Behavioral Metabolution: The Adaptive and Evolutionary Potential of Metabolism-Based Chemotaxis

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Abstract We use a minimal model of metabolism-based chemotaxis to show how a coupling between metabolism and behavior can affect evolutionary dynamics in a process we refer to as *behavioral metabolution*. This mutual influence can function as an in-the-moment, intrinsic evaluation of the adaptive value of a novel situation, such as an encounter with a compound that activates new metabolic pathways. Our model demonstrates how changes to metabolic pathways can lead to improvement of behavioral strategies, and conversely, how behavior can contribute to the exploration and fixation of new metabolic pathways. These examples indicate the potentially important role that the interplay between behavior and metabolism could have played in shaping adaptive evolution in early life and protolife. We argue that the processes illustrated by these models can be interpreted as an unorthodox instantiation of the principles of evolution by random variation and selective retention. We then discuss how the interaction between metabolism and behavior can facilitate evolution through (i) increasing exposure to environmental variation, (ii) making more likely the fixation of some beneficial metabolic pathways, (iii) providing a mechanism for in-the-moment adaptation to changes in the environment and to changes in the organization of the organism itself, and (iv) generating conditions that are conducive to speciation.

Keywords
Metabolism, adaptive behavior, autopoiesis, chemotaxis

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1 Introduction

An important set of simulation models in artificial life have focused upon (proto)metabolic, (proto)cellular systems and artificial chemistries. These models examine phenomena such as chemical and spatiotemporal self-organization and have been applied, for the most part, to questions related to the origin of life, early evolution, and the organization of life (e.g., [14, 20–22]). A second area where artificial life research has made progress is in the study of adaptive behavior through computational models

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of artificial agents. This area of research includes models of minimally cognitive systems, collective behavioral dynamics, and the study of specific neurophysiological mechanisms (see, e.g., [8, 26]). It is noteworthy, however, that there has been little study of the interaction between the chemistry of life and cognitive or adaptive behavior. In general, models that focus on the self-organization of chemical systems work with a set of fixed boundary conditions, making adaptive behavior unnecessary for system survival. And conversely, models that study behavior tend to abstract away everything except the sensory, control, and motor mechanisms.

This is, perhaps, starting to change. There has been a series of recent models that explore the interaction between processes that determine how a system is constituted (metabolism) and mechanisms through which the system influences its interaction with its environment (behavior). These models include computer simulations [16, 17, 45] as well as real chemical systems [25], and they have led to some interesting reconceptualizations: Metabolic processes can be thought of as robust or even adaptive, able to intelligently modulate behavioral strategies [17]; remarkably simple chemical reactions can perform chemotaxis [25]; and in a range of bacteria, metabolism-based behavior appears to be more common than previously thought [2]. This article continues in this effort to explore the interface between metabolism and behavior.

While the role of behavior in evolution has been a central topic in biology ever since Darwin, there have been very few attempts to systematically investigate the relevance of behavior in early evolution and the origin of life. This state of affairs is understandable, since it is only very recently that experimental evidence has shown that prebiotic protocells can indeed *behave*, i.e., move, or in some other way select their environment and/or alter their coupling with it. In this article we propose that metabolism-based behavior could have played an important evolutionary role in early life, providing protocells with an adaptive capability of seeking favorable environmental conditions. We discuss how this capability could facilitate the accumulation of novel metabolic pathways, leading potentially to more sophisticated protocells, and how the mechanisms underlying this behavior-based facilitation of evolution are so simply implemented that they could have played a role in bootstrapping genetic evolution.

We shall start by introducing some central concepts and summarizing the results of previous models on metabolism-based bacterial chemotaxis (Section 2). In Section 3, we introduce the idea of *behavioral metabolution*, illustrating some of the evolutionary possibilities of the coupling between metabolism and behavior with a computational model of protocellular metabolism-based chemotaxis. The model consists of a minimal metabolic system capable of modulating behavior by influencing the probability of flagellar rotation (as in *Escherichia coli* chemotaxis). In the first scenario we explore with the model, the incorporation of a chemical compound into metabolism qualitatively improves the chemotactic strategy. In the second, an encounter with a specific chemical compound opens up a new metabolic pathway, and the metabolism-based behavior of the organism automatically regulates chemotaxis toward the newly metabolizable resource. Both experiments illustrate the adaptive potential of metabolism-based behavior. While we make no direct claims about the likelihood of these specific events occurring, the model nevertheless allows us to elaborate, in Section 4, some principles of behavioral metabolution and discuss their application to early prebiotic evolution and subsequent evolution of chemotaxis.

2 Metabolism and Behavior: The Case of Bacterial Chemotaxis

Metabolism can be conceptualized as the far-from-thermodynamic-equilibrium organization of chemical networks that produce and sustain their components by using available energetic and material resources [22, 30, 33, 50]. There is a long tradition of investigating the origins and essence of life through the study of metabolism. Recently, some of this research has focused upon metabolism in the context of *protocells* [37].

Protocells are theoretical predecessors to cells. They are individuated, self-maintaining systems that have similarities to cells, but are much simpler—lying halfway between life and chemistry. Rarely has

the environment of these entities been considered to be controlled or selected by the protocell itself. However, recent artificial models of self-moving protocellular, autopoietic systems [18, 45, 52] and real, self-propelled chemical systems [49] suggest that even extremely simple forms of protolife may have been capable of selectively modulating their environment through behavior.

In parallel with the omission of behavior in the study of the origin of life, studies of minimal adaptive behavior have almost completely ignored the role of metabolism as sustaining or modulating behavioral patterns. Adaptive behavior is generally understood and modeled as optimizing some value function or as maintaining essential variables under viability constraints. However, there is generally no reference to the dynamics of the biological organization (e.g., metabolism) that serves as the basis of these viability constraints—see [15, 19] for a discussion. The assumption of relative independence of metabolism from behavior and vice versa is not just the case in computational modeling of the phenomena but extends to experimental science, including fields where the connection might be better established. In particular, research on bacterial chemotaxis (a paradigmatic case of minimal adaptive behavior) has long proceeded under the assumption that behavior-generating mechanisms operate in a metabolism-independent manner (i.e., while behavior subserves metabolic survival, the function of sensorimotor pathways is not influenced by short-term metabolic dynamics). This assumption can be traced back to the pioneering work of Julius Adler [1] in 1969, and has since remained almost unquestioned even in the most detailed and systematic simulation models of bacterial chemotaxis [10].

In short, Adler's work (and that of many others) helped establish a conception whereby metabolic processes just provide sufficient energy for flagellar motors and contribute to the general production of components of the chemotactic pathways but, beyond this, do not affect behavior. In this framework, chemotaxis is seen as the result of sensory transduction, the chemical "processing" of "signals" and their associated motor response, all of which operate blindly in relation to the effects of behavior on metabolism (e.g., how energetically or materially profitable an attractant is). The general assumption is that natural selection has selected the appropriate sensorimotor dynamics and the bacteria "reactively" respond to the molecules that bind to their receptors. Some experimental results do in fact support this view. For instance, some chemicals that are extensively metabolized fail to attract bacteria [1]. It has also been shown that there are mutants of *E. coli* that cease to be able to perform chemotaxis toward certain attractants but are still able to metabolize them [1]. These experiments established the idea of metabolism independence, and since then, almost all models of bacterial chemotaxis have accepted this independence as an unquestioned principle and ignored metabolism as a source of behavioral modulation.

However, recent experimental data provides counterevidence for the metabolism-independence assumption. Many bacteria display clear cases of what is called *metabolism-dependent* chemotaxis, including *E. coli* [47, 53], *Azospirillum brasilense* [3], *Rhodobacter sphaeroides* [28], and *Pseudomonas putida* [41]. Such cases have attracted renewed attention to the interplay between metabolism and behavior. Experiments have shown that nonmetabolizable structural analogues of metabolizable attractants (i.e., molecules that bind to chemoattractant receptors but are not metabolizable) do not produce a positive behavioral response in bacteria [5]. It has also been shown that inhibition of the metabolism of a chemical attractant completely abolishes chemotaxis to and only to this attractant [5]. And, in a slightly more complex scenario, when a sufficient quantity of a metabolizable compound is present in the environment, bacteria cease to be attracted to other attractants [5]. The most-studied cases of metabolism-dependent chemotaxis are those concerning energy-taxis, which involve the modulation of behavior in a manner that is sensitive to the energetic needs of the bacteria [3, 51]. The mechanisms involved are not yet completely understood, but sensitivities to electron transport processes in the membrane seem to be involved [2, 4]; other cases of metabolism-dependent chemotaxis have not yet been explained in terms of their underlying mechanisms.

Given that the mechanistic details of metabolism-dependent chemotaxis are still unknown and are expected to be rather sophisticated, we proposed a basic model of chemotaxis that does not include even the need for specific transmembrane receptors [17]. In what we call "metabolism-based chemotaxis," flagellar rotation is directly influenced by the concentration of a metabolite, so that

tumbling probability is directly modulated by metabolism. Figure 1 illustrates the three different types of relationship between metabolism and chemotaxis that we have mentioned: *metabolism-independent* chemotaxis (long thought to be the default case); *metabolism-dependent* chemotaxis, where different aspects of metabolic dynamics (e.g., in the electron transport system) modulate existing sensorimotor pathways; and *metabolism-based* chemotaxis, where metabolites directly modulate motor activity (see [17] for a more detailed discussion of these three relationships between metabolism and chemotaxis).

