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Chemical robotics - chemotactic drug carriers

Mini-review

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Abstract: In this review we show and describe a concept of designing autonomously moving artificial cells (chemical robots) carrying drugs and having tactic behavior based on artificial chemotaxis. Such systems could help to provide new and more efficient drug delivery applications. Chemical robot can be constructed based on the self-organization - natural "bottom-up" way - of fatty acid or lipid molecules into ordered nano- or micrometer size objects that have the ability to move and respond to environmental stimuli. The idea of using tactic carriers in drug delivery applications can be justified by the fact that cancer sites in the living body have different physiological characters (lower pH and higher resting temperature) compared to normal cells. The proposed "bottom-up" design method for self-propelled objects at small scales for targeted drug delivery applications could realize the original designation of nanoscience proposed 50 years ago by Richard Feynman.

Keywords: *Chemotaxis • Targeted drug delivery • Nanorobots • Nanorobotics*

1. Introduction

Nanoscience and nanotechnology can help to maintain the sustainable development providing revolutionary new approaches and solutions in material, environmental and medical sciences. The original notion of nanoscience comes from a fictional vision that was first presented by the Nobel laureate physicist Richard P. Feynman in 1959 [1,2]. He described a special approach where individual atoms, molecules or microscopic components might be manipulated using a set of precise tools to build and operate another smaller set in obviously smaller scales. Using this approach smaller scale machinery sets can be reached. One can describe this idea as a "top-down" approach using miniaturization of devices existing at higher scales. As a possible application he also proposed that a small machine (nanorobot) could be built using his "top-down" approach and put inside the blood vessel in the living body so that it might go to a specific location to carry out surgery with its special knife and tools or to deliver drugs to cure diseases [3].

Many researchers consider the idea of nanorobots to use in targeted drug delivery [1,2,4-9]. Targeted drug delivery is one of the therapy methods where the delivery of the medication causes higher local drug concentration in some parts of the body [10-12]. An important aspect of such treatment is to reduce side effects and increase the efficiency of the therapy. This is especially important in some special cases (e.g., cancer treatment).

Nanorobots can provide advances in medicine due to their size [1,2,13-15]. The concept of nanorobots has not changed or developed much in the past half century. In spite of the enormous efforts in this field just some design issues have been presented and this field has not approached the real engineering level.

The concept and the notion of nanoscience have turned towards new challenges in material science. Nowadays, the primary interest of nanoscience and nanotechnology is to synthesize particles and objects at nanoscale, and to develop materials in that size [16]. Nanoscale materials can be used in many useful and important applications e.g., in nanoelectronic and nano-optic devices, and in biosensors [16,17]. However, the focus of nanoscience and nanotechnology is gradually shifting from the synthesis of individual components to their assembly into larger systems offering new tools and opening up new horizons and their use as nanostructured materials in chemistry, biology, physics or in industry [17].

Application of nanoscopic and microscopic objects

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in biomedicine [18-20] (e.g., drug delivery, diagnostics) can be considered because of their high surface/mass ratio. This ratio is much larger than that of other microparticles, and these particles have the ability to adsorb and carry other compounds. In these applications these objects play passive roles in terms of their transport, and they can reach the target sites by passive transport phenomena inside the living body. There are lots of papers regarding the experimental and theoretical aspects of docking of drug carriers and drug transport from the carrier to the target [21-28]. However, there are no experimental nor theoretical trials to provide and engineer tactic and autonomously moving “robots”. In this paper we will show a simple procedure and provide a hint how to design and build such small tactic drug carriers.

2. Autonomous chemical movers

There are several autonomously moving chemical objects from nano- to millimeter scale [29-32], e.g., nanorods powered by redox reaction on their surface [33], self-powered vesicles [34] and microscopic oil droplet suspended in water based on asymmetric chemical reaction at their interfaces [35,36].

In the micro- and nanoscale there are several phenomena, which can be utilized to design self-propelled objects [37]. In self-electrophoretic motors the governing phenomenon is electrophoresis (the directional motion of charged objects in an electric field). In this type of “machine” an electric field is generated across the motor in a fluid. This electric field drives the motion of the charges on the surface of the motor creating a slip velocity whereby the fluid is allowed to flow around the object. The motor is thus driven in the opposite direction at a given velocity. Experimentally a bimetallic nanorod has been synthesized (~2 mm in length and 400 nm in diameter) with a catalytically active platinum end and a gold end. When it was placed in aqueous solutions containing hydrogen peroxide, the Pt–Au nanorod propelled itself through solution at speeds of approximately ~1 cm s^{-1} [37].

