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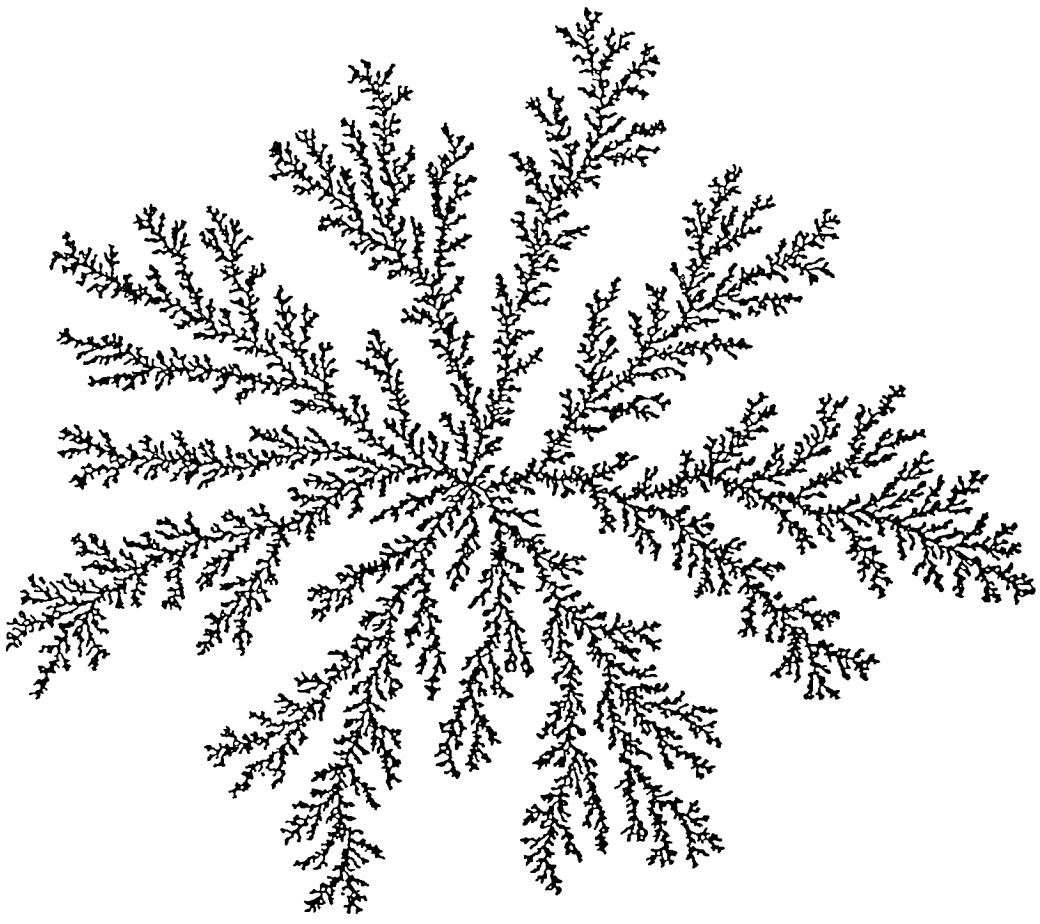

DLA fractal cluster
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FRACTAL PATTERNS AND COMPLEXITY DURING DIFFUSIVE GROWTH OF BACTERIAL COLONIES

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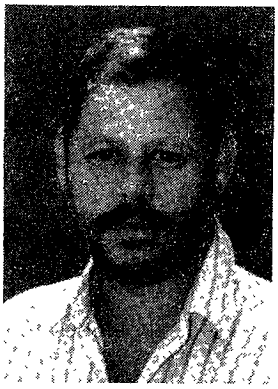

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1. INTRODUCTION

Discovering how patterns emerge spontaneously from orderless and homogeneous environment has been a challenge to researchers in the natural sciences throughout the ages (Kepler, 1611; D'Arcy Thompson, 1964). Is the diversity of patterns found in nature a result of different causes and effects, or is there a unifying picture in which they all share the same underlying principles? Only during the last decade has a satisfying answer started to evolve (Kessler *et al.*, 1988; Langer, 1989; Ben-Jacob and Garik, 1990; Müller-Krumbhaar and Kurz, 1991; Brener and Melnikov, 1991; Ben-Jacob, in press; Ben-Jacob, Kupferman *et al.* 1993). These exciting new developments in the understanding of pattern determination in nature offer the promise that a unified theoretical framework is at hand, one which would also include processes in living systems (Ben-Jacob *et al.*, 1992; Ben-Jacob, Avidan *et al.*, 1994).

The most challenging evolving systems a scientist can investigate are those of living organisms. A biological system is in constant flux relative to the environment as it regulates its growth and survival. The energy balances at the cellular level involve a complicated interplay between the microscopic dynamics and the macroscopic environment, through which life at the intermediate mesoscopic scale (Ablrecht-

Buehler, 1990) is maintained. The development of a multicellular structure, requires nonequilibrium dynamics, as microscopic imbalances are translated into the macroscopic gradients which control collective action and growth (Pelce and Pocheau, 1992; Pelce and Sun, preprint). Much effort is devoted to the search for basic principles of growth (communication, regulation, and control) at the cellular and multicellular levels (Shapiro and Trubatch, 1991; Shapiro, 1988; Rosenberg, 1984; Kessler and Levine, 1993; Haken, 1988; Nicolis and Prigogine, 1989; Wiener, 1948). As in any new field, the first hurdle is to identify problems which are sufficiently simple, so that research can progress, but also well-motivated by the implications of their solutions.

