Chapter - 1

Introduction

1.1 Nanoswimmer

Life is greatly associated with mobility. Cell movement is the essential feature of the living world and exists in many forms such as cell crawling, swimming and walking. Enthrallment of cell motion is as old as the microscope itself approximately 300 Years ago. In 1680s, Antony van Leeuwenhoek discovered tiny moving animalcules at plaque on his teeth named as bacteria [1]. In nature bacteria leave a huge foot prints on our lives because their effect can be seen easily around us. Since then, many researchers and scientists got fascinated to know how bacteria move. After that, study of bacterial behavior was carried out by physiologist Theodor Engelmann and botanist Wilhelm Pfeffer in 1880s. The response of several bacteria towards external stimuli such as oxygen, nutrients, salt and light has been studied. Then, details about the structure of bacteria come into picture that leads to building a new technology. In the next section, how these micro-organisms organize their voyage is presented in detail.

Bacteria are proficient in circumnavigating in an environment such as human body in search of food. Bacteria generally shows run and tumble behaviour [2]. Their presence inside human body could facilitate digestion and improvement of immune system as well as also cause severe infection. These single cell bacteria can travel through body by three ways:

First, beating cilia or rotating flagella protrudes from the surface of the bacteria moves in a coordinated manner to propel. Flagellar motor work same as human designed electric motor, which is rarely happen in nature. Both works on the same principle such as flow of hydrogen (proton motive force) and sodium ions through cell membrane imparts the energy to rotate the flagella, whereas to get electric motors work movement of negatively charged electron takes place.

Secondly, these microorganisms depend on external stimuli to provide thrust to locomote. The motion of these bacteria in the presence of external stimuli such as chemical and light is involuntary. They move towards chemical attractant and away from chemical repellent.

Pfeffer originated the term chemo-taxis first time because of motion of bacteria towards and away from chemicals [3].

Third, bacteria not only needs nutrient for living and moving they also needed bundle of cilia and flagella which moves in coordinated manner. Bacteria utilize their flagellar motion and exhibits random walk while rotating. When it senses a chemical attractant it toggle its rotation triggered the flagella to get assemble and make cluster as a single unit to locomote bacteria in a straight line. When concentration of nutrient (chemical attractant) decreases it again shows tumbling behaviour until concentration get increased [4].

Flagella present on many species of protozoa such as *Ochromonas malhamensis*, *O. danica*, marine *chrysomonad* and *P. cinnamomi* exhibit mastigonemes (branches or hair like structure, 17 nm in diameter and 1.67μm in length) on the surface of flagella [5]. It shows planar mode of propulsion along the length of flagella. As per literature, the presence of mastigonemes on the flagellum surface leads to increase in effective surface area of the flagellum and maximize the effect of locomotion generated by flagellum [6]. It is also mentioned that flexible fibers are also present on the surface of mastigonemes as shown in Figure 1.1, which leads to increase in viscous drag on mastigonemes and therefore making the arrangement of mastigonemes more proficient [7], [8]. In available electron micrographs, mastigonemes on flagella surface in *chrysomonad* are found to be at 90° [9], while orientation of mastigonemes other than 90° need to be investigated.

