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Communication-based regulated freedom of response in bacterial colonies

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Abstract

Bacteria have developed intricate communication capabilities on all levels—the genome, the individual bacteria, the colony, and multi-colonial eco-systems of different bacterial species. All manner of biochemical messages are utilized for communication, including simple and complex abiotic molecules, peptides, proteins and even genetic sequences. These communication capabilities are required for bacterial cooperative self-organization into multicellular hierarchically structured colonies with complex spatio-temporal patterning. A colonial higher complexity is required for better colonial adaptability in a dynamic environment. The communication-based cooperative self-organization goes hand in hand with changes in cell structure and behavior. We identify two classes of such changes: (1) automatic and predetermined changes, which are triggered by inducive messages. (2) Regulated "decision-making" changes, which represent cellular regulated freedom of response to informative (semantic) messages. Each bacterium has internal degrees of freedom and informatics capabilities (storage, processing and interpretation of information). These features are required for the freedom of response in self-alteration (self-plasticity). Additionally, the cell can send messages to alter other bacteria in a self-regulated manner. To convert the above seemingly blurred notions into testable concepts we present the first steps towards quantification of colonial features associated with "regulated freedom". For this we extract a binary representation of the observed patterns to show the existence of Lévy distributions with parameters that range from near the Cauchy limit to the Gaussian limit. The assumption about bacterial "regulated freedom" or "decision-making" appears in contradict the fundamental principle of time causality. We propose, that this apparent difficulty might be resolved by applying the recent understandings of biotic and abiotic self-organization, to the dynamics of the cells' internal biochemical gel.

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1. Introduction

Bacteria have traditionally been perceived as primitive unicellular microbes with limited capabilities that live solitary life or aggregate into simply structured colonies of identical non-interacting passive "particles". This view is slowly changing. It turns out that, bacteria self-organize into hierarchically structured colonies with very complex spatio-temporal patterning [1,2]. Looking at the colonies, it becomes evident that we should view them as multicellular communities (each with $\sim 10^9$–10^{12} bacteria), possessing advanced capabilities to cope with the environment, including division of tasks, self-regulation of gene expression, self-regulation of cell differentiation and even self-generation of special "task forces" (bacteria with special genetic abilities) [1–6].

For this purpose, bacteria have developed and utilize a variety of bio-chemical communication agents, such as simple molecules, polymers, complex proteins, genetic materials and even "CDs of genetic information" (plasmids and viruses) [7–12]. These agents are used for exchange of information at all levels—intracellular and intercellular—across colonies and also with other organisms. We propose that the observed spectrum of bacterial communication demonstrates that two levels of bio-chemical messages can be identified: inducive messages and informative (semantic and meaningful) ones [2,13]. By inducive, we mean that the absorbed message (chemical agents) triggers a specific, predetermined pathway within the receiving cell. Thus, such an inducive message induces a specific response of the cell. For example, the presence of glucose in the environment induces, through a specific pathway, expression of the set of genes responsible for the metabolism of glucose. By informative (semantic) message we mean that the chemical agent, initiates a cellular response, which is not specific and predetermined. Instead, the meaningful information of the message initiates in the receiving cell an individual interpretation process [2,6], according to the current intercellular state and internally stored previously acquired information. The interpretation process involves self-organization of the intracellular gel [14]. It affords the cell freedom to select its response to the message, including self-alteration and broadcast of messages to generate alteration in other bacteria. Such freedom (self-plasticity) implies that the internal self-organization is associated with the generation of new information, so that the response is not predetermined, as we will further explain.

2. Examples of bacterial self-organization phenomena

In this manuscript, we show some patterns exhibited during complex spatio-temporal organization of the *Paenibacillus dendritiformis* and *P. vortex* bacteria, which have