2.1 A Minimal Model of Metabolism-Based Chemotaxis

Many bacteria use a combination of directed, *running* motion with occasional periods of random reorientation (known as *tumbling*) to accomplish motion that is stochastic but, if modulated appropriately, can result in a statistical movement up or down a chemical gradient. In [17], we demonstrated how a simple *selective stopping* behavior can be accomplished by direct modulation of the probability of tumbling by metabolism, an example of metabolism-based chemotaxis. To accomplish this, we simulated a *core metabolism*, modeled as a simple autocatalytic cycle that feeds on a high-energy nutrient E and a *material* nutrient M. The metabolic product, C, is an unstable autocatalyst, in that it catalyzes its own production from resources M and E, but also decays relatively rapidly (for a discussion of the motivations underlying the design of this minimal metabolism see [17]). The concentration of C influences the probability of switching from running to tumbling behavior (see Figure 2). The default mode of behavior is running with a very small background probability of tumbling (i.e., of changing direction). Upon the increased

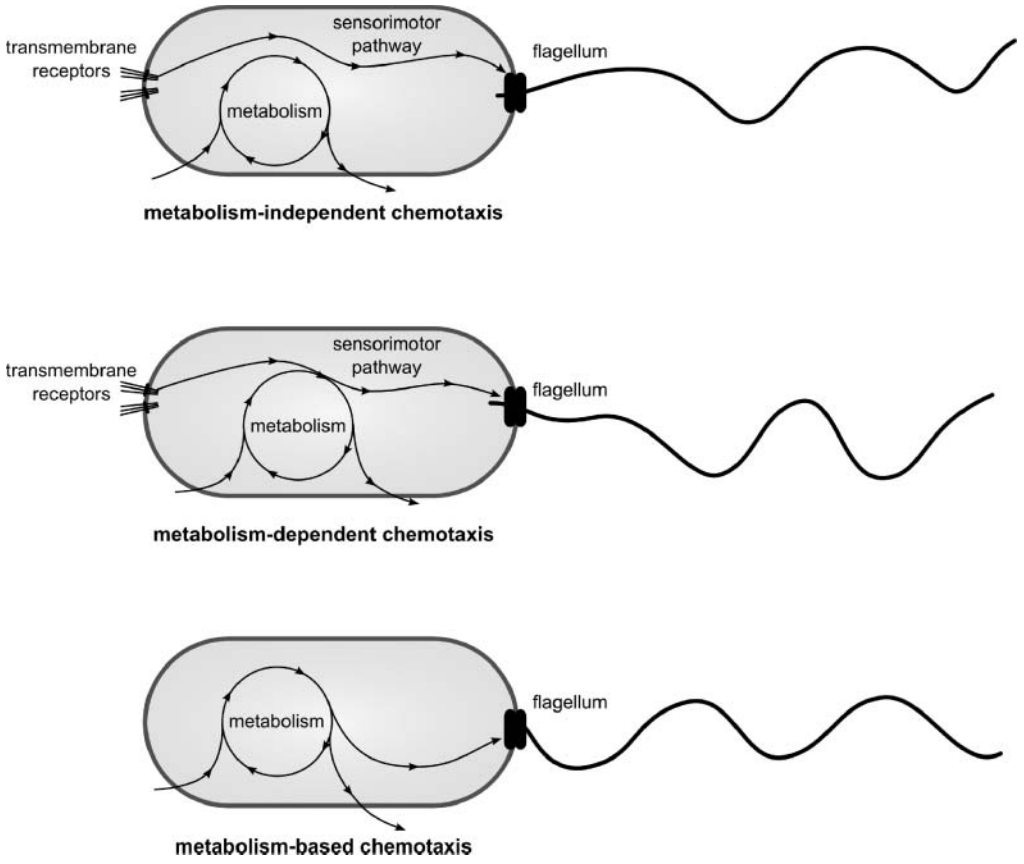

Figure 1. Three different relationships between metabolism and chemotaxis. Arrows indicate only short-term dynamic influence between processes. See text for details. Copyright 2010, Matthew Egbert, Xabier Barandiaran, Ezequiel Di Paolo. Licensed under Creative Commons – Attribution 3.0 Unported (http://creativecommons.org/licenses/by/3.0)

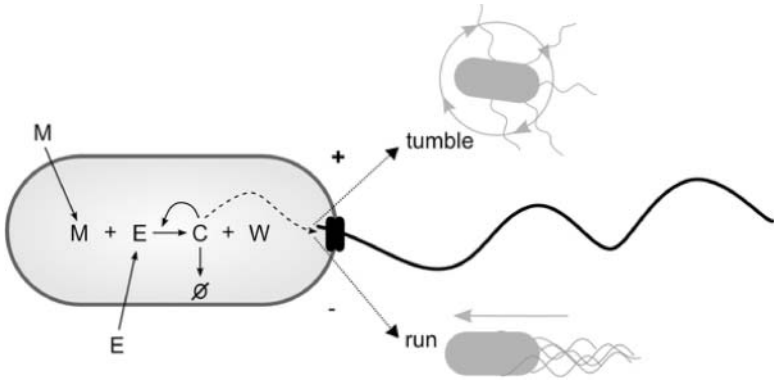

Figure 2. A graphical representation of the metabolism-based chemotactic model: A simple autocatalytic reaction modulates tumbling probability. Copyright 2010, Matthew Egbert, Xabier Barandiaran, Ezequiel Di Paolo. Licensed under Creative Commons – Attribution 3.0 Unported (http://creativecommons.org/licenses/by/3.0)

production of *C*, the probability of tumbling increases, up to a point where bacteria essentially tumble in place. This occurs when metabolism produces enough *C*, which consequently means a good external concentration of nutrients *M* and *E*. We call this strategy "selective stopping" because bacteria tend to run when the environment cannot sufficiently support the metabolism, and tumble on the spot when the environment is conducive to a productive metabolism (see [17]). In [17], we extended this core metabolism by including an additional metabolic pathway and a metabolic toxin to evaluate the adaptive behavior produced by the metabolism-based mechanism. Despite the simplicity of the modeled system, we showed that it is capable of reproducing a number of phenomena reported empirically on metabolism-dependent bacterial chemotaxis, including:

- Chemotaxis to metabolizable compounds
- Inhibition of chemotaxis to metabolic resources due to a local abundance of alternative metabolic resources
- Inhibition of the metabolism of a resource inhibiting chemotaxis to that resource, and that resource alone
- Metabolic inhibitors (i.e., toxins) acting as repellents
- Substantial influence of the history of exposure of the metabolism to reactants on future chemotactic behavior (this is expanded upon in this article)
- The ability to integrate the influence of various environmental factors upon metabolism to produce an appropriate behavioral response to their combined effects

Our explorations led us to the conclusion that when metabolic dynamics are directly coupled to behavior, a number of adaptive phenomena become evident that otherwise pass unnoticed due to the typical abstractions made in models of adaptive behavior (such as conventional models of metabolism-independent bacterial chemotaxis, e.g., [10]). Despite its simplicity (or perhaps thanks to it), metabolism-based behavior is at the root of a number of powerful adaptive capabilities:

1. The metabolic consequences of behavior can be evaluated in the moment (i.e., in ontongenetic time and on relatively short timescales), and behavior can be modulated accordingly.
2. The organisms can adapt not only to the presence of specific chemicals, but also to other environmental conditions (e.g., temperature affecting reaction rates) that might influence metabolism.

3. The organisms can adapt not only to changes in the environment, but to changes in their own metabolic organization by modulating their behavior accordingly (this is elaborated upon more in this article).
4. The organisms can integrate information from the environment and from within, which means that behavioral and metabolic processes of adaptation can feed back to each other.

As a consequence, metabolism-dependent chemotactic bacteria can adapt (respond appropriately) to variations in environmental states, internal states, and interactions between these states that have never previously been experienced by the organism nor even by any of its ancestors. This is due to the fact that the ongoing behavior is directly *evaluated* and modulated by metabolism, meaning that the system will, in general, be attracted to compounds or conditions that increase metabolic rate and will be repelled by those that inhibit metabolism. There remains the possibility of possible maladaptations or parasitic interactions that override the behavioral mechanism or increase the short-term rate of the production of C but damage metabolism in the long term by, e.g., destroying the membrane. Nevertheless, metabolism-based behavior has potential as a powerful mechanism for adaptive behavior at the level of the individual. As we discuss below, the adaptability provided by metabolism-based behavior also has interesting ramifications when considered in the context of evolution.

3 A Synergy of Behavior, Metabolism, and Evolution

The model of metabolism-based bacterial chemotaxis is rather simple, but succeeded in qualitatively matching various empirical observations [17]. In this article, we make some straightforward variations to the model, extending our exploration to study not only the relation between metabolism and behavior, but also its evolutionary consequences. To give a context for these extensions and the results that we draw from our exploration of them, we first provide a very brief review of the role of metabolism in the origins and early stages of evolution.

3.1 Metabolism and the Early Evolution of Autocatalytic Networks

One of the most fundamental open questions about how life originated concerns whether metabolism or replication came first [38]. Could template-replicator molecules such as RNA have spontaneously formed in prebiotic conditions, or are autocatalytic networks of reactants (metabolisms) a prerequisite for their formation? Thus far, there is no known mechanism through which a self-replicating RNA chain (or any other molecule with template-replication properties) could be formed in prebiotic conditions [43]. While these can be synthesized in laboratories, it requires sequences of specific and extreme conditions that are unlikely to have occurred in prebiotic situations—conditions so constraining that, as observed by Fernando and Rowe in [20, p. 356], even proponents of replicator-first theories are starting to concede that self-organizing, autocatalytic cycles—that is, (proto)metabolisms—may have been required to produce the relatively complex and atypical template molecules.

But this metabolism-first conception of the origin of life comes with its own challenges. Foremost we find the low degree of heritable variation available to these systems. A template molecule with four nucleic bases and a length of only 100 bases could take $\approx 10^{60}$ different forms, the vast majority of which are heritably replicable—that is, capable of being duplicated without change (though many of these forms may be functionally neutral). In contrast, metabolic networks do not demonstrate this unlimited heredity [46]. So, even if autocatalytic networks (protometabolisms) could conceivably have arisen in prebiotic conditions, with limited heritable variation these chemical networks are not as amenable to Darwinian evolution as template replicators, and without Darwinian evolution it is not yet clear how they could have facilitated the appearance of template-replicating molecules.