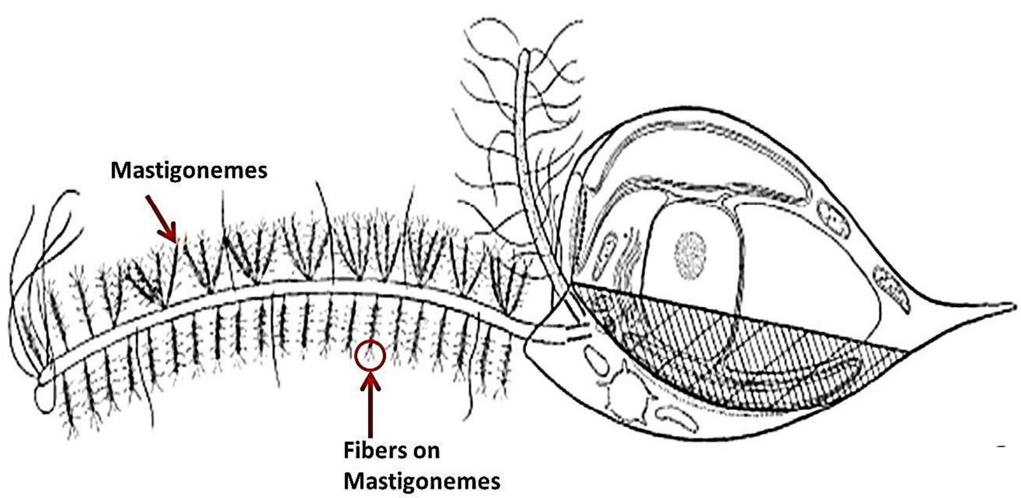


Figure 1.1: Schematic diagram of *Ochromonas danica* showing fibers on mastigonemes [10]

Self-assembly feature of flagella makes it most exciting area to study by nanotechnologist because no fabrication process can built-up such machines at such small scale. Only biological motors such as flagella and cilia have solved the problem. In the subsequent section, nanoswimmer has been bestowed in brief to better understand the biomedical applications.

Nanoswimmer is locomotive design and requirement of more comprehensive machines like nanorobots. Nanorobots embrace the size of robots from 1 nm to few millimetres which is shown on the scale bar with some of cells and organisms exist in nature in Figure 1.2. Nanorobotics is engrossed in many applications detection and measurements of chemical concentration, in biomedical applications for identifying cancerous cell, targeted drug delivery for treatment of cancer to the specific site of body by reducing the chances of destruction of normal cells [11]. The realization of nanorobots in medicinal field is challenging due to its need to propel in fluids, ranging from water, blood, or urine, to more complex environments, such as cerebrospinal fluids, gastrointestinal tract, or brain matter [12].

The origination of nanotechnology is allied with a talk "There is plenty of room at the bottom" given by famous scientist Nobel-prize winner Richard Feynman [13]. Nature has enthused scientists, engineers, mathematicians, physicists and biologist to build useful machinery system. At micron-scale, natural microscopic bacteria such as viruses, bacteria and DNA [14] have gain attention of many researchers to create locomotive micro/nano machines.

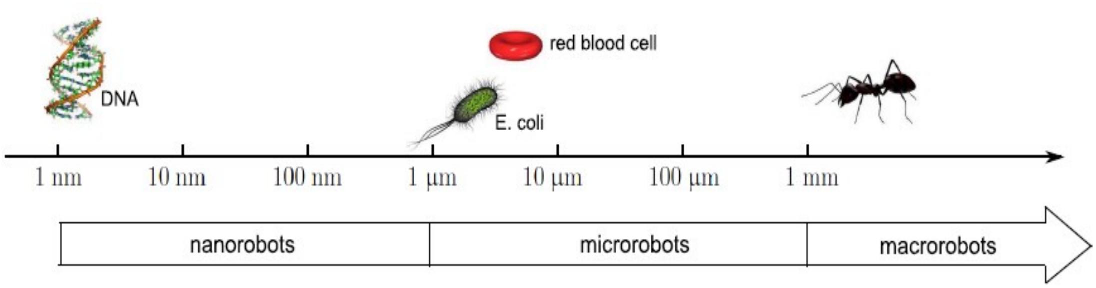


Figure 1.2: Microorganism dimensions available in nature presented on scale bar [15]

Nanoswimmer is one specific structural form of nanorobots, where intense engineering research is going on, to biomimic flagellar microorganisms consisting of a head and flagella. *In-vivo* applications of nanoswimmer makes it suitable for minimal invasive surgery which leads to various benefits to the patient such as lessening of revival time, infection, medical complications to enhance the quality of medical care. Nanoswimmer has capacity to perform task very carefully which is difficult to do at present inside some of the location of human body such as central nervous system, urinary system, blood vessels and circulatory system. Task can be performed by nanoswimmer is depicted very well in Figure 1.3 for various biomedical applications.