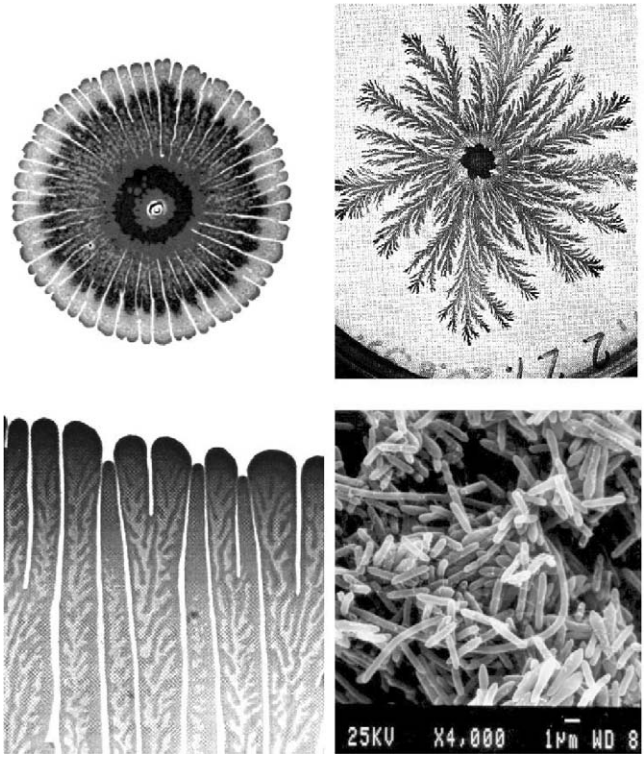

Fig. 1. Patterns exhibited by the branching morphotype of the *P. dendritiformis* bacteria: tip-splitting growth at high peptone levels (top left); "busy" branching at intermediate levels (top right); closer look at the patterns of density variations within tip-splitting branches (bottom left). The latter manifests the additional level of organizations between the individual bacteria and the branches level. Even a closer look via an electron microscope (bottom right) reveals the large variations between cells due to their "regulated freedom". This picture has been taken upon morphotype transitions from branching to chiral morphotype. Note the appearance of very long bacteria.

been isolated studied and classified by Ben-Jacob et al. [1,2]. The former have a special capability to generate two distinct morphotypes: The simple branching (SB or branching morphotype) shown in Fig. 1 and the chiral branching (CB or chiral morphotype) shown in Fig. 2. The latter exhibit self-organization of vortices, as described in Section 5.

It has been demonstrated that the flagella handedness of *P. dendritiformis* bacteria, together with bacteria–bacteria alignment interaction, act as a singular perturbation that generates the colonial chiral organization. The colony can affect the gene expression of its own bacteria, to elongate them and thus activate the singular perturbation required for chiral self-organization.

Each of the *P. dendritiformis* morphotypes is genetically inheritable: the trait can be transferred by an individual cell. Yet, spontaneous morphotype transitions are observed (Fig. 3). In general, the transitions are into the morphotype whose colonies can expand