It is in this origins-of-life scenario that the notion of metabolism-behavior coupling might have a role to play. But before behavior can enter the picture, the autocatalytic system must first have somehow become a cohesive unity—an individual preorganism that can behave: *a protocell*. One way that this might have occurred is through the aggregation of hydrophobic molecules of an autocatalytic set into

coacervates (initially proposed in [34]; see also [42]). Such autocatalytic self-maintaining systems are inherently separated from their environments. This is important, because only after individuation has occurred can behavior and reproduction occur. A rudimentary form of reproduction could occur in which coacervates simply divide due to external fluctuations or changes in surface-area-to-volume ratio caused by coacervate growth [20]. Similarly, a metabolic network capable of producing amphiphilic molecules could spontaneously self-assemble into a vesicle, satisfying the minimal conditions: enclosure of the metabolic network and the possibility of reproduction by membrane growth and division [32, 39].

At this point we can already imagine how autocatalytic networks could start to evolve. Among the molecular collisions involved in the reaction networks some will, occasionally, produce new types of molecules, or new molecules may be present in the environment. Many of them will have a negligible effect on the system. Occasionally, however, some of these randomly created molecules will catalyze reactions that increase their own concentration by direct or indirect autocatalysis. In such cases the new molecule may additionally produce a cascade of new reactions. Such a cascade of reactions will probably have devastating effects on the autocatalytic network, but occasionally one will contribute to its robustness.

Thus, collisions between molecules and environmental changes provide the means for some *variation* in such prebiotic evolutionary process while growth and division provides reproduction. Given that when division happens internal concentrations are, more or less, homogeneously distributed within the protocell, a rudimentary form of *inheritance* or *retention* is given by the transmission of molecular species and their concentrations into newly created protocells. *Selection* will occur insofar as new variations contribute to the stability and robustness of the protocell or accelerate its reproduction (a similar scenario is described by Segre et al. [42] and Fernando and Rowe [20]). Thus, a rudimentary form of prebiotic evolution may occur without necessarily requiring complex molecular replicators to begin with. The growth rate of the protometabolic network and the robustness of its dissipative organization define a complex space—a space characterized by how new molecular species can contribute differentially to increasingly robust and proliferating units—and this space can be searched by pregenetic evolution. Artificial chemistry simulation models [20] have shown that in some conditions, these types of protocells are likely to increase their organizational complexity, unlike in vitro self-replicating molecular templates [29]. But, as mentioned above, these systems lack template molecules and therefore have limited heritable variation. Some mechanisms have been proposed to partially solve this conundrum, such as natural selection of autocatalytic sets, selecting for sets that maximize the production of biomass [20, 21], or self-organization of autocatalytic networks [30], but it remains unclear how metabolisms, given their apparent limited heredity, could have enough evolutionary flexibility—enough *evolvability*—to evolve into more modern forms of life, capable of template replication and so on.

In this article, we describe how behavior can play a role in facilitating the evolution of metabolic individuals through facilitating and directing adaptation via self-sensitive behavior-based plasticity, partially offloading heritability into the environment (in a sort of epigenetic inheritance [27]), and creating situations that are likely to induce speciation. In order to illustrate this evolution-facilitating influence of metabolism-based behavior, we now introduce a model. We use the model to demonstrate a synergy of behavior, metabolism, and evolution called *behavioral metabolution*, where behavior influences the evolution of the metabolism and vice versa in a cycle of adaptive evolution.

3.2 A Model to Illustrate the Evolutionary Potential of Metabolism-Based Chemotaxis

We consider metabolism as the self-production of a far-from-thermodynamic-equilibrium chemical network through the transformation (by the network) of available energetic and material resources into constituents of the network. The essence of this process can be modeled as an autocatalytic reaction whereby energetic and material resources (E and M, respectively) are transformed by network constituent C into more C and low-energy waste (V) thus: $M + E \xrightarrow{C} C + 2V$. This single reaction can be thought of as an abstraction of a larger, more complicated autocatalytic network. To capture the notion of "far from equilibrium," C and V are taken to be unstable and degrade rapidly. Their continued presence is therefore only possible through a *dynamic* stability [36] of degradation countered

by production. We label this reaction the *core metabolism* and expose it to various other reactants in different experiments. Table 1 and Figure 3 show all of the chemical reactions that can be active in our model (only a subset of these occur in experiment 1). The upper left quarter indicates the core metabolism described in this section. The other pathways are described in Section 3.3.

In our model, agents (*bacteria*) are simulated in a 2D square *petri dish* of 200 units. Each bacterium has its own simulated metabolism. Resources encountered in the environment diffuse into the bacteria at a rate proportional to the local concentration of the environmental resource. The rate constant for this diffusion, $k_d = 0.04$, is the same for all resources.

The metabolic dynamics are described by the differential equations in Table 2. These equations include some reactants that are only used in some of our experimental scenarios and are explained later in the text. The rate constants (k_{fn} and k_{bn}) in the differential equations have been determined by assigning free energies to each reactant and activation energies for each reaction such that the system fits the criteria of being far from equilibrium and of self-production as described above. Given the chemical free energies and reaction activation energies, we can calculate $k_f = \exp(A)$ and $k_b = \exp(A + R - P)$, which are the reaction rate for forward (exergonic) reactions and backward (endergonic) reactions, respectively. In these equations, A represents the activation energy of the reaction, and R and P represent the combined energy levels of the reactants and the products, respectively, of the reaction. Figure 4 indicates why the forward and backward equations are different. This method of determining reaction rates allows the exploration of abstract chemistries while remaining congruent with the second law of thermodynamics. Reaction activation energies and molecular free-energy levels were chosen by hand to provide the kinetic constants (shown in Table 1) that match the required dynamics.

Each bacterium is modeled as having a set of flagella. In analogy to the working of flagellar rotation in *E. coli* chemotaxis, when the overall movement of flagellar rotation is counterclockwise the bacterium is propelled in one direction (what is generally called the *running mode*), whereas when the flagella rotate clockwise, the bacterium rotates on its axis, changing direction randomly (*tumbling mode*).

As in our previous model [17], by default, bacteria are always running, that is, moving in a straight line in the direction of their orientation, α; thus $\frac{dx}{dt} = 0.05 \cos \alpha$, $\frac{dy}{dt} = 0.05 \sin \alpha$. A baseline probability of tumbling allows for the direction to be changed occasionally. Tumbling bacteria remain at the same location, with α changed to a random value selected from a flat distribution between 0 and 2π. Certain metabolic products influence the chance of tumbling. Specifically, C increases the chance of tumbling, and W (not part

Table 1. A list of the chemical reactions in each simulated metabolism. Also indicated are the forward reaction rate constant (k_f) and backward reaction rate constant (k_b). These rates are referred to in Table 2 by the number indicated in the leftmost column. Reactions 3–6 represent the degradation of the reactants into inert products that are assumed to have no effect on the concentrations of the other chemicals in the simulation. Thus, there is no need to simulate them in detail.

No.	Reactants	Products	k_f	k_b
0	$M + E + C$	$\rightleftharpoons 2C + 2V$	0.61	4.7×10^{-63}
1	$H + C$	$\rightleftharpoons H + W$	0.006	0.006
2	$H + C + 2V$	$\rightleftharpoons 2H + C + 2W$	0.37	1.5×10^{-41}
3	$C + 2V$	$\rightarrow \{\}$	0.006	n/a
4	$C + 2W$	$\rightarrow \{\}$	0.006	n/a
5	H	$\rightarrow \{\}$	0.02	n/a
6	S	$\rightarrow \{\}$	0.0001	n/a
7	$S + F + N + C$	$\rightleftharpoons 2C + 2S + 2V$	0.99	9.6×10^{-67}

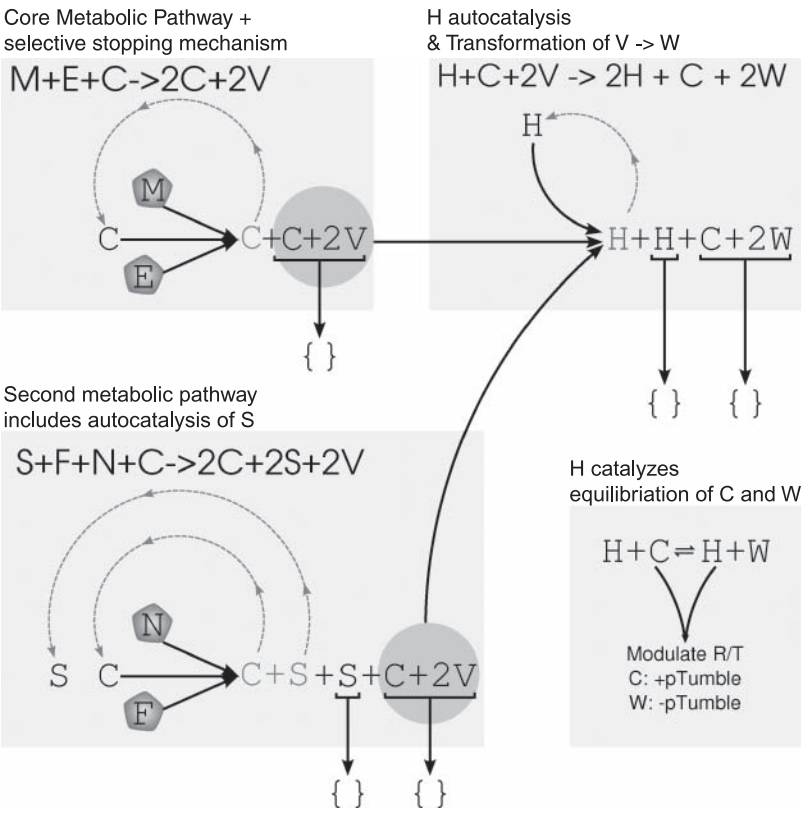

Figure 3. Reactions grouped conceptually by their role in the model. Degradation of reactants is indicated by an arrow to the empty set. Quarters of the figure indicate conceptual groupings of reactions.

of the *core* metabolism and therefore introduced below) decreases the chance of tumbling. This is an abstraction of the influence of metabolites upon flagellar rotation that has been observed in various bacteria [12, 35] and is simulated according to the following equation that governs the probability of tumbling of the modeled bacteria: $P_{\text{tumble}} = 0.001 \max(-0.1 + [C]^2 - 0.9[W]^2, 0.01)$. These relationships between metabolites and flagellar rotation were chosen because they can accomplish two different forms of metabolism-based chemotaxis, *selective stopping* and *gradient climbing*. These are explained in the following sections.