In another system motors can utilize motion due to the bubble formation on their catalytic side and the force from the release of the bubbles causes the motion [37]. In such bubble propulsion system the difference in the rate of bubble generation is important on one side compared to the other. Therefore, there should be a change in the rate of bubble production with distance.

Chemotaxis is a common and driving phenomenon in biological systems and similar behavior has been observed in some non-living systems [37-39]. Platinum-gold rods of 2 μm length exhibit directed motion towards higher hydrogen peroxide concentration. When a catalytic motor experiences different diffusivities at different substrate (fuel) concentrations, it will move towards areas of higher diffusivity. Movement occurs in this direction because with higher diffusivity the motor experiences a higher average displacement, therefore, it will continue to move farther as it travels up the gradient. Over time the density of the rods began to increase in the area of the highest concentration of hydrogen peroxide (where the diffusivity was highest) [38].

One of the most interesting and challenging problems attributed to the directional and tactic motion is to find the shortest path in a maze [40]. Solving maze problems using adaptive systems is not only relevant to the everyday issues of urban transportation and to experimental psychology, but is also one of the model problems of network and graph theory as well as robotics [41]. Several groups have thus explored the possibility of maze solving by physical, chemical or even biological systems: microfluidic networks [42], chemical waves [43] or plasmas [44], or microorganisms growing in response to nutrition gradients within the maze [45]. Recently, we designed a new adaptive system, in which an inanimate/chemical construct (a small fatty acid droplet suspended in basic water) can self-propel and solve mazes in response to chemical stimuli [46] (Figure 1).

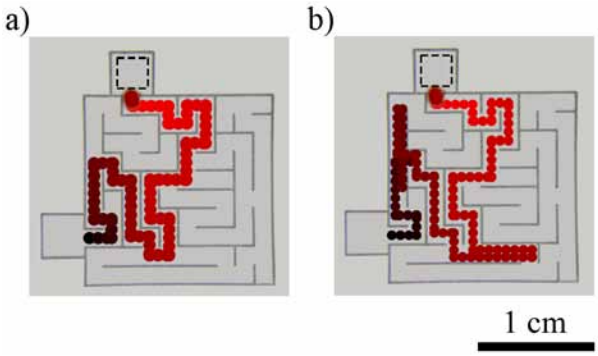

Figure 1. Autonomous motion of droplets utilizing artificial chemotaxis in a pH gradient in a maze. Position of the gel soaked with HCl at the maze’s entrance is indicated by dashed-line boxes. Reprinted with permission from Ref. 46. Copyright 2010 American Chemical Society.

This is the first example where an individual chemical construct can directionally move in a chemical gradient and solve a simple mathematical problem. Maze solving by fatty acid-containing (2-Hexyldecanoic acid, HDA) drops can be explained by surface tension effects stemming from non-uniform distribution of HDA at the liquid-air interface. Droplet releases fatty acid molecules, and these fatty acid molecules partly deprotonate in the pH gradient. Importantly, more protonated HDA is found towards lower pH. This asymmetric distribution translates into a gradient of surface tension which is determined predominantly by the concentration of the protonated HDA at the liquid-air interface. The surface tension gradients give rise to a convective flow (Marangoni flow), and this flow can be maintained and controlled by this fatty acid droplet. This behavior could change our imagination about what the effective targeted drug delivery should look like. This approach offers the possibility to design and construct construct new and more powerful autonomous movers having important implications in targeted drug delivery. Such adaptive systems can be used to imitate a primitive intelligence, and the examination of fatty acid stabilized chemical movers can lead us back even to questions raised regarding the origin of life [47].

3. Chemical robotics

Chemical robotics would be a totally new research field with a new notion including the design of autonomously moving objects (artificial cells) and using them to reach special target location by an artificial tactic motion and perform efficient drug delivery or control chemical reaction via release of chemical species from the artificial cell. However, this terminology can be found in the literature with different notion. A Japanese group synthesized a special polymer, and a piece of that gel using a special surface can “walk” on it and generate peristaltic motion [48]. The self-motion is produced by dissipating chemical energy of an oscillating reaction. They call this polymer object as a chemical robot. It should be noted that in all concepts the common part is that the object (robot) utilizes chemical energy.