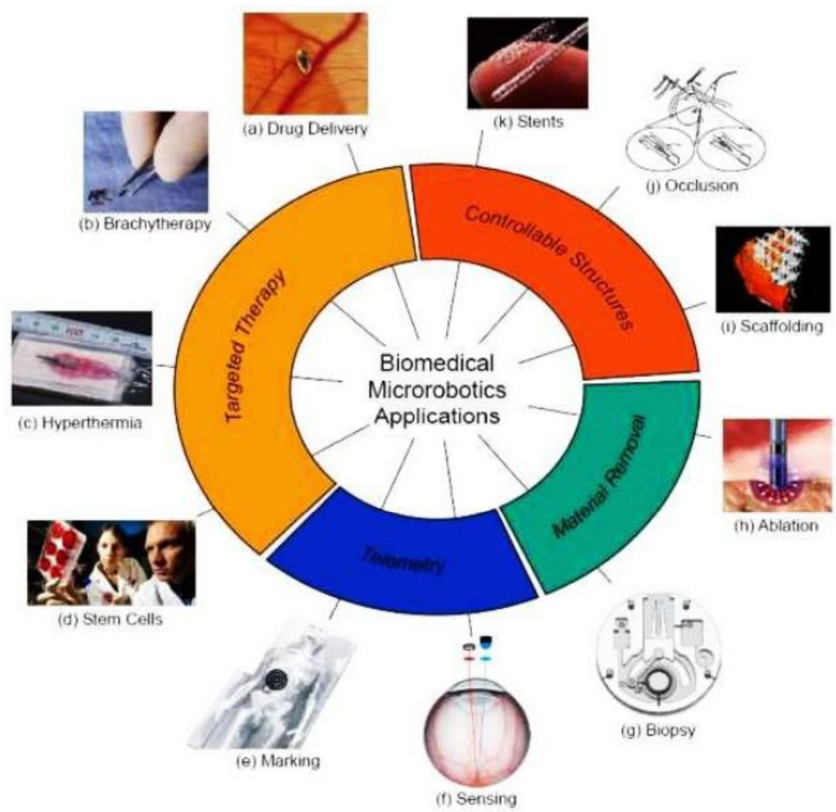


Figure 1.3: Various biomedical applications of nanorobots are shown diagrammatically [15]

If nanodevices inside human body is cogitated, human body involves a responsive complex system in which immune system get triggered on encountering any foreign body inside it. Biocompatible nanorobot is required which can play safely and accomplish its task for biomedical applications. To biological *in-vivo* applications it is possible for nanoswimmer to encounter the biological fluid. Fluid enormously viscous at micron/nano scale causes Reynolds number to be extremely low. Two mechanical motion of nanoswimmer such as flexible oars and corkscrew motion is proposed by

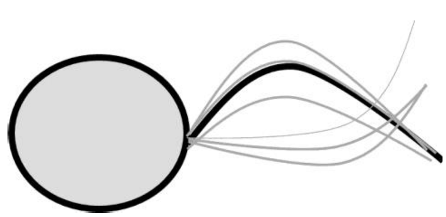
Purcell in his seminal talk "Life at low Reynolds number" which is discussed in the following section.

1.2 Significance of Low Reynolds Number

In nature eukaryotic and prokaryotic bacteria utilize rotating helical flagella and beating cilia for their propulsion at micro-scale using molecular motors [16]. At micro/nanoscale robot experiences viscous forces and inertial forces become insignificant. Different propulsion methods for designing micro/ nanoscale robot have been used in liquid than robots at macro scale [17]. Reynolds number is a dimensionless quantity. It is defined as the ratio of inertial forces to viscous forces and can be expressed as presented below in equation

$$\mathrm{Re} = \frac{\text{Inertial Forces}}{\text{Viscous Forces}} = \frac{\rho v \ell}{\mu}$$

where, ρ is density, v is velocity, ℓ is dimensional length and μ is dynamic viscosity. Mostly micro-organism moves at low Reynolds number regime in the range of 10^{-2}-10^{-4} because viscous forces dominate over inertial forces. In 1977, Purcell in his seminal talk "Life at low Reynolds number" state that at low Reynolds environment non-reciprocal motion is required for net displacement [18]. Eukaryotic and prokaryotic bacteria swim at low Reynolds number and shows non-reciprocal motions. In 1977 Purcell stated that two methods of motions are adopted by swimming micro-organisms to engendered non-reciprocal motion: a flexible oar oscillation (planar motion utilize by eukaryotes such as *spermatozoa*), corkscrew motion (helical rotation exhibit by *E. coli* prokaryotic bacteria) [18] shown in Figure 1.4. Planar mode of propulsion is still less explored experimentally which is also the focus of the current thesis along with different designs of flagellated artificial swimmer.