3.3 Experiments and Results

We now present two experiments to provide a demonstration of how, in metabolism-based chemotaxis, small changes in metabolism can lead to qualitative changes in behavior (experiment 1) and how behavior can automatically adapt to a variety of changes in metabolism and lead to the discovery and fixation of new metabolic pathways (experiment 2). In a sense, the experiments are meant to capture the idea of a positive feedback effect between the evolution of behavior and the evolution of metabolism (see Figure 5). Experiment 1 is a case of a change in metabolism improving behavior (metabolism → behavior), whereas experiment 2 is a case of behavior facilitating the evolution of metabolism (behavior → metabolism). Note that the goal of the above experiments is not to provide *evidence* for this phenomenon, but to illustrate the *possibility* and how it could occur.

3.3.1 Experiment 1: A Change in Metabolism Qualitatively Changes Behavior

In this experiment, we demonstrate how a small change in metabolism can lead to a substantial, qualitative difference in behavior. Specifically we demonstrate a scenario whereby one form of chemotaxis

Table 2. Differential equations specifying how chemical concentrations change within each simulated bacterium (excluding influence of the environment). k_{fn} and k_{bn} represent the reaction rate constants for the nth reaction in the forward or backward direction. $\in(\rho, \mathbf{x})$ in the final term of some of the equations represents the local concentration of the reactant ρ outside the bacterium, which is a function of its location $\mathbf{x}$.

$dE/dt =$	$-k_{f0}EMC$	$+k_{b0}C^2V^2/4$	$+k_d\in(E, \mathbf{x})$
$dM/dt =$	$-k_{f0}EMC$	$+k_{b0}C^2V^2/4$	$+k_d\in(M, \mathbf{x})$
$dC/dt =$	$-k_{f0}EMC$	$+k_{b0}C^2V^2/4$	
	$-2k_{b0}C^2V^2/4$	$+2k_{f0}EMC$	
	$-k_{f1}CH$	$+k_{b1}HW$	
	$-k_{f3}CV^2/2$		
	$-k_{f4}CW^2/2$		
	$-k_{f7}CFNS$	$+k_{b7}C^2V^2S^2/6$	
	$-2k_{b7}C^2V^2S^2/6$	$+2k_{f7}CFNS$	
$dV/dt =$	$-2k_{b0}C^2V^2/4$	$+2k_{f0}EMC$	
	$-2k_{f2}CHV^2/2$	$+2k_{b2}CH^2W^2/4$	
	$-2k_{f3}CV^2/2$		
	$-2k_{b7}C^2V^2S^2/6$	$+2k_{f7}CFNS$	
$dW/dt =$	$-k_{b1}HW$	$+k_{f1}CH$	
	$-2k_{b2}CH^2W^2/4$	$+2k_{f2}CHV^2/2$	
	$-2k_{f4}CW^2/2$		
$dH/dt =$	$-k_{f2}CHV^2/2$	$+k_{b2}CH^2W^2/4$	
	$-2k_{b2}CH^2W^2/4$	$+2k_{f2}CHV^2/2$	
	$-k_{f5}H$		
$dF/dt =$	$-k_{f7}CFNS$	$+k_{b7}C^2V^2S^2/6$	$+k_d\in(F, \mathbf{x})$
$dN/dt =$	$-k_{f7}CFNS$	$+k_{b7}C^2V^2S^2/6$	$+k_d\in(N, \mathbf{x})$
$dS/dt =$	$-k_{f6}S$		
	$-k_{f7}CFNS$	$+k_{b7}C^2V^2S^2/6$	
	$-2k_{b7}C^2V^2S^2/6$	$+2k_{f7}CFNS$	$+k_d\in(S, \mathbf{x})$

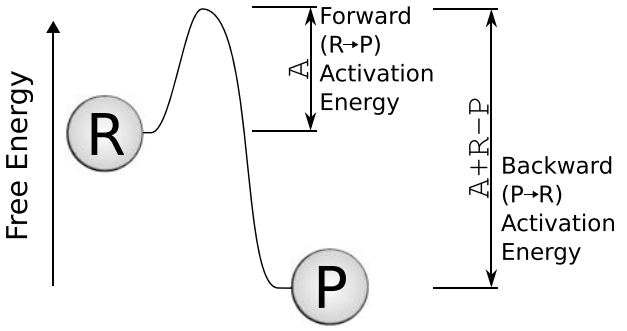

Figure 4. Energy required for a reaction to take place. The line traces the free energy of the reactants as the reaction takes place. Copyright 2010, Matthew Egbert, Xabier Barandiaran, Ezequiel Di Paolo. Licensed under Creative Commons – Attribution 3.0 Unported (http://creativecommons.org/licenses/by/3.0)

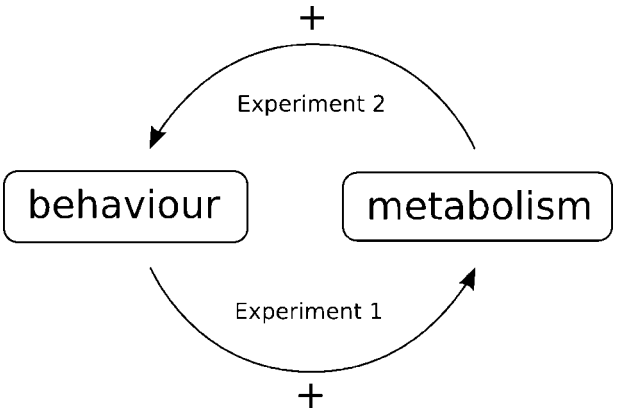

Figure 5. Behavioral metabolution: a two-sided potentially cyclical positive influence between behavior and metabolism in protocell evolution. Copyright 2010, Matthew Egbert, Xabier Barandiaran, Ezequiel Di Paolo. Licensed under Creative Commons – Attribution 3.0 Unported (http://creativecommons.org/licenses/by/3.0)

(*selective stopping*) is transformed into a more sophisticated form (*gradient climbing*) through exposure to a new reactant. To do this, we compare two different types of bacteria, placing 100 of each type evenly distributed on a simulated square petri dish containing at its center a resource of $M + E$, the concentration of which decays with distance following a Gaussian distribution (indicated in the histograms of Figures 6 and 7). The control group bacteria start with only $[C] = 0.5$. This provides a functioning core metabolic pathway—see Figure 3, top left. The experimental group is the same as the control except that it starts with an additional reactant, $[H] = 1.0$. The presence of this chemical produces a self-maintaining gradient-climbing mechanism by enabling reactions 1 and 2 (see Table 1, and Figure 3, top right and lower right). These two conditions allow us to examine the differences between bacteria that have not encountered H (control group) and those that have (experimental group).

Figure 6 indicates the behavior of the control group, which demonstrates the selective-stopping mechanism accomplishing a simple form of chemotaxis. The histogram at the top indicates the number of bacteria at different distances from the peak resource at the end of the trial (data taken from 10 trials, each with the same even distribution of 100 bacteria). The three plots at the bottom of the figure indicate the spatial distribution of the bacteria in the petri dish at the start of, halfway through, and at the end of a typical trial.

The behavior of these bacteria is a simple result of the metabolism and its influence on motion. In the absence of W, the concentration of C drives the behavior of the bacterium. If the metabolic activity (i.e., the production of C) is high, the probability of tumbling will increase until the bacterium is effectively staying still by tumbling in place. If $[C]$ is low, the probability of tumbling will decrease and the bacterium will move, still in a random walk, but with increasingly long durations of directional movement until C is produced again (e.g., when the bacterium finds a place where M and E are abundant). This is the same mechanism as in our model of metabolism-based chemotaxis described in Section 2.1. The mechanism resembles the Ashbyan principles for adaptation [6] except that the system is altering its relation to the environment, instead of reconfiguring itself internally. In this way, behavior is directly modulated by the rate of metabolic production in a selective-stopping manner that is beneficial for metabolism: "stay where you are if the metabolism is running sufficiently well; otherwise go somewhere else." This is perhaps the simplest example of what we call *metabolism-based chemotaxis*, where the sensorimotor pathway is the metabolism itself [17].

Bacteria with $[H] > 0$ are capable of the more sophisticated gradient-climbing strategy (similar to that widely found in bacterial chemotaxis). These bacteria are capable of comparing, as they move, the current concentration of a chemical compound with its earlier concentration. To explain how this is accomplished, we must describe the dynamics of H. The control group H is autocatalytic in the presence of C and V, so once a functioning metabolism encounters H, its concentration will be maintained above 0 (reaction 2). When present, H performs two roles. It catalyzes an equilibration between C

and *W* (reaction 1) and additionally, in its autocatalysis, transforms *V* into *W*, which inhibits tumbling (reaction 2). These equations produce a system that is described conceptually in Figure 8, whereby (1) stoichiometry and reaction rates cause *W* to change more rapidly than *C*, (2) *W* and *C* tend to equilibriate to equal concentrations, and (3) *W* inhibits the probability of tumbling and *C* enhances it. Figure 9 shows this system of chemicals reacting to increases and decreases in resource levels from different base levels of resource. These reactions produce an adaptive gradient-climbing mechanism (adaptive in the sense used by bacteriologists to describe the ability to adapt to a wide range of base levels of stimulus). We do not claim that the simulated mechanism is as adaptive to as wide a range of stimuli as the mechanism found in nature, but it can be seen how in both conditions bacteria approach the resource center but *H* produces a more efficient result due to its adaptation. This is evident when comparing Figures 6 and 7. The gradient-climbing bacteria move to the highest concentration of resource, unlike the selective stoppers, which stop when the resources are above a threshold, producing the volcano effect—a ring of bacteria around the highest concentration of resource. (In both cases, a secondary peak around a distance of 190 can be observed due to the effect of the petri dish wall.)