This new finding in artificial chemotaxis [46] suggests that either new chemicals can be used to construct chemotactic systems or new tactic systems can be designed (e.g., thermotactic, phototactic systems). The idea of using these tactic droplets in drug delivery applications can be justified by the facts that cancer sites in the human body have pH lower than healthy tissues [49] or cancer cells have higher resting temperatures (37.5°C) compared to normal cells (~37°C) [50] because of their higher rates of metabolism.

Cells in the living body consist of a self-assembled bilayer of phospholipids, and a compartment stabilized by a self-assembled layer of fatty acid molecules is usually considered as a prototype of a living cell. Therefore, it is an obvious choice to use the fatty acid chemistry to design the shell of an autonomous mover. A chemical robot (artificial cell) could be a micelle, vesicle or micrometer size oil droplet stabilized by a mono- or bilayer of a fatty acid or phospholipid molecules that has ability to move and respond to environmental stimuli. This can contain either drug or other drug carriers like nanoparticles, and the membrane of this small compartment will protect the drug from leakage. Autonomous motion can be governed by either asymmetrical chemical reaction at the leading and ending edges of the cell’s membrane [34] or Marangoni effect (in a chemical gradient the protonation rate of fatty acid molecules in a membrane can be different, which can induce a surface tension gradient in the membrane and this can maintain an autonomous and tactic motion of fatty acid stabilized compartments) [35,36] rather than using “molecular” rotors or engines, and this motion can be controlled by taxis of the artificial cell.

Combination of tactic motion of the chemical robot to the target and drug delivery from the artificial cell to the target through the membrane of the cell is a next important aspect. This small tactic droplet can carry drugs to the specific location (e.g., low pH region, higher temperature), where this drug can be released (Figure 2). This release can be either passive (by diffusion through the membrane) or active (by a specific donor-acceptor reactions between the cell and the target surface). This part of the action (drug delivery from the carrier to the target) is well-understood and examined, and this is a hot topic of the research and investigations in medicine, chemistry, and physics [21-28].

While the miniature machine would be designed for multipurpose action, carrying out activity depending on how it is programmed, the artificial cell could be speci-

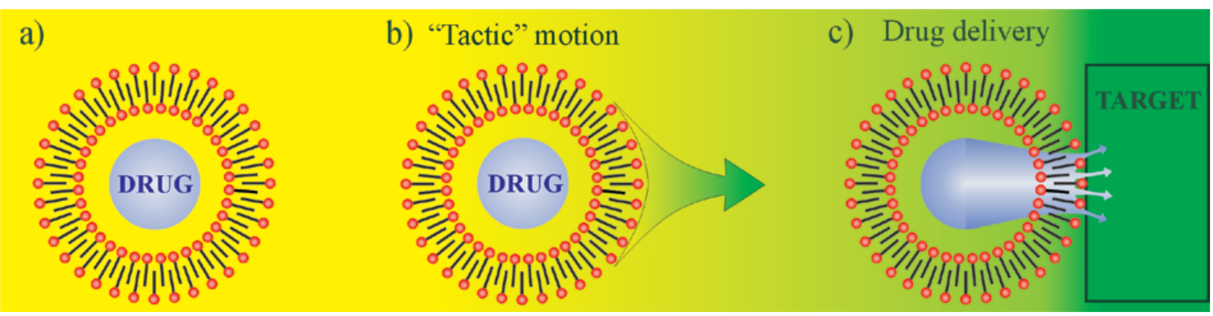

Figure 2. Drug delivery by a chemical robot (artificial tactic cell).

fied for one single action, in possession of all and only those abilities that are required to carry out that activity. This means that depending on the purpose, we can design chemo, photo, and other tactic chemical robots reducing the risk of malfunction compared to a multipurpose machine. If we are considering drug delivery applications, the system also includes the possibility to “fine tune” the properties of the carrier for a single patient’s case. Finally, this artificial “bottom-up robot” is built from biocompatible materials, thus the side effect of a possible therapy could be dramatically reduced. Table 1 contains comparison between the original idea of nanomedicine/nanorototics (“top-down”) and the proposed new (“bottom-up”) approach.

Table 1. “Nanorobotics” versus “Chemical robotics”.