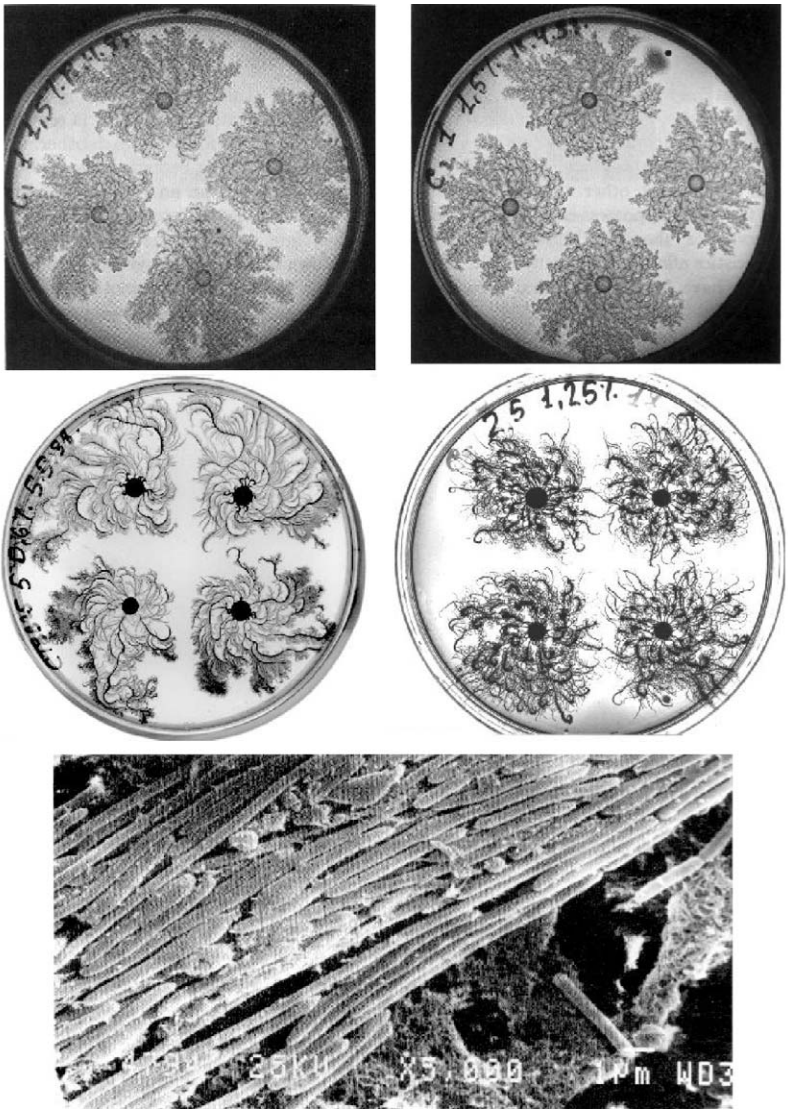

Fig. 2. Patterns exhibited by the chiral branching morphotype of the *P. dendritiformis* bacteria. Different growth conditions lead to the formation of different patterns. The similarity of the four colonies on each plate demonstrates their tolerance and robustness and indicates that their high complexity is not accidental. Even more impressive is the similarity between the two plates at the top, demonstrating the reproducibility of our experiments of growth at the same levels of peptone and agar. Electron microscope view (bottom) shows the orientational co-alignment of these long bacteria.

faster and organize into a more complex pattern at the imposed growth conditions. It is also possible to initiate morphotype transitions in a predesigned (engineered) manner, as shown in Fig. 3.

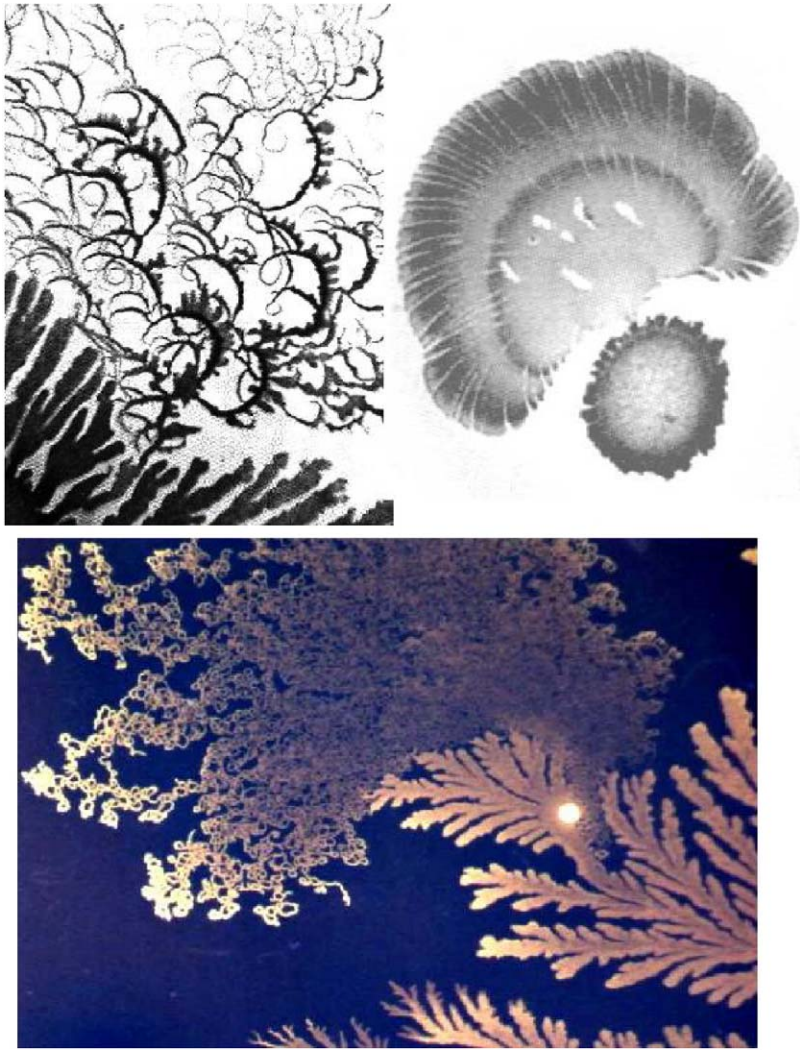

Fig. 3. Morphotype transitions between the simple branching and the chiral branching morphotypes. The top left picture shows spontaneous transition into chiral morphotype during growth on soft substrate. On the right, the spontaneous transition is from chiral back to tip-splitting during growth on hard substrates. In both cases, the transition is into the faster and more complex morphotype for the given growth conditions. The bottom picture shows a transition into the chiral morphotype initiated by "engineered perturbation" (fungi located at the bright spot). The higher flexibility of the chiral morphotype enables it to cope better with the perturbation. Note that it changes its ordinary geometrical organization to deal with the perturbation, a change possible thanks to its higher flexibility.

The morphotype transitions manifest that the colony can reach down and initiate a genetic transition of the individual cell, leading to an autocatalytic genetic transformation required for the morphotype transition.