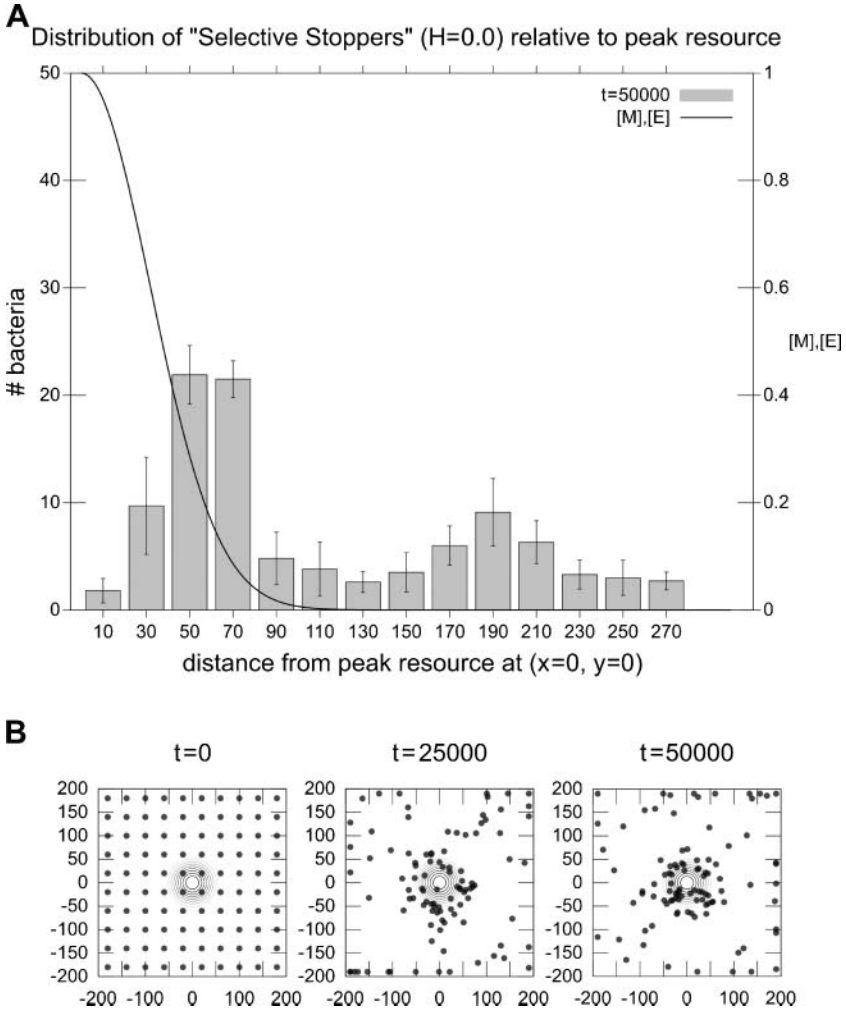

Figure 6. Distance of selective-stopping bacteria from peak resource after 50,000 iterations (A), and spatial distribution (B).

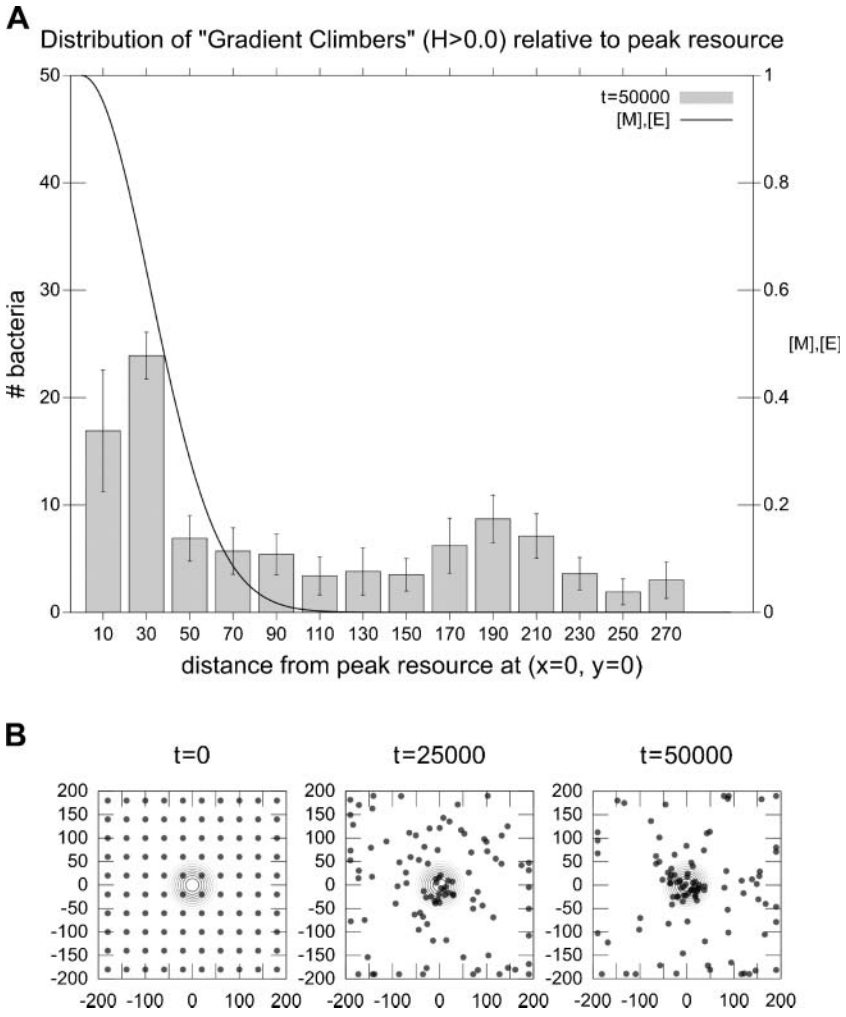

Figure 7. Distance of gradient-climbing bacteria from peak resource after 50,000 iterations (A), and spatial distribution (B).

The experiment shows how changes in the metabolic network of a metabolism-based chemotactic agent can lead to qualitative adaptive changes and improvement on its behavior, through fairly simple means. While moving through its environment, a bacterium can encounter a new component *H* that is incorporated into the metabolism through its self-catalytic activity and through its capacity to improve the adaptive behavior of the bacterium. The specific changes that have occurred here have been designed to make the system as simple to understand as possible, not to suggest that the transformations described are likely to have occurred in this particular way.

3.3.2 Experiment 2: Influence of Behavioral Change on Metabolism

In this experiment we include a second metabolic pathway. In this pathway, two new energetic and material resources, *F* and *N* respectively, are converted into *C* and *V*. Like the core metabolic pathway, this is an autocatalytic production requiring *C* to be present to occur. However, unlike the core metabolic pathway, this reaction is also autocatalytic with respect to a new metabolite, *S*. This means that *S* is both produced by the reaction and required for the reaction to occur (see Figure 3, bottom left).

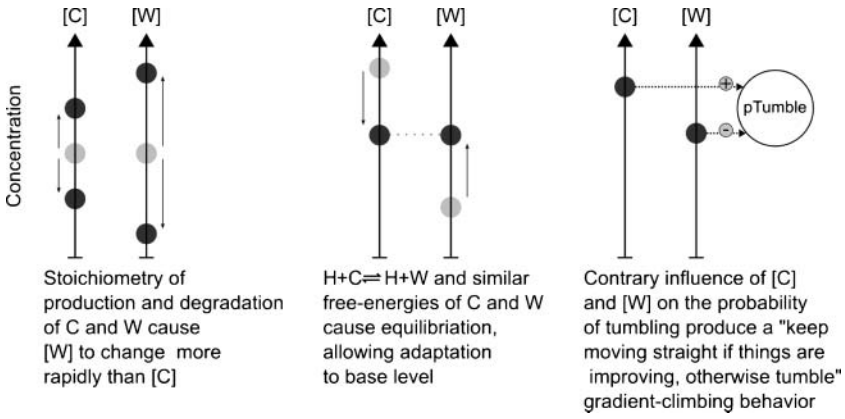

Figure 8. Concepts underlying the simulated gradient-climbing mechanism. Copyright 2010, Matthew Egbert, Xabier Barandiaran, Ezequiel Di Paolo. Licensed under Creative Commons – Attribution 3.0 Unported (http://creativecommons.org/licenses/by/3.0)

Bacteria (initialized with $C = 0.5$, $H = 1.0$, and $S = 0.0$) are evenly distributed around a petri dish containing two sources of E and M, located at $(x = -75, y = 0)$ and $(x = 75, y = 0)$. One source of F and N is located at $(x = 0, y = 0)$. There is no S in the environment except within a circle of radius 0.5 around the left peak of resource $E + M$ $(x = -75, y = 0)$, where $[S] = 1.0$.