For reasons to be clarified below, we have chosen to study complex patterning of bacterial colonies during growth under adverse conditions. Typically, bacterial colonies are grown on substrates with a high level of nutrient and intermediate agar concentration. Under such 'friendly' conditions, the colonies develop simple (almost structureless) compact patterns with smooth envelope. This behavior fits well the contemporary view of the bacterial colonies as a collection of independent unicellular organisms (or non-interacting 'particles' using terminology borrowed from physics). However, in nature, bacterial colonies regularly have to cope with hostile environmental conditions (Stainer *et al.*, 1957). What will happen if we try to simulate such adverse growth conditions in a petri dish, say, by using very low level of nutrients or a hard surface (high concentration of agar), or both? The bacteria reproduction rate, which determines the growth rate of the colony, is limited by the level of nutrients concentration available for the bacteria. The latter is limited by the diffusion of nutrients towards the colony (for the appropriate adverse conditions as is explained below). Hence, the growth of colony seems to be similar to diffusion limited growth in azoic systems, such as solidification from a supersaturated solution, growth in Hele-Shaw cell, electrochemical deposition etc. (Ben-Jacob, and Garik, 1990). From the study of diffusive patterning in azoic systems, we understand that the diffusion field drives the system towards decorated (on many length scales) irregular fractal shapes. Moreover, we now understand the competition between the action of the diffusion field and that of the microscopic effects (surface tension and surface kinetics) in the determination of the evolved pattern (Kessler *et al.*, 1988; Langer, 1989; Ben-Jacob and Garik, 1990; Müller-Krumbhaar and Kurz, 1991; Brener and Melnikov, 1991; Ben-Jacob, in press; Ben-Jacob, Kupferman *et al.*, 1993). The microscopic effects, when present, compete with and channel the diffusive instability towards regular and less decorated structures. Generally speaking, the morphology changes from fractal-like (Vicsek, 1989; Feder, 1988), when the diffusive instability dominates the growth, to compact patterns (Eden, 1961) when the diffusive instability is weaker than the action of the microscopic effects.

In view of the above, one would naively expect that whenever bacterial colonies are grown on very low-nutrient agar (diffusion limited) it will lead to a branching growth (instead of compact) so it will be easier for the colony to reach out for food. Indeed, bacterial colonies can develop patterns reminiscent of those observed during growth in azoic systems (Fujikawa and Matsushita, 1989; Matsushita and Fujikawa, 1990; Matsushita *et al.*, 1993; Ben-Jacob *et al.*, 1990; Ben-Jacob *et al.*, in press, Ben-Jacob *et al.*, 1992; Ben-Jacob, Avidan et al., 1993; Ben-Jacob, Avidan *et al.*, 1994; Ben-Jacob, Tenenbaum et al., 1993), such as solidification from supersaturated solution, liquid-crystal solidification, electrochemical deposition etc., (Ben-

Jacob and Garik, 1990). One wonders, whether complex patterning of bacterial colonies is simply an additional example (albeit more involved) of spontaneous emergence of patterns that may be explained according to the theory of patterning in azoic systems, or is this theory merely the key to a new understanding required for biological systems.

We will show that comparison of the behavior in the two worlds will enable us to identify both the common principles and the additional features of the bacterial colonies. As we demonstrate, growth of bacterial colony presents an inherent additional level of complexity compared to azoic systems. In the former case the building blocks themselves are living systems; each having its own autonomous (at times 'selfish') self-interest and internal degrees of freedom. At the same time, efficient adaptation of the colony to adverse growth conditions requires self-organization on all levels – which can be achieved only via cooperative behavior of the bacteria. It can be viewed as the action of a singular interplay (Ben-Jacob *et al.*, 1992; Ben-Jacob, Avidan *et al.*, 1994; Ben-Jacob, Tenenbaum *et al.*, 1993) (singular perturbation or regulation and singular feedback or control) between the micro-level (the individual bacterium) and the macro-level (the colony) in the determination of the emerging pattern. In general, for more adverse growth conditions we observe a more complex global structure together with a higher micro-level organization.

To do so, the bacteria have developed sophisticated communication channels on all levels (Stainer *et al.*, 1957; Sar *et al.*, 1990; Adler, 1973; Silverman and Simon, 1977; Tso and Adler, 1974; Budrene and Berg, 1991; Devreotes, 1989; Lackiie, 1981; Devreotes and Zigmond, 1988); from direct (by contact) bacterium-bacterium physical interaction and chemical interaction, through indirect physical and chemical interactions via marks left on the agar surface and chemical (chemotactic) signaling, to genetic communication via exchange of genetic materials. The communication enables each bacterium to be both actor and spectator (using Bohr's expressions) during the complex patterning. In the azoic world, we are used to the particles-waves duality. The bacteria developed a particle-field duality: each of the bacterium is a localized (moving) particle which can produce a chemical and physical field around itself. For researchers in the pattern formation field, the above communication regulation and control mechanism opens a new class of tantalizing complex models which exhibit a much richer spectrum of patterns than the models for azoic systems.

Here we present a communicating walkers model (Ben-Jacob, Vicsek *et al.*, 1993) to study the effect of local bacterium-bacterium interaction. We will demonstrate how communication enables the colony to develop complex patterns in adaptation to adverse growth conditions. This model represents a generic modeling approach which is similar in spirit to the model proposed by Kessler and Levine (1993) to describe aggregation of *Dictyostelium* and Kessler's approach (1985) in the study of 'microbial convection pattern'.

An additional inherent level of complexity, in comparison with azoic systems, which we do not discuss here, is the potential of the individual bacterium to perform inheritable genetic metamorphosis in response to the growth conditions (Ben-Jacob *et al.*, 1992; Ben-Jacob, Avidan *et al.*, 1994; Ben-Jacob, Tenenbaum *et al.*, 1993). Indeed, as the bacteria are exposed to more adverse growth conditions, new modes (mutations) with more sophisticated communication strategies which

enable more complex behavior were observed. Hence, pattern selection during complex patterning is directly related to the issue of genome cybernetics, as the colony organization (being the environment) can directly affect the genetic metamorphosis of the individual and vice-versa (Ben-Jacob *et al.*, 1992; Ben-Jacob, Avidan *et al.*, 1994; Ben-Jacob, Avidan *et al.*, 1993).