3. Colonial self-organized patterning of gene expression

Intricate patterns of gene expression were observed in *Escherichia coli* colonies even without apparent geometrical structure [5]. In more recent studies of the morphology diagram and patterns of gene expression in colonies of *Bacillus subtilis*, it was discovered that under certain growth conditions the patterns of gene expression diverge significantly from the geometrical patterns [15]. Apparently, in some cases, several rings of bacteria activate a gene, and in others, the gene expression activity propagates back and forth along branches of stationary bacteria. These observations provide a direct demonstration of colonial genetic communication.

Under ordinary growth conditions, colonies of *Proteus mirabilis* develop a very stable terrace structure of concentric rings. It turns out that the bacterial cells switch identities from swarmers to swimmers and back. To a certain cue, yet unknown, the swimmer cells stop dividing and grow into elongated, hyper-flagellated swarmers. The swarmers form collective "rafts" (reminiscent of the *P. vortex*) that can move efficiently on the surface. After a while, these cells differentiate back to swimmers, filling in new regions of a "consolidation phase" [5,16]. This dynamics forms very smooth rings compared, for example, with the ring structures observed in *B. subtilis*, which are quite ragged. This implies colonial regulation capable of generating synchronized gene expression.

The predator *Myxobacteria* afford the richest set of phenomena observed during colonial development, including cooperative feeding on other bacteria, group motility, cell differentiation, aggregation and cohesion, rippling and formation of fruiting bodies for a more efficient dissemination of spores in response to starvation [1,4,7,17–19]. The challenge is to understand how cell behavior is coordinated in a self-consistent manner with gene expression, in order for multicellular behavior to emerge.

4. Testing the hypothesis about "communication-based regulated freedom of response"

It has been proposed that "regulated freedom" of response is a necessary requirement for bacterial cooperation, so that enhancement of "regulated freedom" and cooperation are mutually connected, in contrast with the common perception of them being in competition [2]. The challenge is to convert these seemingly blurred statements into a testable biotic principle. The first crucial step in this direction is to demonstrate that the problematic intuitive notions of colonial regulation and freedom can be associated with corresponding quantifiable features in the observed colonial patterns. Note that freedom here is in the physics sense of "degrees of freedom", and regulation is in the sense of self-control, borrowed from engineering. We encountered a similar difficulty in understanding the temporal patterns of activity recorded from neuronal networks [20–24]. Motivated by our newly developed approach in the studies of neuro-complexity, we set out to study the distributions and correlations in the observed colonial spatial patterns. To do so, we first extract from a scanned pattern a binary sequence along a spiral or a set of spirals (adapted to the observed patterns as will be explained

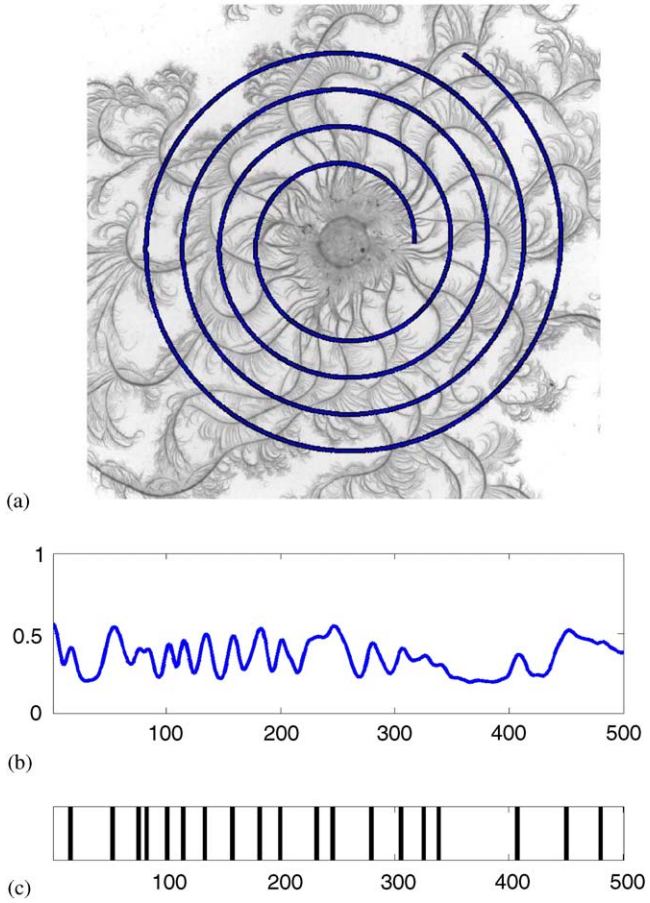

Fig. 4. Illustration of the extraction of a binary sequence from an image of a bacterial colony, (chiral in this case). First a spiral line is drawn on the grayscale image of the bacterial colony (a). Along the spiral, the gray levels (0;256) are sampled into an array, to form a continuous presentation of the variations in the bacterial densities (b). The array in (b) is then converted into a binary sequence in which "1" marks the location of each local density maximum, following appropriate coarse graining and above the noise level (c).