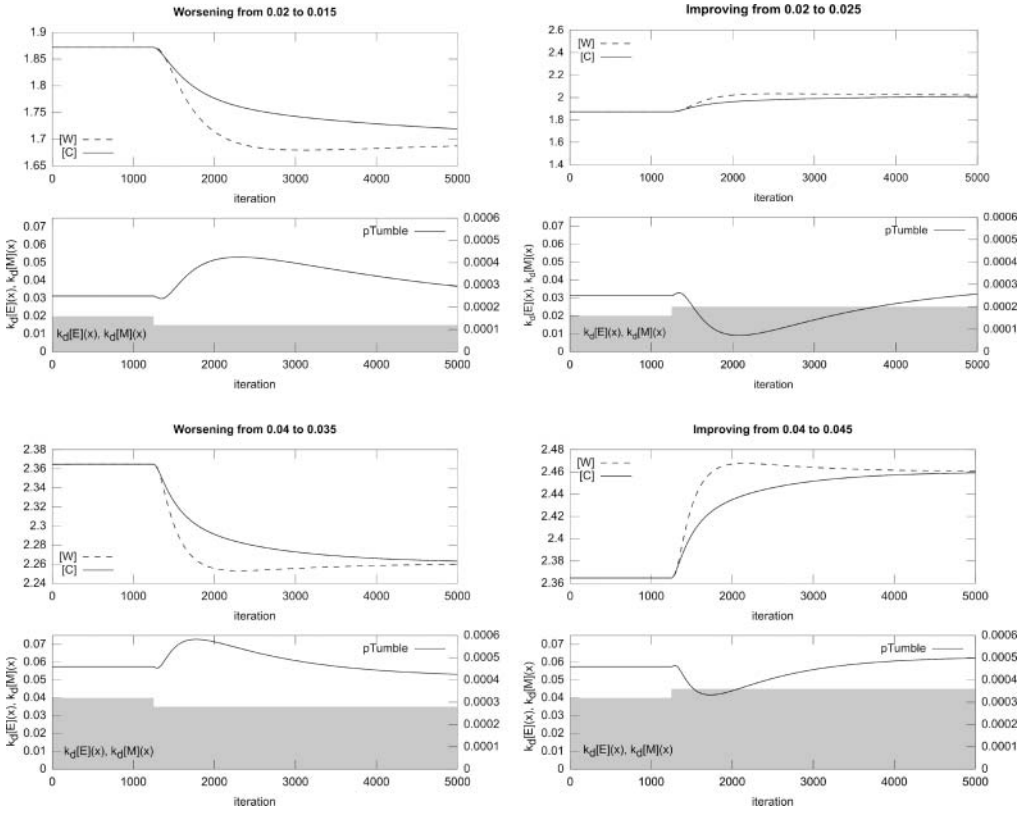

Figure 9. Simulations demonstrating sensitivity to *change* in metabolic rate. *C* and *W* tend to equilibriate over time, but a change in environmental conditions causes *W* to change more rapidly than *C*. Inverse influences of *C* and *W* upon chances of tumbling produces a rough gradient-climbing mechanism. Copyright 2010, Matthew Egbert, Xabier Barandiaran, Ezequiel Di Paolo. Licensed under Creative Commons – Attribution 3.0 Unported (http://creativecommons.org/licenses/by/3.0)

Figure 10 indicates the distribution of the bacteria over the course of the simulation. The bottom figures are as in Figures 6 and 7, but the histogram now indicates the distribution of bacteria along the x axis, comparing the distributions of bacteria that have zero and nonzero concentrations of S. Data have been collected at the end of 10 different trials, each of 100 simulated bacteria. As before, at the start of the simulation, the bacteria are evenly distributed around the dish. The gradient-climbing mechanism attracts the bacteria to one of the sources of $E + M$. At this stage, none of the bacteria have any S, so $F + N$ are not metabolizable and have no effect on the behavior of the bacteria, as the metabolism-based mechanism automatically ignores resources that are irrelevant to the metabolism. As time progresses, bacteria tend to gravitate toward the highest concentrations of $E + M$, and those that are at the left source have an increasingly high chance of encountering the pocket of S. Those bacteria that come into contact with S become capable of autocatalyzing S.

The bacteria that have encountered S have gained a new metabolic pathway, and the odds of this change occurring have been significantly influenced by the behavior of the organisms, as the chance of

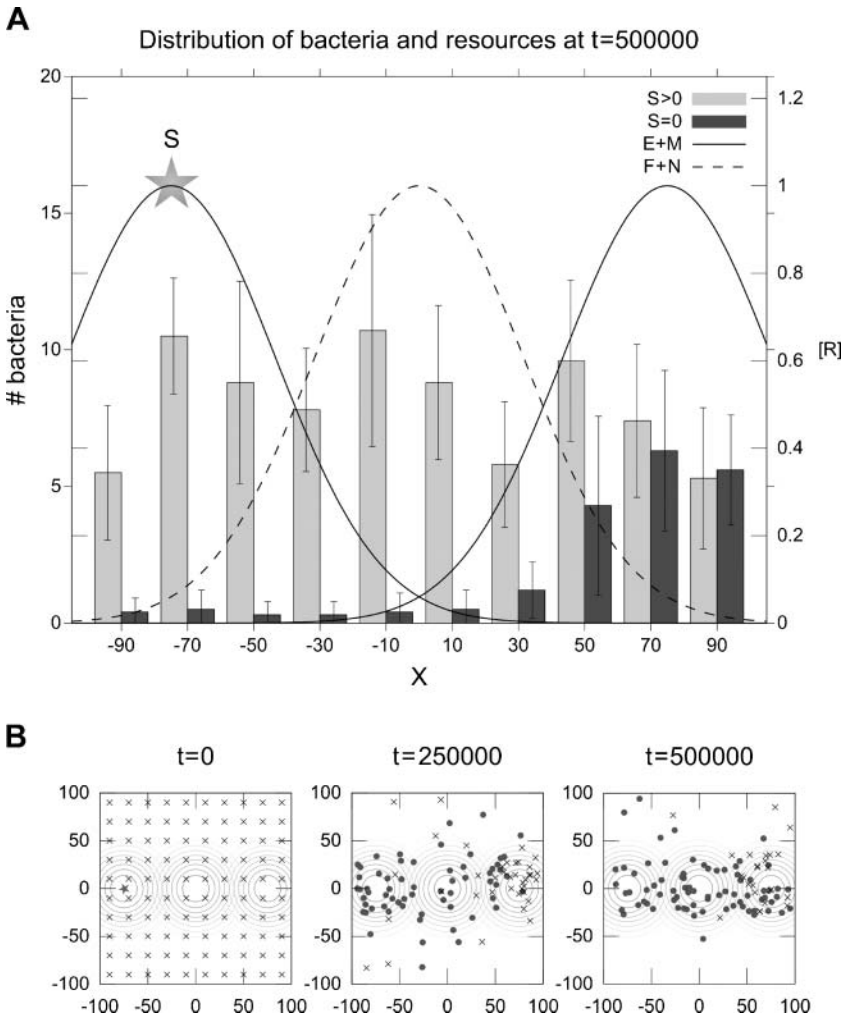

Figure 10. Experiment 2. Bacteria are initially attracted to sources of $E + M$, but those that encounter the metabolic-path-opening reactant S also automatically become attracted to new resources $N + F$. Copyright 2010, Matthew Egbert, Xabier Barandiaran, Ezequiel Di Paolo. Licensed under Creative Commons – Attribution 3.0 Unported (http://creativecommons.org/licenses/by/3.0)

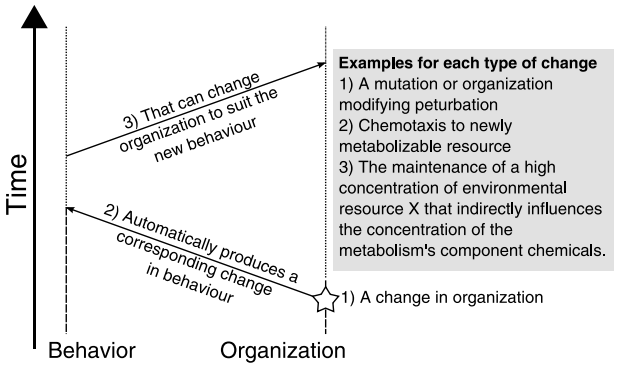

Figure 11. A cycle of mechanisms contributing to adaptation. Copyright 2010, Matthew Egbert, Xabier Barandiaran, Ezequiel Di Paolo. Licensed under Creative Commons – Attribution 3.0 Unported (http://creativecommons.org/licenses/by/3.0)

encountering S would be radically less if there were no chemotaxis. Interestingly, the bacteria that were initially attracted to the rightmost source of $E + M$ never encounter S and accordingly never are drawn away from their initial $F + N$ resource source, so that at the end of the simulation there are in a certain sense two species of bacteria—one that consumes and is attracted to both pairs of resources, and one that is only attracted to and only consumes the original pair of resources.

There are three aspects of this second experiment that we wish to highlight. First, the behavior of these organisms has increased the likelihood of the encounter with S, thereby causing a long-lasting change in metabolism that allows for the consumption of new resources $F + N$. Second, subsequent to an encounter that opens a new metabolic pathway, the behavior automatically adjusted to this new ability of the organism, and the bacteria perform chemotaxis to the newly metabolizable resources. And third, the new behavior exposes a subset of the population to a new environment, which in nature would likely involve different selection pressures, increasing the likelihood of further speciation. In the next section we discuss and elaborate upon these and other evolution-facilitating dynamics.

4 Behavioral Metabolution, the Very Idea

Not only does metabolism-based behavior underlie a powerful form of short-timescale adaptation for individuals [17, 19], but it also exposes an interesting evolutionary potential. The type of interactions shown in the experiments above, between behavior, metabolism, and evolution, we have termed *behavioral metabolution*, which we define as the evolution of behavior and metabolism in such a way that: (a) behavior drives the evolution of metabolism (by exploring, selecting, and/or climbing chemical environments that are beneficial to metabolism), and (b) changes in metabolism affect behavior and the evolution of behavioral patterns (e.g., changes in metabolism could lead to the improvement and fixation of the adaptive response). We can see the cycle of influence in Figure 11, where a change to the metabolic organization of an agent causes it to automatically behave differently, in a way appropriate to its change in organization. The new behavior brings the system to a new environment where new mutations (or old mutations) and/or new environmental conditions might be beneficial for metabolism, or, as demonstrated in experiment 1, can produce a new (possibly improved) behavioral mechanism. In this way, a push-me–pull-you dynamic interplay can be established between changes in behavior and changes in metabolism, influencing evolutionary processes in ways that remain mostly unexplored.