(a)

(b)

Figure 1.4: (a) Planar motion and (b) Helical motion of bacteria

There are certain parameters which need to investigate for studying the propulsive characteristics of flagellated artificial swimmer at low Reynolds regime. The parameters such as number of mastigonemes called as branches in the present work, orientation of branches, spacing between branches on flagella surface and effect of environmental parameters such as speed of motor and viscosity of fluidic medium are considered for enhanced propulsive force generation using planar motion of flagella. The parameters taken into consideration for propulsive force generation of flagella are shown schematically in Figure 1.5.

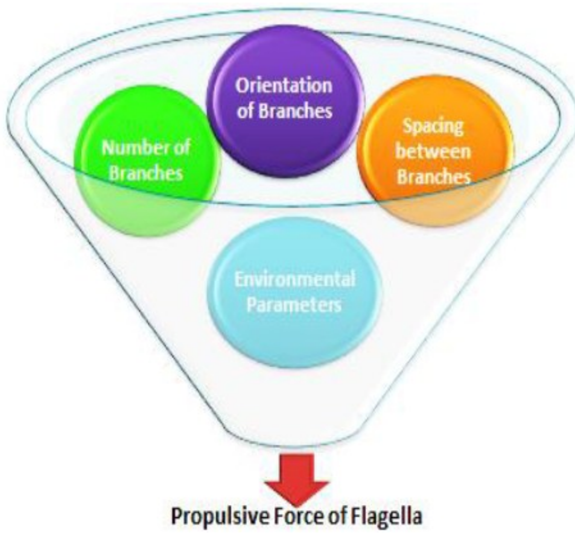


Figure 1.5: Factors contributing in generation of propulsive force of flagella

After designing of various kinds of flagellated swimmer, there is a requirement of on-board energy transduction system for locomotion of an artificial nanoswimmer. Scientists and engineers are mimicking natural biological bacteria such as *E. coli* and *Paramecium* for their design and fabrications of machines at nano levels. Researchers [19], [20] are also imitating the mode of propulsion (planar and helical) exhibit by natural bio-organisms and investigated it theoretically. To propel artificial nanoswimmer, different propulsion mechanisms are being developed to date and presented in the succeeding section.

1.3 Powering of Nanoswimmer and Biocompatible Piezo-material

Actuation is an important part in realization of nanoswimmer. Several actuation schemes have been investigated experimentally and published in literature such as chemical actuation, magnetic actuation and bacterial actuation mechanism [21]. The principle behind the chemical propulsion is the generation of bubbles upon mixing of two chemical species. While most of the literature is based on oxygen bubble generation due to catalytic decomposition of hydrogen peroxide, few attempts have also been made using acidic environment. Among various actuation schemes, magnetic method seems more feasible inside the human body because it can externally control and navigate magnetic nanoswimmer. Several magnetic and non-magnetic techniques have been attempted to move or control the nanoswimmer and are bio-inspired directional control using chemical gradient [22], photo tactic control, controllable magnetic field, assuming a ferromagnetic component of the nanorobot [23], [24], MRI controlled motion of magneto tactic bacteria, techniques based on thermal, electrostatic and piezoelectric properties [25], electric fields [26] and optical tweezers [27]. Each and every actuation mechanism has some pros and cons [21]. Till now, *in-vitro* actuation of artificial nanoswimmer has been employed by many researchers, which involves integration of many parts like chemistry, electronic circuitry and control system, leads to complexity and difficulty in realization at smaller scale. To realize the actuation scheme of nanoswimmer, a well-designed on board energy transduction system is required, which must overcome various challenges and issues significant in nanodomains [28].