elsewhere), as illustrated and explained in Figs. 4 and 5. Each sequence is a binary vector of N_b elements such that: $B(l) = 1$ if the lth bin corresponds to a local maximum in the recorded bacterial density and zero otherwise. To evaluate the variations of the observed bacterial densities, we first define the intervals between the local density maxima

$$IMI(l) \equiv B(l) - B(l-1)\,. \tag{1}$$

In Fig. 6 (top) we show two examples of the probability density functions (pdf) of the IMI sequences. The following features (common also to the pdf of neuronal temporal organization) are clearly detected: (1) A minimal cutoff interval $I_{\min}$. (2) Most

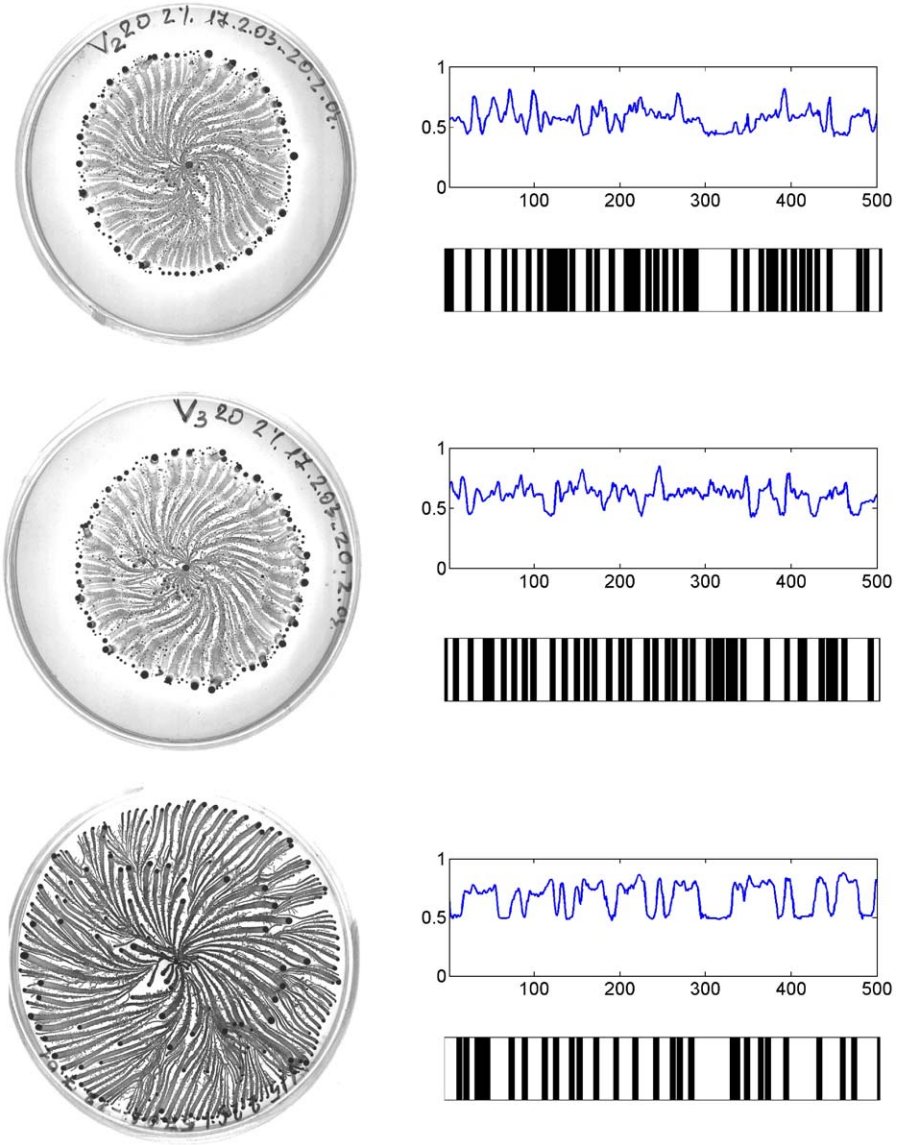

Fig. 5. Colonies of *P. vortex* bacteria and their corresponding binary sequences. The two similar-looking patterns are for growth at 20 g/l pepton level and 2% agar concentration. These patterns yielded ~ 0.75 correlation. The third pattern is for 15 g/l pepton level and 2.25% agar concentration. It yields ~ 0.25 correlation level with the other two patterns. The boxes on the right of each image show the measured bacterial densities (gray levels) along a ring at similar radii (top) and the corresponding binary sequence of the local maxima (bottom).