To envision the influence of metabolism-based chemotaxis upon evolutionary dynamics requires the consideration of populations of individuals over long timescales where these kinds of events could occur repeatedly, despite their rarity. In this vein, consider the hypothetical scenario illustrated in

Figure 12, where we compare the responses of a population of metabolism-independent chemotactic protocells with a population of metabolism-based chemotactic protocells. How do these two populations differ when a mutation (genetic or otherwise inheritable) to one or more metabolic pathways occurs in an individual that permits it to metabolize a new environmental resource? The behavior of metabolism-independent chemotactic agents (left) is directed not by a sensitivity to metabolic dynamics, but by a sensitivity to environmental conditions (as in the case of metabolism-independent systems, where chemotaxis is driven by the binding of *attractant(s)* to transmembrane receptors). It will therefore remain attracted only to those resources it was attracted to before the mutation and will not seek out the newly metabolizable resource. The benefits of the mutation will likely, therefore, be missed (unless there are highly unlikely coincidental mutations that make transmembrane receptors sensitive to the new metabolic resource *and* generate a motion to it). Genetic drift dictates that although such a mutation has a *potentially* beneficial effect, it will most likely be lost, since it has no immediate effect. In contrast, metabolism-based chemotactic agents (right) will immediately and automatically be attracted to the new resource whenever it is encountered in sufficiently high concentration to positively affect metabolism. These bacteria are more likely to benefit from the mutation; hence the mutation is more likely to be retained, and a new population could emerge in the new resource-rich environment, leading potentially to speciation. Thus, what is a neutral mutation for the metabolism-independent population is a beneficial mutation for the metabolism-dependent population.

For metabolism-dependent agents, there is no need for an additional sensorimotor mutation to take place, although, of course, such a mutation might subsequently occur that enabled a potentially more sensitive metabolism-independent sensorimotor pathway, via the effect proposed by Baldwin in which the ongoing behavior of a population of organisms can influence the selection

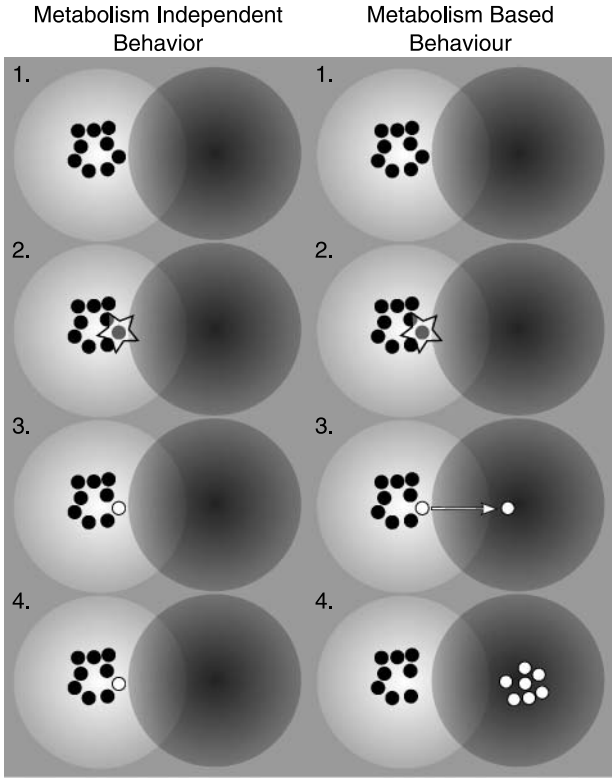

Figure 12. Metabolism-independent and metabolism-dependent responses to a change in organization (represented by a star in Frame 2) that allows them to consume a new resource (dark circle). Copyright 2010, Matthew Egbert, Xabier Barandiaran, Ezequiel Di Paolo. Licensed under Creative Commons – Attribution 3.0 Unported (http://creativecommons.org/licenses/by/3.0)

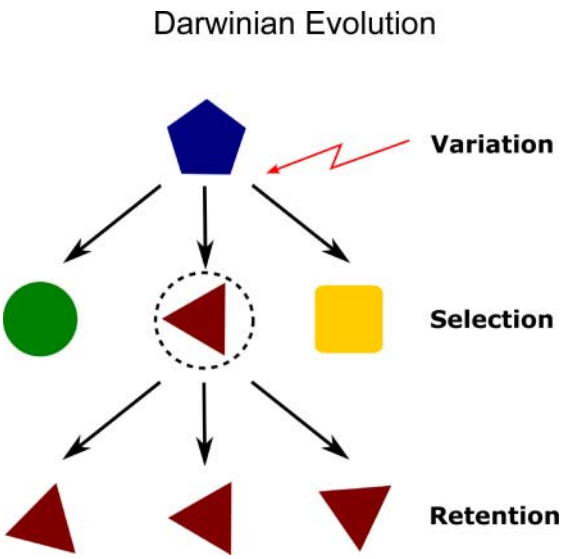

Figure 13. The conventional view of Darwinian evolutionary theory: An individual produces variations that are selected by the environment and retained by differential reproduction. Copyright 2010, Matthew Egbert, Xabier Barandiaran, Ezequiel Di Paolo. Licensed under Creative Commons – Attribution 3.0 Unported (http://creativecommons.org/licenses/by/3.0)

pressures to which it is exposed [7]. In this way, metabolism-based chemotaxis could scaffold the evolution of a variety of metabolism-independent mechanisms, helping to explain why we see so many metabolism-independent mechanisms in modern organisms.

4.1 Behavioral Metabolution and the Principles of Evolution

One way to consider the implications of behavioral metabolution is to move up one level of abstraction and interpret the phenomenon as an instantiation of evolutionary principles. At the highest level of abstraction, evolutionary phenomena can be seen as the result of the combination of three types of processes or principles: variation, selection, and retention (or "blind variation and selective retention," to use Campbell's terminology [11]; see Figure 13). The standard view of Darwinian evolutionary theory provides one instance of this combination. But the received view has been limited to a very narrow conception of evolution, in some cases confusing a particular instance with the general principles.

Many oversimplifications of the story of evolution have been made. Many of these are true in *most* cases, but inappropriately constrain our understanding of some of evolution's tricks. For example, influence is thought to travel only in one direction, from the genes to the organism, meaning that at the evolutionary scale, the *only* information that matters for defining an organism is that encoded in the genes and that the organism itself is only the result of its genes [13]. Genes are inherited and unaffected over the lifetime of an individual, making genetic mutations in the germ line the only variation relevant to evolution. The environment is seen as establishing a set of conditions for replication, thus operating as a selector of the variation among genes, in a manner uninfluenced by the organisms. Behavior is seen as the result of the expression of selected genes (however complex the chain of expression might be) and is only relevant in its influence upon reproductive success. As a result, in this extreme and simplified view, real patterns of behavior are largely decoupled from the evolution of the organism, since they do not themselves shape the selective pressures. All that matters is the end result of behavior as an inheritable trait determined by the genes, leaving out the ongoing dynamic interaction between processes of self-maintenance (metabolism) and environmental interactions (behavior) during the life of the organism.

Needless to say, this traditional, neo-Darwinian view has been criticized from various angles. Especially questioned have been the uniqueness of the genetic system of inheritance and the Weismannian

barrier [9, 27], and the independence of selective pressures from the evolving populations, frequency-dependent effects, niche construction, and so on (for a good introductory criticism of the adaptionist program, see [24]). But even in these revised versions, the same three principles of variation, selection, and retention suffice for constructing an evolutionary account, only they are now too deeply interrelated and too little confined to genetic, population, and environmental containers to play clean roles.

The case of behavioral metabolution is similar in this respect to critiques of the neo-Darwinian view. It can be seen as a sort of inversion or displacement of the principles of variation, selection, and retention. In the standard approach, variation is internal and selection is considered as an environmental feature (see Figure 14), but in behavioral metabolution (see Figure 15) it is the environment that provides a variety of chemicals to be selected by the behaving protocell and retained by its metabolism and/or recurrent chemotactic patterns. If the environment is sufficiently stable in its provision of a specific chemical species, the retention of a reactant beneficial to the protocells' metabolism can be inherited through continued interaction with that environment. Metabolism-based chemotactic protocells can therefore be considered to instantiate the evolutionary principles in this nontraditional way (Figure 14): Variation can be both internal (the result of molecular encounters/collisions giving rise to new molecular species) and external (the result of behavioral encounters in a rich environment), and selective retention can also be internal (by contribution to autocatalysis) or external (by repetitive gradient climbing or behavioral selection of an environmental compound).

It is no coincidence that the selective-stopping and gradient-climbing behavioral strategies directly resonate with evolutionary terminology. In fact, the behavioral analogy between biological evolution and adaptive behavior has been long established [6, 11, 48]. The novelty of behavioral metabolution

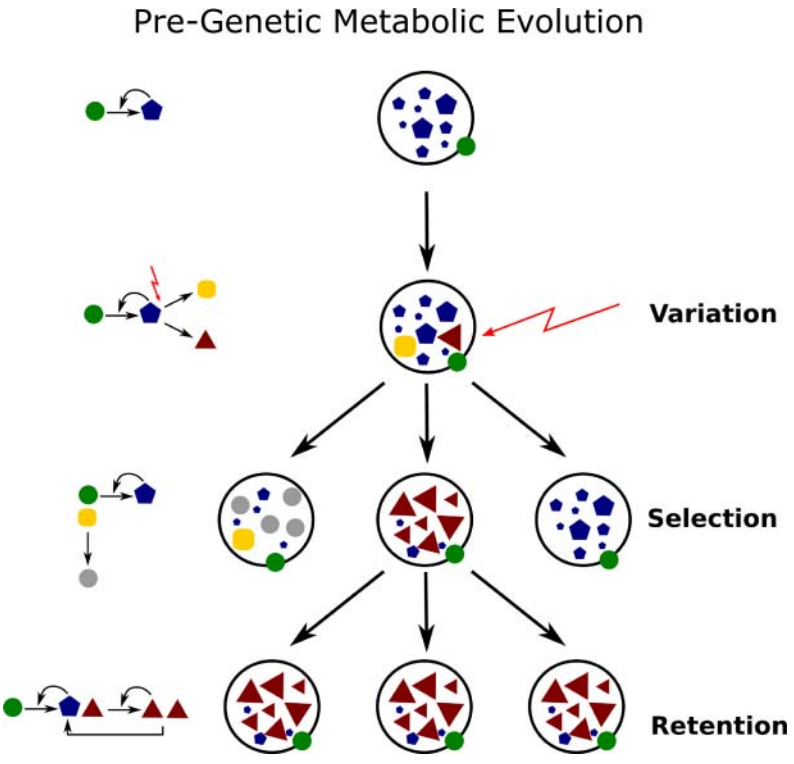

Figure 14. The same template of Darwinian evolution (see Figure 13) applied to metabolic protocellular evolution: The small diagrams on the left-hand side indicate reactions between constituent components of the metabolic protocell. Those new reactions that contribute to autocatalysis are selected. Copyright 2010, Matthew Egbert, Xabier Barandiaran, Ezequiel Di Paolo. Licensed under Creative Commons – Attribution 3.0 Unported (http://creativecommons.org/licenses/by/3.0)