Small size of the order of few hundreds of nanometers on-board actuation mechanism is itself advantageous, because of being comparable to biological species and therefore a possible use in bio-medical applications. Scientists and engineers have shown a great interest to conceptualize model, analyze and realize various actuation scheme for nanoswimmer in last two decades by fabricating it, using polymers, nanoparticles, biocompatible materials such as gold, piezoelectric materials, shape memory alloy and so on. Keeping in mind *in-vivo* medical applications, the material should be biocompatible [29], means it should not produce any toxic effects, degenerate inside the body, do not loose it's functionality when come into contact with different media at different locations.

The engrossment of nanorobots for various activities necessitates four fields: (a) energy storage, (b) energy transduction (c) control and (d) transmission [30]. Energy transduction is the essential component in designing of nanorobots. Energy is classified in numerous ways such as mechanical, electrical, light, heat and chemical. Among various kinds of energy, electricity is the most commonly used form because of it simply transformation into other types of energy. The term "Powering" generally implies conversion of any other form of energy into electrical energy. The most commonly used mechanism for conversion of mechanical energy into electrical energy is electrostatic [31], piezoelectric [32], and electromagnetic [33]. The application of electromagnetic and electrostatic mechanisms as energy harvesting purpose possesses some limitation [34]-[35]. The electromagnetic harvesters are larger in size which makes them impracticable to be used in MEMS [34]. It remains a challenge to design and fabricate an electromagnetic energy harvester in nano/micro domain due to poor properties of magnet and coil. Electrodes are used as parallel plate capacitor in electrostatic energy harvester, which needs to be charge initially to start the conversion process [35]. Now a day, energy harnessing using piezoelectric materials proves to be a more feasible material in the field of realization of energy transduction mechanism of a nanoswimmer due to low cost, biocompatibility, flexibility, and light weight, generation of electricity on stretching and vice a versa. The benefits of piezoelectric material can be utilized by designing a self-powered device for artificial nanoswimmer. Few experimental investigations using piezoelectric materials have been published in literature [36]. So, there is a lot of scope to work on the proposed area. Lead based piezoelectric materials are toxic in nature and may not suitable for *in-vivo* biomedical applications. To eradicate this problem, researchers are interested in synthesizing lead free biocompatible piezoelectric material such as polyvinylidenefluoride (PVDF). The biocompatibility of PVDF makes it appropriate to be used for energy harnessing in human body such as on board powering of nanoswimmer for various disease detection and drug delivery which is endeavored through simulation using COMSOL Multiphysics in the present thesis to ensure the betterment of designs of branched flagellated artificial swimmer at nanoscale.

1.4 Motivation

Nanotechnology allows the coalition of different research field such as mechanical, biological, magnetic, electronics, mathematics to design nanomachines [37] and creating a great impact on our life. The utmost important task in today's world is to comprehend the mechanism and behaviour at nano scale. Computational world has abilities to show us how these nanorobots work and their interaction towards surrounding environment. The motivation of present work comes from the existence of mastigonemes/cilia. The presence of cilia helps in the motion of cell like *paramecium*. The motion of cilia like structures for production of energy can be utilized which can be used further for propulsion of nanoswimmer.

This thesis sets the ground work for technology that is envisaged to be commercially available in next 30 years. By that time, it is envisaged that wireless, *in-vivo* medical device will be accessible to scrutinize environments of less space. One of the challenge that is considered during their development is propulsion through different location of human body. As the feasible environment is extremely different, this work aims the fluid filled environment to maintain low Reynolds number.

Therefore, this work is perceived as a stepping stone towards the designs of branch flagellated artificial nanoswimmer which is able to operate in fluid filled environment as human body. Helical swimmer at scaled up level is attempted most experimentally in literature. Very few attempts have been made on the mastigonemes bearing flagella (which demonstrate planar propulsion) and its effect on propulsive force. Hence, main purpose of the current study is to develop conceptual design of swimmer that is innocuous, biocompatible and simple. Moreover, the design should be developed at the proof-of-concept level at macro-scale. As the fabrication of branched flagellated nanoswimmer conquered, flagellated swimmer at millimetre scale can be easily scaled down in future.