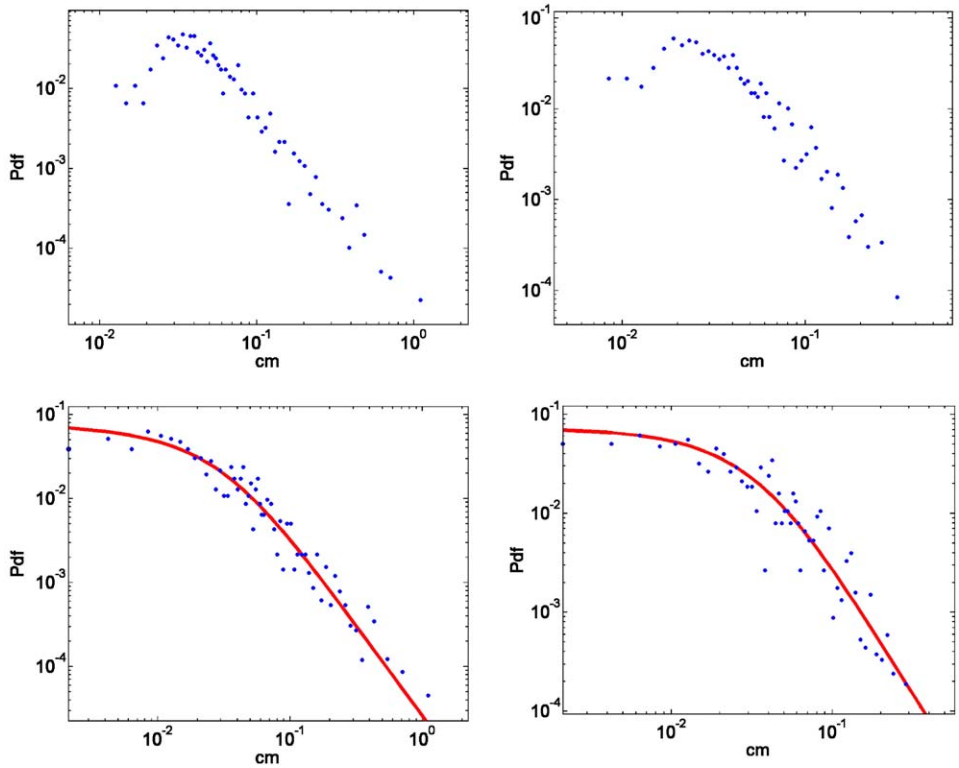

Fig. 6. Top: the pdf of the intervals sequences the chiral patterns shown in Fig. 4 (left) and the third *P. vortex* bacteria shown in Fig. 5 (right). Note that the sequences exhibit minimal interval and a most probable interval (maxima in the distribution). Bottom: The pdf of the increments are plotted with the Lévy fit (solid line) with parameters: $\alpha = 1.07$ and $\gamma = 12$ (chiral) and $\alpha = 1.60$ and $\gamma = 18$ (vortex).

probable interval I_{peak}, which marks the maximum of the pdf. (3) An average interval I_{av}, which is larger than I_{peak}. (4) Long (algebraic) tail. The intervals distributions can be fitted with the positive side of (non-symmetric or shifted) Lévy distributions, since the intervals are positive. In order to extract information about the sequences directionality (the colonial outward development) and organizational motives below I_{av}, we evaluate the corresponding sequence of increments of IMI by defining

$$\Delta(l) \equiv IMI(l) - IMI(l-1)\,. \tag{2}$$

We discovered that the probability density functions of the increment sequences, Δ, for different bacterial strains, e.g. the chiral patterns (Fig. 2) and the vortex organization (Fig. 5), are well fitted with the symmetric Lévy distribution, as is shown in Fig. 6 (bottom). We propose, that the sequences Δ of intervals and increments can be utilized as quantified observables associated with the notion of "regulated freedom", motivated by the argumentations presented next.