	Nanorobotics	Chemical robotics
Main idea	Miniaturization: “top-down”	Self-assembly: “bottom-up”
Shell	Artificial “shell”	Membrane by mono- or bilayer of fatty acid or phospholipid molecules
Navigation	Molecular engine and rotors	Asymmetric chemical reaction at the membrane or tactic motion
Drug release	Injection	Mass transport (e.g., diffusion) through the membrane
Purpose	Multipurpose	Designed for a single action

4. Discussion

In this paper, we describe a new approach to design and build a self-propelled chemical construct based on artificial tactic behavior (e.g., chemotaxis). The proposed chemical “bottom-up” approach has several advantages compared to the more difficult, highly technical and hence, more risky miniature machines: (i) we can use “natural” tools (processes) – self-organizing mono- or bilayers of fatty acids or phospholipids molecules and chemical energy as a fuel for induced tactic motion of nanoobjects – to drive and control the assembly and motion of nanoobjects; (ii) the need for difficult and expensive miniaturization can be eliminated since the scale of the chemical processes involved, and size of the system itself is already comparable to that of living cells. Furthermore, the use of chemical species and processes provides us a greater degree of freedom in the design of such systems that can be appropriately adjusted to the purposes of the application reducing the risk of malfunction that can occur in man-made systems. Using these tools a new field called chemical robotics can be established, where an object (artificial cell) - based on the self-organization (natural “bottom-up” way) of fatty acid or lipid molecules into ordered nano- or micrometer size objects - can navigate, move, and do tasks (e.g., drug delivery, controlling chemical reaction) transforming and using its chemical energy as a power supply. These cells can also have ability to respond to environmental stimuli.

The recently discovered chemotactic behavior of a fatty acid droplet [46] suggests that new chemicals can be used to construct chemotactic systems. It is easy to imagine that new systems (chemical construct) based on chemotaxis can be designed, which have the ability to move not only from high pH to low pH, but also from low pH to high pH. The key engineering point here is to design membranes using either monolayer or bilayer of fatty acid and/or phospholipids, which have different surface tensions in a chemical gradient. Chemical gradient is not limited just to a pH gradient, it could be gradients of electrolytes or other chemicals. However, this gradient should induce a difference in forces between the two opposite parts of the membrane to maintain the autonomous motion of a chemical robot. Second possible idea controlling the motion of the artificial cell is to use chemical reaction, where its reaction rate depends on the chemical gradient in the systems. This asymmetry in chemical reaction rate could generate autonomous motion. This chemical reaction can be the fatty acid formation by reaction of fatty acid anhydrite (soluble in organic phase) with water at the w/o interface [36]. Similarly an interesting idea would be to construct phototactic and thermotactic systems based on fatty acid chemistry. In the first case photoisomerization can drive the autonomous motion of a cell incorporating photo-surfactant [51]. Probably the most trivial part of the design procedure would be the construction of autonomous movers based on the surface tension difference of membranes in a temperature gradient.

It should be noted that using such chemical robots is highly speculative and much more research is needed to extend it to any in-vivo or in-vitro biological applications. In the macroscale, the volume of an object is large compared to its surface area (relative surface area is low), and this involves that properties related to the volume of the object will determine its behavior. In smaller scales (micro- and nanoscale) the relative surface area is high, therefore, surface effects tend to dominate. For small objects the rate of energy dissipation is proportional to its surface area. This becomes relatively large for its capacity to store “fuel”. Therefore, such small objects must actively harness energy from outside sources (e.g., external fields, chemical gradients). Surface forces (e.g., Van der Waals force) also become important in these small scales, and these forces can dramatically affect the navigation of small objects compared to machines operating and existing in the macroscale. Moreover, application of tactic drug carriers at small scales raises some questions about the randomizing effect of Brownian motion (which becomes significant at small length scales) and its control [52]. However, we do believe that any small success can open up a totally new horizon in targeted drug delivery. This can initiate totally new research not only in biology, but also in related fields. Our final aim is that such small autonomous movers in nano- and microscales can carry drugs to the specific location (e.g., cancer site), where this drug can be released. Based on this idea, a very sensitive and specific treatment can be achieved that could be far more effective than currently existing methods. Using this “bottom-up” approach that is based on our accumulated knowledge on chemical systems and nanoscience over the last decades since the original idea was presented, we could finally be able to realize the original idea of the nanoscience envisioned by Feynman.

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