2. BRANCHING GROWTH

We have chosen to start our experimental endeavor with *Bacillus subtilis* 168 which is not a wild type strain. We have grown bacterial colonies under adverse growth conditions, using standard petri dishes covered with a thin layer of substrate (12 *ml*). The growth conditions varied from extremely poor level of nutrient (0.1 gram pepton per liter) to a rich mixture of 10 *g/l*, and from soft substrate (about 1 per cent agar concentration ≅ 1 gram per 100*ml*) to a very hard substrate (4 per cent). When the colonies were grown on rich substrate, simple compact structures evolved as expected. Next, we inoculated the colonies on poor agar, expecting to observe branching growth. Surprisingly, the experiments yielded different results. Compact patterns with rough interface were observed. More adverse growth conditions led to a stronger roughening and more complex micro-level organization. But the overall structure remained compact. This growth form is described in detail in (Ben-Jacob, Avidan, *et al.* 1994; and Ben-Jacob, Shochet *et al.*, 1994).

Seeking experimental answers to the above questions, Ben-Jacob *et al.* (in press, 1992, and Avidan 1993, 1994, 1990) have performed experiments in which numerous numbers of colonies of the *Bacillus subtilis* 168 were grown under a wide range of adverse conditions. Occasionally, bursts of spectacular new modes of growth exhibiting branching patterns were observed. This new branching modes are inheritable, i.e. inoculation of bacteria (and even single bacterium after dilution in liquid) from the new bursting mode leads again to a branching colony. The latter propagates much faster than the original *Bacillus subtilis* 168 colonies. Hence the bacteria are 'smart' enough to develop a new strategy, via genetic change, for better adaptation to the environment.

The new branching mode can adopt various shapes as the growth conditions are varied. In Figure 1 we present the typical patterns which are observed as the level of pepton is decreased. In general, the patterns are compact for high pepton (Fig. 1d) levels and become more ramified (fractal like) at low levels (Fig. 1a and Fig. 2). Surprisingly, at even lower pepton levels (below 0.25 *g/l* and not shown in the figures), the colonies again adopt a more organized (well defined circular envelope) structures. This feature is due to chemotaxis (Ben-Jacob, Vicsek *et al.*, 1993) and shall not be discussed here.

Microscope studies reveal that the bacteria perform a random walk like movement within a well defined envelope. The latter is formed by chemicals which are excreted by the bacteria and/or by fluid drawn by the bacteria from the agar. The envelope slowly propagates as the bacteria collide with it. Many collisions are required for the envelope to move. At very low pepton levels, the bacteria density is very low – the distance between the bacteria being up to several times the size of individual bacterium. In this range, the bacteria are longer (about 5 μm in length)

and the movement seems to be more organized. At high agar concentration there is a boundary layer of high bacteria density at the leading tips of the growing branches. In this range the colonies also have a pronounced structure in the perpendicular direction.