The symmetric Lévy distributions are characterized by two parameters: The index of stability α subjected to the range $0 < \alpha \leqslant 2$ that describes the slope of the scale-free (algebraic) tail part (the slope is $-(1+\alpha)$), and a scale factor $\gamma \geqslant 0$ that determines the location of the bending point (defined as the location at which the pdf is 0.5 of the maximal value). The general form of $P_{\alpha,\gamma}(x)$ is given by

$$P_{\alpha,\gamma}(x) = \frac{1}{\pi}\int_0^\infty \exp(-\gamma q^\alpha)\cos(xq)\,\mathrm{d}q\ . \tag{3}$$

Two special limits of the symmetric Lévy distribution are:

1. The Cauchy limit for α=1, in which the distribution converges to

$$P_{1,\gamma}(x) = \frac{\gamma}{\pi(\gamma^2 + x^2)}\ . \tag{4}$$

2. The Gaussian limit for $\alpha = 2$, in which the distribution becomes an exponentially decaying Gaussian and loses its scale-free properties. For the range $1 < \alpha < 2$, the first moment of the distribution (we consider $0 \leqslant x < \infty$) is bounded, and all higher moments are unbounded. For $\alpha < 1$, the first moment is also unbounded. In this regard, the asymmetry in the first moment between positive and negative increments represents additional features related to the sequence directionality.

It has been shown that the increments of the intervals of biotic time series are well fitted with the Lévy distribution [25]. In the context of neuronal activity, we have shown that both the increments of the neuronal inter-firing intervals (on the neuronal level) and the increments of the inter-burst intervals (on the whole network level) are well fitted with symmetric Lévy distributions over many decades in time. The long tail (α) is a manifestation of the "freedom" in the biotic behavior as it corresponds to scale free regime or "freedom" in scale adjustment. Deviations in the long tail between the pdf of the intervals and of the increments are associated with hierarchical organization, while the changes in γ are associated with regulation. In the context of the colonial pattern, it represents the colonial "regulation" in the self-organization of branches ordering. Thus, the Lévy distributions in the increments of the intervals together with the intervals pdfs directly illustrate both the notion of regulation (γ) and of freedom (α), with smaller α being related to an enhanced "freedom" and smaller γ to a more strict "regulation". The Cauchy limit of $\alpha = 1$ represents the limit of co-enhancement of regulation and freedom. Thus, in this limit, the colonial structure has higher flexibility for better colonial adaptibility. Additional manifestation of the above is provided by the increase in α with a decrease in γ (reduced freedom and elevated regulation) in response to imposed antibiotic stress (Fig. 7). Exposing the bacteria to chemical agents that temper with communication leads to increase in γ (lower regulation) (Fig. 7).

To quantify the similarity between two observed patterns, say nth and mth, a direct approach is to evaluate the cross-correlations between the vectors of the measured bacterial densities (following an appropriate deconvolution of the background noise). Alternatively, one can evaluate the cross-correlation $C(n,m)$ between the two