Due to recent advancement in nanotechnology, there is a growing requirement of portable power supply as conventional battery has limited life time. In the current research, investigations of various structure of flagella (i.e. elastic tail) of an artificial nanoswimmer is carried out to explore it's suitability for on-board energy transduction through COMSOL multiphysics simulation. The structure's quintessential requirement is piezoelectric behavior which is to be used for energy transduction for nanoswimmer. In this work, the basic design for on-board energy harnessing for nanoswimmer is obtained using simple beam shaped like structure of PVDF fixed at one end through simulation to prove the concept of branches on flagella for enhancement of thrust force. Planar propulsion is also simulated by stipulating oscillatory motion to one end of flagellated artificial nanoswimmer to investigate energy flux generation for on-board powering.

1.5 Summary

In the present chapter, we discussed about the origin of bacteria, their structure, how they locomote in the environment? Motivation of the research work is also discussed in the present chapter. Different actuation mechanisms of nanoswimmer are presented chronologically in the next chapter. The purpose of the review is to discuss about propulsion mechanism that is being designed in fluidic environment for different biological application and for *in-vivo* application that has not been fully reconnoitred yet along with experimental studies being performed at scaled up level to validate the theories.

References:

[1] C. Dobell and A. Van Leeuwenhoek, “Antony Van Leeuwenhoek and his ‘Little Animals,’” *The American Journal of the Medical Sciences*, vol. 186, no. 2, pp. 1–12, 1933.

[2] H. C. Berg and D. A. Brown, “Chemotaxis in Escherichia coli analysed by three-dimensional tracking,” *Nature*, vol. 239, no. 5374, pp. 500–504, 1972.

[3] H. C. Berg, “Feature Article Site Index Motile Behavior of Bacteria,” *Physics today*, vol. 9, pp. 1–8, 2001.

[4] R. Meadows, “How bacteria shift gears,” *PLoS biology*, vol. 9, no. 5, pp. 1–2, 2011.

[5] A. R. Hardham, “Microtubules and the flagellar apparatus in zoospores and cysts of the fungusPhytophthora cinnamomi,” *Protoplasma*, vol. 137, no. 2–3, pp. 109–124, 1987.

[6] D. R. Pitelka, "*Electron-Microscopic Structure of Protozoa: International Series of Monographs on Pure and Applied Biology: Zoology,"* Elsevier, pp. 1-336, 2013.

[7] I. Manton, “The fine structure of plant cilia,” in *Symp. Soc. Exp. Biol*, vol. 6, pp. 306–319, 1952.

[8] D. R. Pitelka and C. N. Schooley, "Comparative morphology of some protistan flagella," University of California Press, pp. 73-91, 1955.

[9] T. L. Jahn, M. D. Lanman, and J. R. Fonseca, “The mechanism of locomotion of flagellates. II. Function of the mastigonemes of Ochromonas,” *The Journal of Protozoology*, vol. 11, no. 3, pp. 291–296, 1964.

[10] G. B. Bouck, “The structure, origin, isolation, and composition of the tubular mastigonemes of the Ochromonas flagellum,” *The Journal of cell biology*, vol. 50, no. 2, pp. 362–384, 1971.

[11] M. Venkatesan and B. Jolad, “Nanorobots in cancer treatment,” in *Emerging Trends in Robotics and Communication Technologies (INTERACT), 2010 International Conference on*, pp. 258–264, 2010.

[12] K. E. Peyer, S. Tottori, F. Qiu, L. Zhang, and B. J. Nelson, “Magnetic helical micromachines.,” *Chemistry-A European Journal*, vol. 19, no. 1, pp. 28–38, 2013.

[13] B. C. Crandall and J. Lewis, “Nanotechnology: research and perspectives,” in *First Foresight Conference on Nanotechnology*, pp. 1–8, 1992.

[14] E. Lauga and T. R. Powers, “The hydrodynamics of swimming microorganisms,” *Reports on Progress in Physics*, vol. 72, no. 9, pp. 96601–96636, 2009.

[15] T. Xu, “Propulsion characteristics and visual servo control of scaled-up helical microswimmers,” Paris, pp. 1–166, 2014.

[16] H. C. Berg and R. A. Anderson, “Bacteria swim by rotating their flagellar filaments,” *Nature*, vol. 245, no. 5425, pp. 380–382, 1973.

