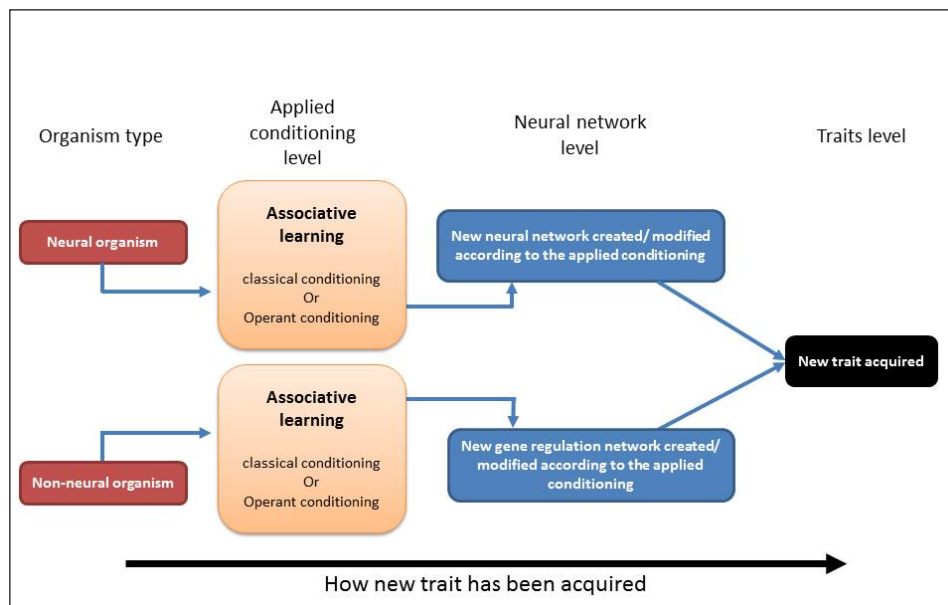
**Figure 2.** A diagram briefing the difference between neural and nonneural organisms while learning a new behavior.

could be considered as associative learning (Fernando *et al.*, 2009; Tagkopoulos *et al.*, 2008). According to an original study (Mitchell *et al.*, 2009), they found that one type of sugar, "lactose," is followed by a second sugar, "maltose," in the human intestine. The team checked *E. coli*'s genetic response to lactose and found that the gene network for utilizing maltose was partially activated alongside the genes that enable the same bacterial cells to digest lactose. When they reversed the order of the sugars, maltose at first, they found no corresponding activation of lactose genes, ensuring that bacteria have naturally adapted (or learned) to prepare for utilizing maltose after lactose. Generally speaking, bacterial evolution for adaptive purposes could be considered also as long-term learning by association. Several bacterial evolution experiments make it evident that bacteria are capable of hanging and choosing between several carbon sources (Feldgarden *et al.*, 2003; Görke and Stülke, 2008; Hua *et al.*, 2007; Mazurie *et al.*, 2010; Trevors, 1997).

**Object sensing**

In a series of tests, James Shapiro reported that *Myxococcus xanthus* worms were guided toward three-dimensional objects. Worms were directed toward either biologically noticed (a clump of prey cells) or chemically inert (sterilized glass beads) objects. The mechanisms should be studied through replicated experiments (Dworkin, 1983).

**Bistability**

Bistability to cognition in higher organisms, as well as its involvement in perception, memory, and learning is important.

**Endogenous activity**

The discovery of endogenous, oscillatory activity in the brain that is independent of external stimuli is one of the classic views of cognition. This oscillatory activity in prokaryotic regulatory circuits can serve as a guide to the processes related to endogenous brain activity (Bechtel, 2012).

**Nanobrain**

The cluster of chemoreceptors that mainly drives motility in *E. coli* may provide a tractable model for explaining the integration of signals from numerous sources into a behavioral response, which still represents a challenge.

**Valence**

The mechanisms of integration of external stimuli combinations of varying valence with interoceptive cues to form a coherent behavioral response in either bacteria or humans are still unknown. Except for circadian (24-hour) frequency, little information is available on the power spectrum (i.e., intensity and frequency) of signals to which each microorganism in any natural habitat is exposed. Stress responses in prokaryotes have been well investigated, especially those with diverse behavioral alternatives that represent potentially good research platforms (Lyon, 2015).

**Memory and learning**

Although the mechanisms by which the bacterial memory occurs have been characterized in many species, they need to be further investigated. In prokaryotes, the possibility of associative learning is likewise unknown. Given the large number of genes involved in generating serine/threonine protein kinases (STPKs) in this diversified predator, *M. xanthus* could be a viable candidate for such research. CaMKII is an autophosphorylating STPK that is engaged in numerous signaling pathways in animal homeostasis and is also hypothesized to play a role in human memory and learning in the reisany sequence homology between CaMKII and any of the myxobacterial STPKs (Goldman *et al.*, 2006).

**Communication**

The ability of quorum sensing molecules to influence the behavior of dispersed cells, particularly in response to stress, suggests that they may be precursors of hormone messengers, and certain homologies, such as between Acyl-homomserine lactones (AHLs) and ghrelin, have been discovered (Lyon, 2015).

## CONCLUSION AND FUTURE ASPECTS

There would be a relation between the degree of development of an organism and the repetition of the stimulus to achieve the desired conditioning. It may be suggested that the higher organisms could get the stimulus from the first few repetitions, but the nonneural organisms sometimes need years of conditioning to achieve the specific behavior. However, a condensed number of events on a regular basis with a focus on the bacterial generations could lead to the solution of how to teach bacteria a new behavior. Psychologically informed studies are urgently needed to facilitate change and evaluate the effectiveness of theory-based interventions targeting reducing antibiotics, including the promotion of biological alternatives.

Since the concept of microbial learning is, scientifically, acceptable as shown previously, then the future of training bacteria is limitless. Numerous possible future applications could be invented in regard to that aspect of bacterial learning, which could represent a breakthrough in future cellular communication. A review in 2004 titled "Teaching bacteria a new language" (Gerchman and Weiss, 2004) derived the inspiration of many synthetic biology scientists as they were wondering about the new ways of bacterial communications other than the known chemical or physical signaling and recently electrical signaling (Bassler, 2002; Farhadi, 2014; Humphries *et al.*, 2017; Marx, 2014; Von Bodman *et al.*, 2008). The first thought that came to our mind was electromagnetic (EM) signaling. Few resources have discussed cellular communication based on EM waves, especially radiofrequency (RF). In general, the studies on EM and its impact on bacterial cells are very limited (Farhadi, 2014; Kučera and Cifra, 2013; Montagnier *et al.*, 2009; Soghomonyan *et al.*, 2016; Tessaro *et al.*, 2015; Trushin, 2003). Besides limited resources, no biological receptor has been discovered yet to receive only a specific range of RF. However, the magnetic locomotor mechanism present in magnetotactic bacteria would imply the presence of EM cellular signaling in bacterial cells (Chen *et al.*, 2017). Thus, here comes the importance of microbial psychology and classical conditioning; it could be possible to train the bacterial cell to evolve by developing a reception system for RF using stress as a stimulus. However, there are many unanswered questions and unexplained avenues of research to be explored.

## AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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## ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

## DATA AVAILABILITY

All data generated and analyzed are included within this research article.

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