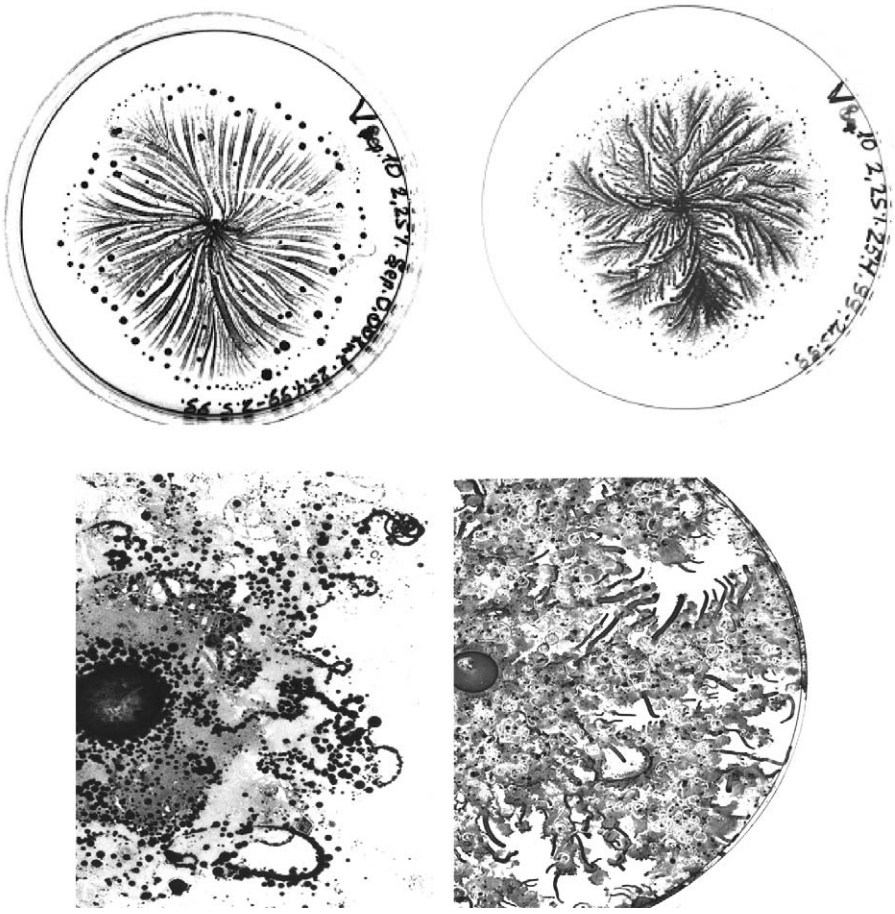

Fig. 7. Top right: normal growth of *P. vortex*. Top left: the effect of exposure to antibiotics that possess stress (for further details refer to Ref. [2]). This exposure results in an increase in α (reduced freedom) and a decrease in γ (higher regulation) for better response to the induced stress. Thus, the original low α and high γ afford the colony with the required flexibility to produce such responses. Bottom patterns illustrate the effect of reduction of bacterial communication via chemical agents, antibiotics (right) and chemotherapeutic material (left).

corresponding sequences of the intervals or the increments using the standard definition

$$C_{n,m}(l) \equiv \frac{\sum_{l'=1}^{N_b} [\Delta_n(l') - \langle \Delta_n \rangle][\Delta_m(l'-l) - \langle \Delta_m \rangle]}{\sqrt{\sum_{l'} [\Delta_n(l') - \langle \Delta_n \rangle]^2} \sqrt{\sum_{l'} [\Delta_m(l') - \langle \Delta_m \rangle]^2}} \,. \tag{5}$$

For illustration, the direct inter-patterns correlation between *P. vortex* colonies grown under the same growth conditions (Fig. 5) is about 0.75, while the correlation between colonies, grown under different growth conditions, is about 0.25.

5. Can bacterial "decision-making" co-exist with time causality?

Semantic (meaningful) bacterial communication can be understood as bacterial self-interpretation of chemical messages [2,6], that is, the internal ability of the receiving cell to assign its own interpreted meaning to the message. The self-interpretation is not strict, neither it is entirely arbitrary. Instead, the cell has regulated freedom to assign meaning from a bounded range of possible meanings (which can vary over longer times). It does so according to both its internally, stored, pre-acquired knowledge and its present circumstances [2]. The self-interpretation (i.e., meaningful and operational), is reflected in a response selected in accordance with it; the response is not pre-determined. Next, we shortly discuss the features required for such bacterial regulated freedom in "decision-making".

From physics and chemistry perspective, each bacterium is an open system with a complex and flexible internal structure of the intracellular gel, which is composed of $\sim 10^{11}$ interacting macromolecules [14]. External stimuli (received chemical messages) cause changes in the internal structure and the consequent dynamical behavior of this system, which can be unpredictable to us, external observers.

Our inability to predict the changes does not imply that they result from "decision-making". After all, unpredicted response to stimuli is also expected in the case of a complex "soup" of polymers of unknown composition, yet it will not be termed "decision-making" of the "soup".

Thus, "decision-making" capabilities in bacteria require that their intracellular biochemical gel qualitatively differ from an artificially made "soup" of polymers and proteins. The dilemma of "decision-making" is not limited to bacteria, but is valid to any living organism including humans, and is directly associated with the fundamental question of the distinction between inanimate and living systems. It is just best reflected and sharpened in the case of bacteria—which are the simplest organisms. Returning to the physics perspective, many might say that the dilemma simply does not exist. It is argued that even in the case of human beings, freedom of choice is a mere illusion of underlying pathways leading to an automatic and in principle-predetermined responses. This point of view stems from the fact that "decision-making" is perceived as "free will", which is in contradiction with the fundamental principle of time causality.

6. Concluding remarks: the possible role of the intracellular biochemical gel

The natural immediate reaction to the apparent difficulty with the notion of bacterial "decision-making" is to assume that the proposed interpretations of the observed phenomena are simply wrong and misleading. However, the recent advancements in understanding biotic and abiotic self-organization bear a promise to resolve this apparent difficulty [2]. We specifically propose that these developments provide a new perspective on the cells internal biochemical gel. This gel is a web, composed of $\sim 10^{11}$ interacting macromolecules (polymers and proteins), each with its own internal structure that can assume many different possible states [14]. Consequently, the gel itself is a self-organizing web with high plasticity. It continuously re-organizes itself and its

composition in response to external stimuli (received chemical messages) together with the information stored in its own organizational state and the information stored in the DNA. This picture implies that the gel of interacting macromolecules together with the DNA possess informatics capabilities. If this is correct, the intracellular biochemical gel can provide the features required to sustain bacterial regulated freedom of response.

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