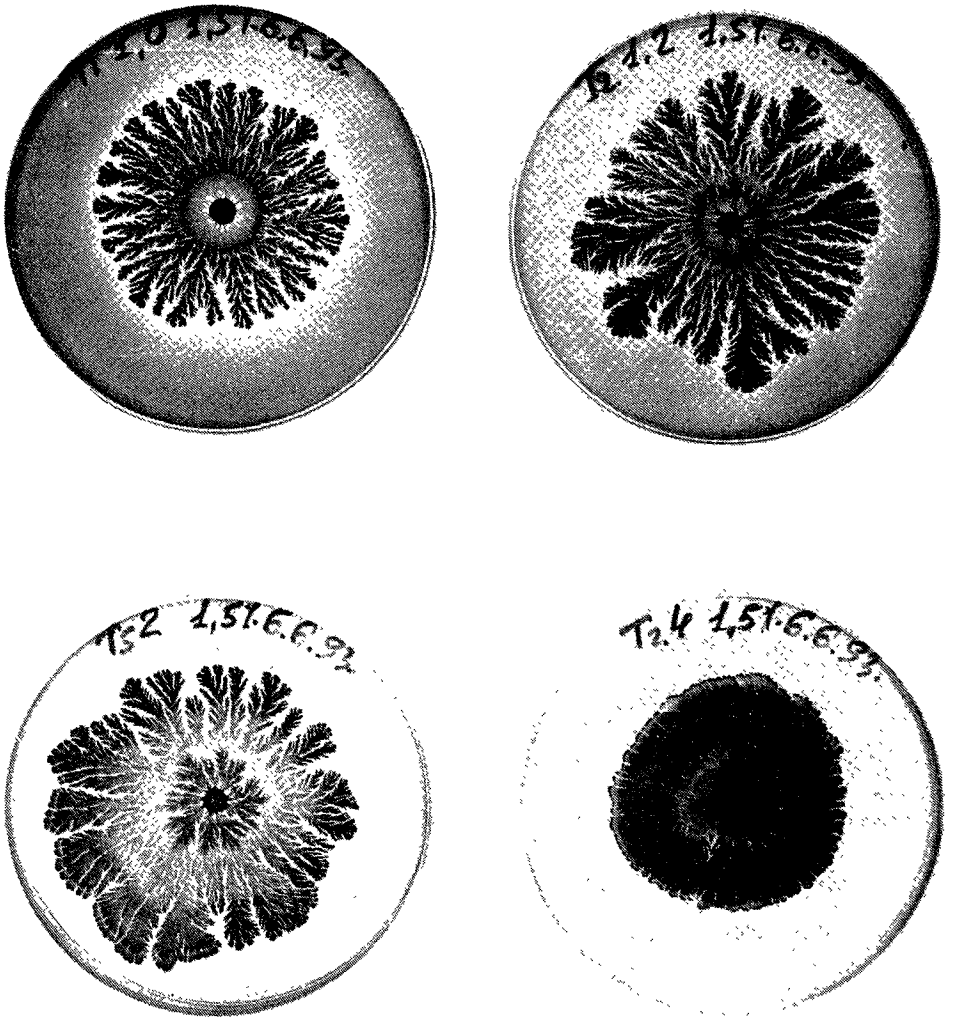

Figure 1: Observed patterns of phase T grown on 1.5 per cent agar concentration. The pepton level is 1*g/l*, 1.2*g/l*, 2*g/l*, and 4*g/l* for (a), (b) (c) and (d) respectively. At high pepton level the branches are wide, the pattern is very reminiscent of Hele-Shaw patterns (Ben-Jacob and Garik, 1990) and the fractal dimension is close to two. As the pepton level is decreased, the patterns become more ramified similar to DLA simulations.

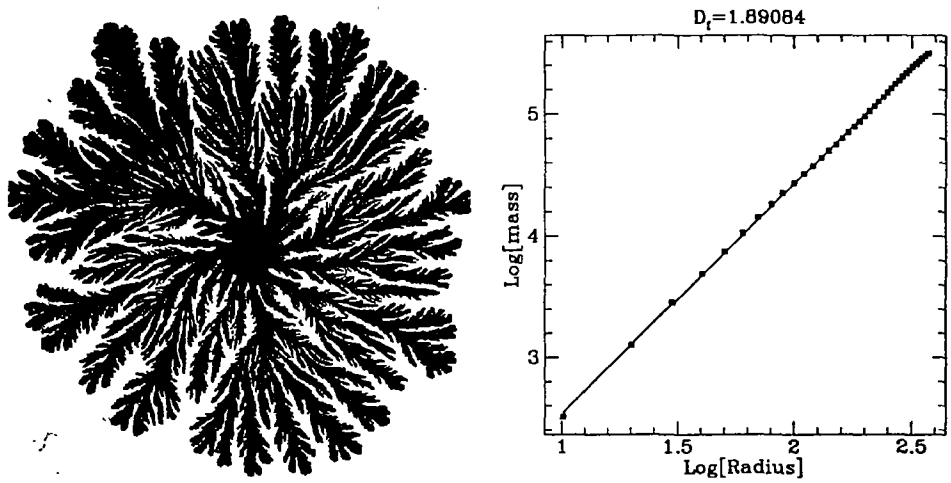

Figure 2: A typical tip-splitting growth and its fractal dimension. In order to perform this calculation, the bacterial colony shape was digitized. The fractal dimension, D_f, is defined such that $m \sim r^{D_f}$, where m is the mass of the cluster whose distance from the center of the colony is less than r. The fractal dimension was measured using Log-Log plot of the mass distribution *vs.* cluster radius.

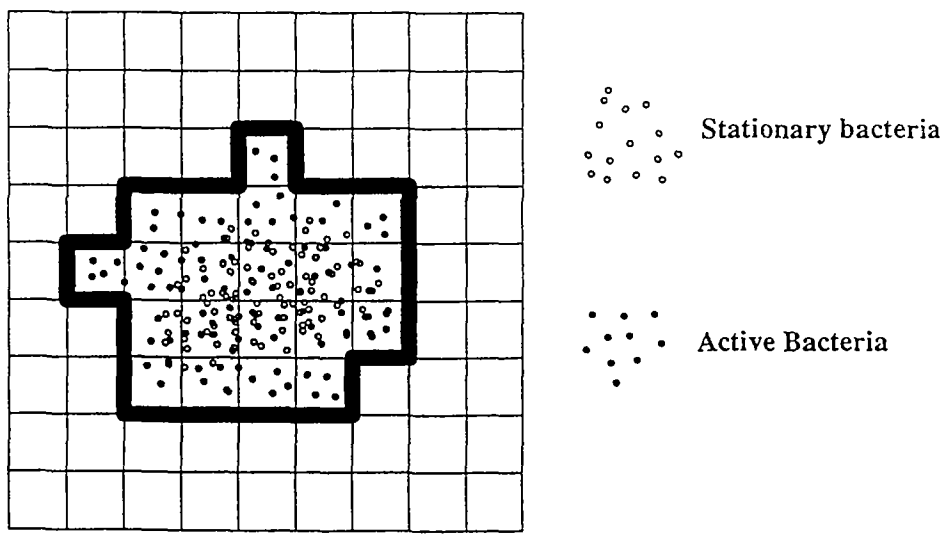

Figure 3: Schematic illustration of the 'communicating walkers' model. The active walkers are moving within a well defined envelope. The envelope moves after a walker try to cross into a nearest cell N_c times. The food concentration obeys a diffusion equation and is solved numerically on the same lattice. A triangular lattice was used for the simulations.

3. THE 'COMMUNICATING WALKERS' MODEL

To model the growth we include the following generic features: (1) Nutrients diffusion. (2) Movement of the bacteria. (3) Reproduction and sporulation. (4) Local communication. Nutrients diffusion is handled by solving the diffusion equation for the nutrients concentration c on a triangular lattice. The bacteria are represented by walkers, each of which should be viewed as a mesoscopic unit (coarse graining of the colony) and not as an individual bacterium. The model is drawn schematically in Figure 3.

Each walker is described by its location r_i and an internal degree of freedom ('internal energy' W_i), which affects its activity. The walker looses 'internal energy' at a rate e. To increase the internal energy it consumes nutrients at a fixed rate cr, if sufficient food is available. Otherwise, it consumes the available amount. When there is not enough food for an interval of time (causing W_i to drop to zero), the walker becomes stationary (sporulation). When food is sufficient W_i increases, and when it reaches some threshold tr, the walker divides into two (reproduction).