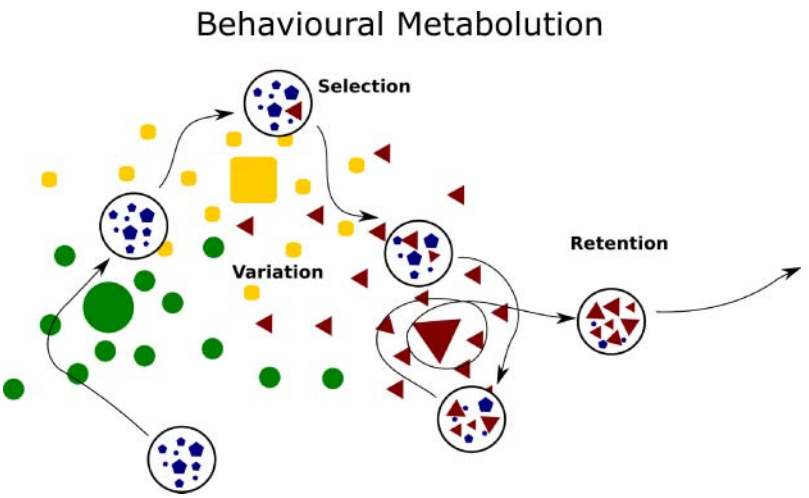

Figure 15. In behavioral metabolution, variation is provided by the environment, and the protocell selects the most favorable variations. Retention is accomplished through integration into the autocatalytic set (metabolic integration) or through recurrent behavior (behavioral integration). Copyright 2010, Matthew Egbert, Xabier Barandiaran, Ezequiel Di Paolo. Licensed under Creative Commons – Attribution 3.0 Unported (http://creativecommons.org/licenses/by/3.0)

is to bring this phenomenon down to the level of (proto)cellular behavior-metabolism interplay and to link it with early chemical evolution and the scaffolding of later evolution.

In short, behavioral metabolution overlaps the exploration of the chemical space by means of classical natural selection with the behavioral exploration (variation and selection) of the chemical space, with each evolutionary process feeding back to the other.

4.2 Back to the Origins of Life

How could metabolism-based behavior and behavioral metabolution have played a role in the early history of life? Assuming an origins-of-life scenario where membrane compartments enclose proto-metabolic reaction networks undergoing natural selection [20, 40, 43, 44], it is evident that any tendency to move (even randomly) would tend to benefit such systems, as local metabolic resources would soon be consumed and random movement would lessen competition for local resources. It is also the case that any bias of random movement toward metabolically more beneficial environments would be strongly selected. Ignoring, for the moment, the details of flagellar rotation and transmembrane receptors, the chemodynamic pathways generating the selective-stopping chemotactic strategy have been shown to be easily evolved in an artificial chemistry [23]. It seems likely that, provided that some form of modulation of behavior is under metabolic control, a selective stopping behavior or a similar metabolism-based mechanism could easily emerge. It also seems probable that this mechanism is more likely to be metabolism-based than metabolism-independent. We say this because the metabolism-based mechanism is a general one, generating adaptive responses to any environmental feature that affects its metabolic health, and yet is simpler (less intricate) than metabolism-independent mechanisms of chemotaxis that involve specific sensors and signaling pathways to generate the appropriate response to specific environmental features.

Admittedly, we have implemented an abstract version of a sophisticated flagellar movement, which is highly unlikely to be found at the earliest stages of evolution. However, early movement could be implemented in a wide variety of ways under the regulation of metabolism. For instance, simple reaction-diffusion spots have been shown to be capable of movement [31, 52], and more recent work on oil droplets [49] also provides an example of potential early prebiotic lifelike self-movement. Perhaps one of the simplest movements could be instantiated by some kind of control of protocell buoyancy (e.g., by a reaction's contribution to protocell density) that would lead to upward and downward selective movement. This mechanism could be used to navigate chemical gradients on a stratified

liquid or other vertically varying metabolism-affecting properties (such as temperature).[1] Finally, in its most simplified form, movement could be completely random and provided by environmental factors. In this situation, behavioral metabolution could be accomplished through changing the permeability of the membrane in a metabolism-based manner (as in the work of Ruiz-Mirazo on the metabolism-dependent modulation of membrane selectivity in protocells [39, 40]).

Whatever the mechanism of agency may be, what remains central to the idea of behavioral metabolution (and its relevance to early forms of life) is the potential of the coupling between metabolism and behavior and the resulting ability to explore and select environments based not on direct properties of the environment per se, but rather on the how the environment influences the metabolism. When we consider the integration of behavior, metabolism, and evolution rather than erecting conceptual walls between these phenomena, we see the possibility of protocells and other organisms benefiting not only from exploring their environment, but from exploring the possible interactions between the environment, metabolism, and behavior. This allows for the offloading of certain challenges (such as the limited heredity of metabolic networks) into environmental or behavioral domains.

Also relevant to the origins (or very early evolution) of life are the potential speciation-producing effects of behavioral metabolution. We described (and demonstrated in a limited fashion in experiment 2) how differences between the behavioral trajectories of protocells could lead to differences in their metabolic and behavioral organization. Speciation-like events can be said to occur when behavioral patterns cause irreversible effects on metabolic organization. Thus, for instance, if a protocell continuously moves toward certain types of environments where resources of a certain redundant metabolic pathway are not available, it could lose its capacity to metabolize those resources.

In any of its possible instantiations, the coupling between metabolism and movement could function as an evolutionary mechanism in itself or as a support to other evolutionary processes. We have focused on showing the potential benefit of such a coupling with two proof-of-concept experiments. The present model might be extended to compare the long-term chemical evolution of protocells with and without movement. The extension would include a wide or open-ended set of chemical reactions—similar to the work developed in [20]. Under this scenario some forms of pregenetic evolution could take place whereby internal and external variation is selected behaviorally and through integration with the metabolism. Through this process, (a) motion through and selection of chemistry-rich environments would serve to explore the internal metabolic space (discovering new metabolic pathways, etc.), and (b) such metabolic evolution would, in turn, also explore the space of behavioral strategies (since changes in metabolism and its dynamics could automatically lead to changes in behavioral dynamics).

5 Conclusions

We have shown, through a model of metabolism-based chemotaxis, how

1. changes to metabolic pathways can qualitatively improve behavioral strategies (e.g., from a selective stopping to a gradient climbing strategy, as shown in experiment 1);
2. behavior can serve to explore, discover, and fixate new metabolic pathways (experiment 2);
3. metabolism-based behavior can automatically adapt to changes in the metabolism (such as the chemotaxis toward the newly metabolizable resources in experiment 2 and as described in Section 4).

These illustrate the complex interactions that may occur between metabolism and behavior. They show how modifications of metabolism (due to mutations or interactions with novel compounds)

1 Thanks to Ben Shirt-Ediss for pointing out this possibility.

can produce behavioral changes that alter the environmental conditions that influence metabolism. The resulting exposure to specific environments can be behaviorally maintained and metabolically selected (since behavior is modulated by metabolic efficacy), thus introducing forms of selection and retention of the variation present in the environment. We have coined the term "behavioral metabolution" to describe this interplay. Our model illustrates some of the shapes it may take, but does not address the question of how likely or significant these effects have been in early evolution. Subsequent models and experiments will be able to focus on this problem.

What the examples disclose is the potential evolutionary role of behavioral metabolution. With the evolutionary scale in mind, a number of properties of behavioral metabolution can be described as providing an unorthodox, yet powerful, form of evolutionary process able to act at the very origins of life in the absence of (or in conjunction with) complex genetic inheritance. We can summarize the results of this article in five key aspects of behavioral metabolution:

1. Behavior provides a way to increase the chemical *variation* that a protocell is exposed to—an increase in the number of possible chemicals that could eventually become new reactants in metabolic and behavioral pathways.
2. Behavior modulated by metabolism can produce an *in-the-moment automatic adaptation* to certain changes (a) in the environment or (b) in the organization of the organism itself, generating behavior that acts in response to the present interaction between metabolism and the environment. This can result in the behavioral amplification (utilization) of new beneficial metabolism-environment interactions, increasing the chance of their retention (i.e., fixation) (detailed in Section 4).
3. The *behavioral plasticity* provided by in-the-moment metabolism-based behavior can scaffold the subsequent evolution of supplementary metabolism-independent behavioral mechanisms (cf. the Baldwin effect [7]).
4. Metabolism-based chemotaxis can produce conditions conducive to *speciation* events through rapid spatial separation of a newly capable individual from its previous population. In addition, the behavioral tendency to preferentially approach new environmental resources could lead to the irreversible loss of the capacity to metabolize previous resources, further establishing speciation.
5. Recurrent patterns of attraction to a given resource and the higher probability of reproduction in those locations can provide a means for *environmental inheritance*, potentially offloading some heredity into the environment.

All these phenomena are possible thanks to the recursive interplay between metabolism and behavior that is present in metabolism-based forms of chemotaxis. We have shown that, when behavior is directly sensitive to metabolic dynamics (as in the models presented here), a set of nested positive feedback effects emerge. When observed at the evolutionary scale (i.e., in large spatial and temporal scales), the consequences are nontrivial.

The family of phenomena that we have termed behavioral metabolution is not the ultimate response to the many questions that still surround the origins and early evolution of life (and later development). But we hope to have shown that behavior might have played a role. It does certainly hold the potential to scaffold and facilitate some answers, and also to ask many new and exciting questions.

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