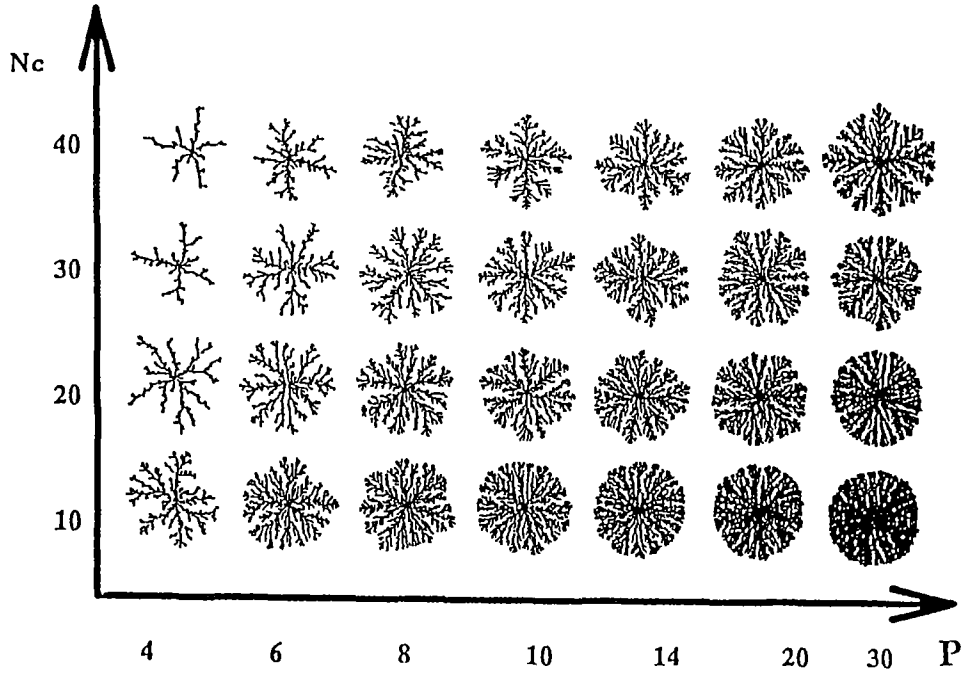

Figure 4: Morphology diagram of the 'communication walkers' model. $D = 1.4$, $dt = 0.4$ $dx = 1$, food consumption per second = 0.04, divide at threshold = 1.0, maximal jump for a walker = 0.2, $e = 0.2$, initial radius of colony = 3, initial number of walkers = 20. In the late stage growth the number of walkers is about 10^5. P (represents the pepton level) is the initial concentration measured in units of the threshold.

The walkers perform off lattice random walk within a well defined envelope (defined on the triangular lattice). Each segment of the envelope moves after it has been hit N_c times by the walkers. This requirement represents the local communication or cooperation in the behavior of the bacteria. Note that, to a first approximation, the level of N_c represents the agar concentration, as more 'collisions' are needed to push the envelope on a harder substrate. More details are presented in (Ben-Jacob, Vicsek *et al.*, 1993).

A typical morphology diagram produced by the communicating walkers model is shown in Figure 4. As in the growth of bacterial colonies, the patterns are compact at high pepton levels and become more ramified with decreasing the food level. For a given pepton level, the patterns are more ramified as the agar concentration increases. In Figure 5 we show the growth velocities, and the fractal dimensions as function of pepton level. Although the growth is limited by diffusion of nutrients,

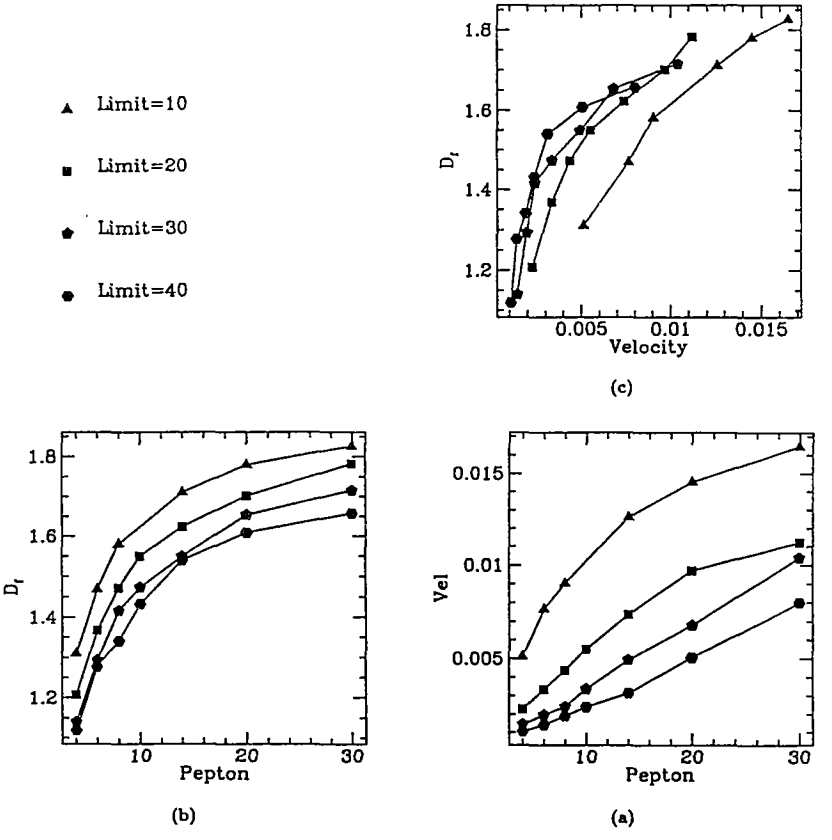

Figure 5. (a) Growth velocity versus food concentration for different N_c. The velocity increases as more food is available for the walkers. As N_c increases, it is harder for the colony to advance and the growth velocity decreases. In all cases the velocity appears to be a smooth function of the growth parameters. (b) The fractal dimension (of mass distribution) versus food concentration for different N_c. The patterns are more compact for high pepton level. (c) The fractal dimension versus growth velocity. A high correlation is observed between these two observable.

the fractal dimension becomes lower then the DLA fractal dimension (Vicsek, 1989; Sander, 1986; Witten and Sander, 1986; Meakin, 1983) at low nutrients. It results from the fact that the local communication we have introduced acts both as surface tension and surface kinetics. It also introduces a nontrivial dependence of the interface motion on the gradient of the diffusion field. The latter is similar to the case of dielectric breakdown (Nittman, Daccord, and Stanley, 1985) and Hele-Shaw cell with non-Newtonian fluids (Niemeyer, Pietronero, and Weismann, 1984).

3.1 Comment about modeling

How should we approach the modeling of the bacterial colonies patterning? One extreme approach would be to devise a set of computer rules which will mimic the observed patterns. Doing so does not reveal (directly) the biological functions and behavior. It does reflect though understanding of the geometrical nature of the patterns, which indirectly might help in revealing the biological functions. Another approach would be to simply construct an algorithm which includes the known biological facts about the system. Such an approach sets a trajectory of ever including more and more details. The model keeps evolving to include so many parameters that it looses any predictability power.

Here we try to promote a different approach – one which is based on generic modeling (Kessler and Levine, 1993; Azbel, 1993; Parnas and Segel, 1977 and 1978; Mackay, 1978). In this approach we seek to reveal the generic features and the basic principles in order to explain the biological behavior. For example, here we studied the effect of local communication versus the effect of nonlocal communication, in order to find out whether the nonlocal communication (such as chemotaxis) is essential for explaining the observed patterns irrespective of the exact details. We believe that generic modeling along with a close comparison of experimental observations will promote the development of a new understanding of biological systems. In other words, generic modeling is not using sophisticated (as it may) mathematical description to dress pre-existing understanding of the biological behavior. Rather, it means a cooperative approach, using existing biological knowledge and understanding together with mathematical tools and synergetic point of view for evolving complex systems to reach new understanding (which will be reflected in the model). Naturally, such an approach, in order to be efficient, calls for interdisciplinary collaboration of biologists, chemists, physicists and mathematicians.

4. CHIRAL GROWTH

Assume we expose the bacteria to a low level of nutrients on soft agar (easier mobility). Can we envision a more sophisticated tactics that will benefit from the easier mobility? Using the settlers metaphor, they are now facing soil that is poor but easy to move on. Hence, it is now possible to send forward small groups for fast exploration of further territories, with the hope of finding better conditions ahead. But, at the same time, the rest of the group left behind should use the resources available in the empty spaces not covered by the advancing groups. It turned out that the bacteria learned to do exactly so via the chiral growth described below.

During growth of the branching mode on soft agar (about 1 per cent) bursts (inheritable) of new patterns which overgrow the branching ones are observed (Ben-Jacob *et al.*, 1992; Ben-Jacob, Avidan *et al.*, 1994). The new patterns consist of thinner branches all having the same handedness of twisting (Figs. 6 and 7). We name this type of growth chiral growth, and refer to the new inheritable phase as phase *C*. Chiral asymmetry exists in the whole range from subatomic particles to human beings, and seems to have played an important role in the evolution of living systems (Hegstrom and Kondepudi, 1990; Avetisov, Goldanskii, and Kuzmin, 1991). Hence, it is not surprising that bacteria display chiral properties. Back in the seventies, Mendelson *et al.* (1978, 1982) showed that long cells of *Bacillus subtilis* can grow in helices, in which the bacteria form long strings that are twisted around each other. These observations show that the bacteria possess chiral properties. In other observations they have shown that the chiral characteristics affect the structure of the colony. Recently we have found that chiral growth was actually reported long ago (Smith and Clark (1938; Shinn, 1938; Stainer, Doudoroff, and Adelberg, 1957).

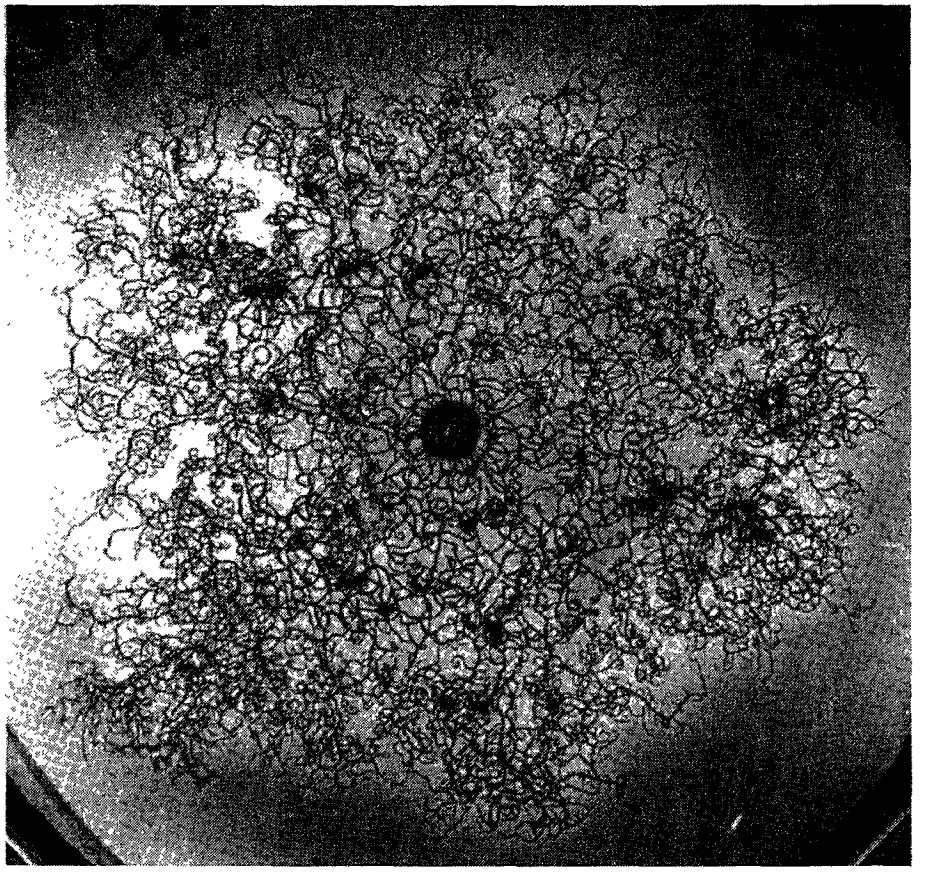

Figure 6a: Example of pattern observed during growth of phase *C* (the chiral phase).

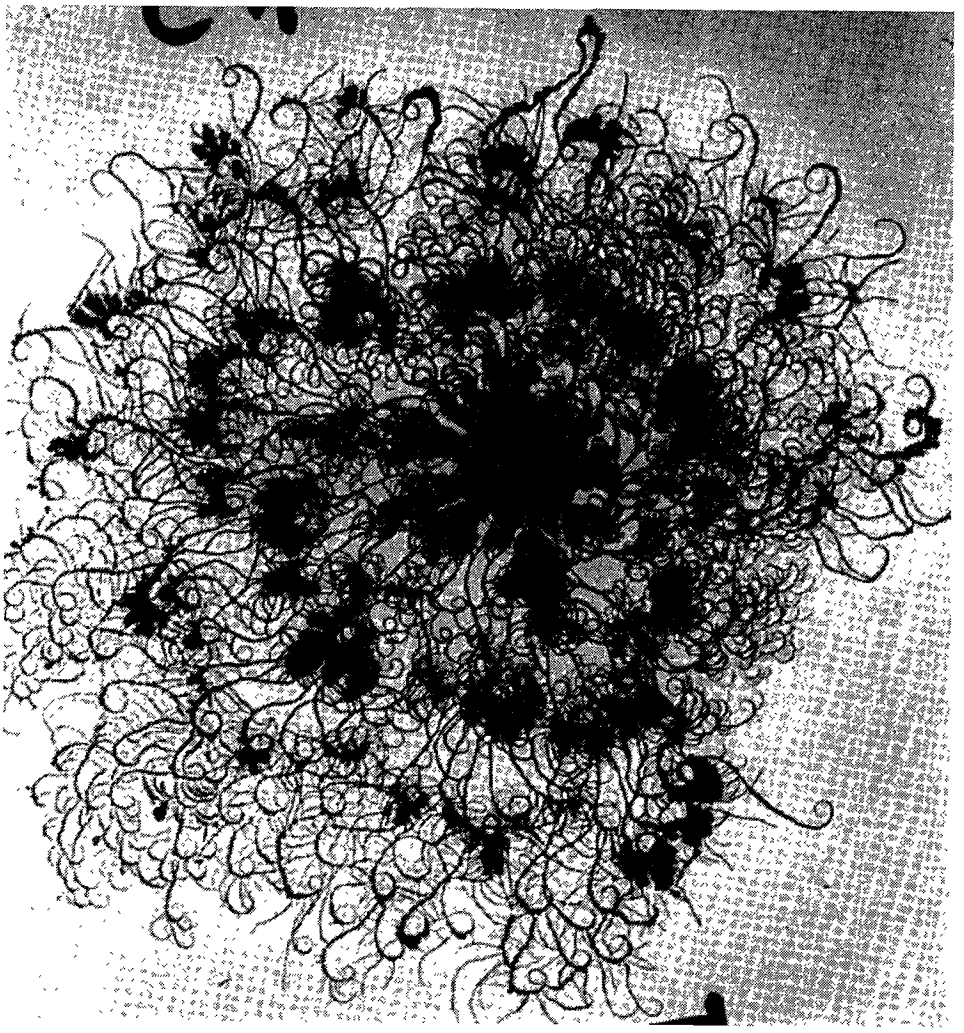

Figure 6b: Example of pattern observed during growth of phase *C* (the chiral phase).

Optical microscope observations indicate that during chiral growth the colony consists of moving bacteria. The individual bacteria are longer than those in tip-splitting growth and have a string-like shape, but the individual ones do not show chiral structure. The micro-level dynamics show a slow swarming of the long bacteria. Unlike in tip-splitting growth, the motion is coordinated. The bacteria seem to move along parallel trails following each other. For a defined handedness, the bacteria have to be able to distinguish between up and down. The growth in an upside-down petri dish shows the same chirality. Therefore, we think that the determination of up *vs.* down is done via the vertical gradient of the nutrient concentration or chemotaxis materials. Detailed more of chiral growth is presented in (Ben-Jacob *et al.*, in preparation).

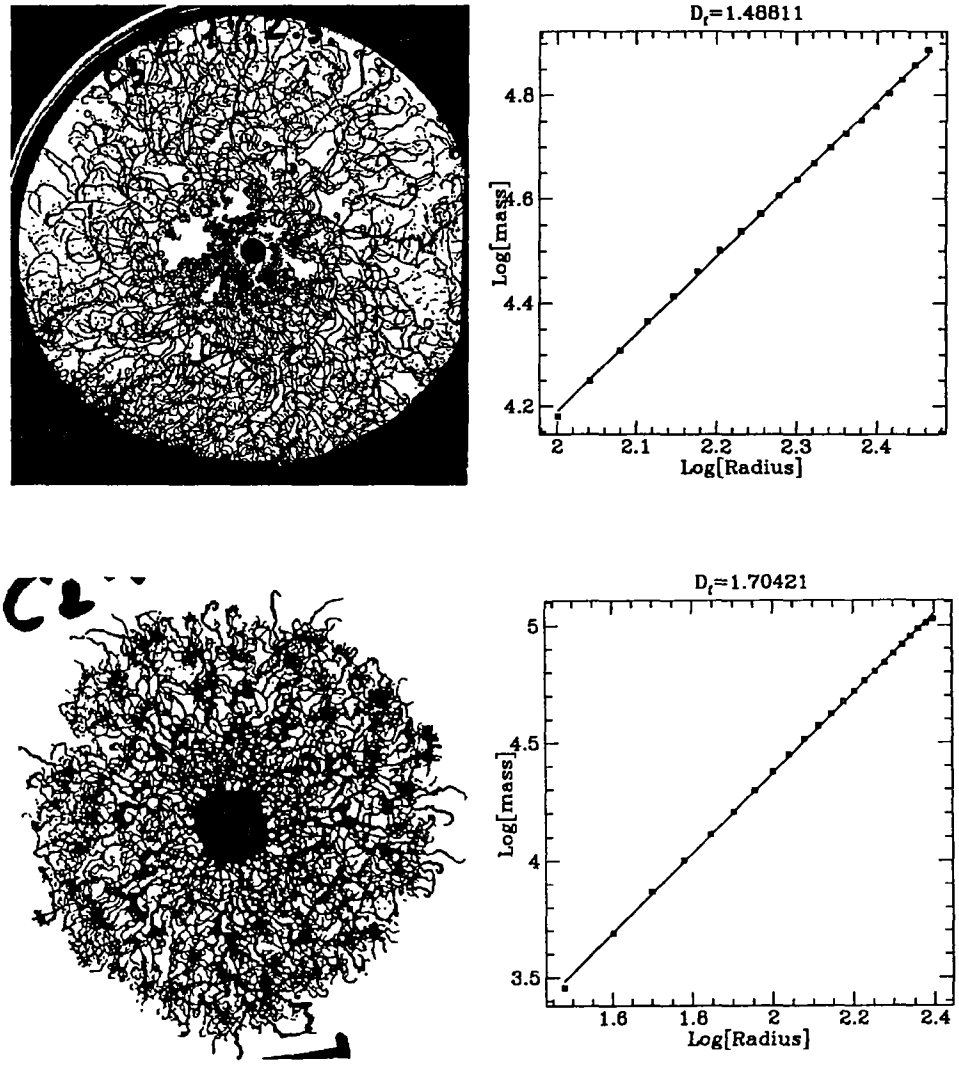

Figure 7: Measurements of the fractal dimension of the chiral growth.

5. CONCLUSIONS AND FURTHER DIRECTIONS

It is now understood that bacteria paved the way and are crucial to maintaining life on earth. Yet, the view of bacteria as unicellular microbes has persisted for generations. Recently, Shapiro (1988) has promoted the notion of 'Bacteria as multicellular organisms'. Following Shapiro, we would like to emphasize that understanding cybernetic processes (communication, regulation and control) during complex patterning of bacterial colonies can be a crucial step to understanding cybernetic

process in all organism, both within a given organism and in groups (colonies, schools and societies) of organisms.

Shapiro concluded his paper saying: "Although bacteria are tiny, they display biochemical, structural and behavioral complexities that outstrip scientific description. In keeping with the current microelectronics revolution, it may make more sense to equate their small size with sophistication rather than with simplicity. There is little reason to doubt that insight gained from studying the interactions between billions of bacteria, living together in a volume of less than a few cubic millimeters, will enhance understanding of all forms of life."

At the same time, studies of complex patterning of bacterial colonies have a lot in common with studies of diffusive patterning in azoic systems. Hence, we believe that here in the definition of complexity (Haken, 1988; Nicolis and Prigogine, 1989) lies a bridge between synergetics and complexity of azoic systems and living systems. In particular we would like to emphasize the following: In azoic systems at equilibrium we are used to view the system on two levels – the micro level and the macro level. The interplay between these levels is manifested via the introduction of the entropy as an additional variable (and a functional for isolated systems) on the macro level. The entropy is a measure of the number of possible microscopic states for a given state of the system. Hence, it can be viewed either as our lack of information about the micro-level (looking from the macro-level) or the freedom of the microdynamics for given imposed macroscopic conditions (looking from the micro-level). During the last decade we have learned that, as an azoic system is driven away from equilibrium, there is a singular interplay between the two levels which determines the self-organization of the entire system. The interplay can be viewed as balancing between the constraints that each level imposes on the other one. It is tempting to introduce the concept of complexity as a quantitative measure of the interplay. At present we lack a definition of complexity, and it is not clear that indeed such a new real variable does exist – real in the sense that a measurement of the variable can be defined. Ben-Jacob, Avidan *et al.* (1994) have argued that, to maintain singular interplay between the level of the individual bacterium and the colony, we need a regulating channel to a level below that of the individual bacterium. If correct, it implies that we need more than two levels to describe the interplay in the colony. We might use the lesson learned from the bacterial colonies as a hint for the development of the concept of complexity as a real variable for evolving azoic systems, in analogy to entropy for nonevolving processes (equilibrium).

Crossing the bridge will involve interdisciplinary activity, a level of risk and an ability to accept frustration in a way that is not faced in regular disciplinary activity. However, we hope that the potential prospects will attract many to join us in the avenues of this new scholarly endeavor.

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Equipotential lines around a charged DLA cluster, (F. Family and T. Vicsek).