[17] F. Qiu and B. J. Nelson, “Magnetic helical micro-and nanorobots: Toward their biomedical applications,” *Engineering*, vol. 1, no. 1, pp. 21–26, 2015.

[18] E. M. Purcell, “Life at low Reynolds number,” *American journal of physics*, vol. 45, no. 1, pp. 3–11, 1977.

[19] K. Deepak, J. S. Rathore, and N. N. Sharma, “Nanorobot propulsion using helical elastic filaments at low Reynolds numbers,” *Journal of Nanotechnology in Engineering and Medicine*, vol. 2, no. 1, pp. 11009–11015, 2011.

[20] R. S. Kotesa, J. S. Rathore, and N. N. Sharma, “Tapered Flagellated Nanoswimmer: Comparison of Helical Wave and Planar Wave Propulsion,” *BioNanoScience*, vol. 3, no. 4, pp. 343–347, 2013.

[21] S. Nain and N. N. Sharma, “Propulsion of an artificial nanoswimmer: a comprehensive review,” *Frontiers in Life Science*, vol. 8, no. 1, pp. 2–17, 2015.

[22] K. Nogawa, M. Kojima, M. Nakajima, M. Homma, and T. Fukuda, “Motion control of bacteria-driven micro objects by Nano/Micro pipettes,” in *Nanotechnology (IEEE-NANO), 2010 10th IEEE Conference on*, pp. 1028–1031, 2010.

[23] R. Dreyfus, J. Baudry, M. L. Roper, M. Fermigier, H. a Stone, and J. Bibette, “Microscopic artificial swimmers.,” *Nature*, vol. 437, no. 7060, pp. 862–5, 2005.

[24] O. S. Pak, W. Gao, J. Wang, and E. Lauga, “High-speed propulsion of flexible nanowire motors: Theory and experiments,” *Soft Matter*, vol. 7, no. 18, pp. 8169–8181, 2011.

[25] G. Kósa, M. Shoham, and M. Zaaroor, “Propulsion method for swimming microrobots,” *Robotics, IEEE Transactions on*, vol. 23, no. 1, pp. 137–150, 2007.

[26] G. Hwang and S. Régnier, “Remotely powered propulsion of helical nanobelts,” in *Encyclopedia of Nanotechnology*, Netherlands: Springer, pp. 2226–2237, 2012.

[27] S. Hu and D. Sun, “Automated transportation of single cells using robot-tweezer manipulation system.,” *Journal of laboratory automation*, vol. 16, no. 4, pp. 263–270, 2011.

[28] N. N. Sharma and R. K. Mittal, “Nanorobot movement: Challenges and biologically inspired solutions,” *Int. Journal of Smart sensing & Intelligent Systems*, vol. 1, no. 87, pp. 1–23, 2008.

[29] R. Majumdar, N. Singh, J. S. Rathore, and N. N. Sharma, “In search of materials for artificial flagella of nanoswimmers,” *Journal of Materials Science*, vol. 48, no. 1, pp. 240–250, 2013.

[30] J. S. Rathore and N. N. Sharma, “Engineering nanorobots: chronology of modeling flagellar propulsion,” *Journal of Nanotechnology in Engineering and Medicine*, vol. 1, no. 3, pp. 31001–31007, 2010.

[31] P. D. Mitcheson, P. Miao, B. H. Stark, E. M. Yeatman, A. S. Holmes, and T. C. Green, “MEMS electrostatic micropower generator for low frequency operation,” *Sensors and Actuators A: Physical*, vol. 115, no. 2, pp. 523–529, 2004.

[32] A. Truitt and S. N. Mahmoodi, “A review on active wind energy harvesting designs,” *International Journal of Precision Engineering and Manufacturing*, vol. 14, no. 9, pp. 1667–1675, 2013.

[33] D. P. Arnold, “Review of microscale magnetic power generation,” *IEEE Transactions on Magnetics*, vol. 43, no. 11, pp. 3940–3951, 2007.

[34] S. P. Beeby, M. J. Tudor, and N. M. White, “Energy harvesting vibration sources for microsystems applications,” *Measurement science and technology*, vol. 17, no. 12, pp. 175–195, 2006.

[35] S. Roundy, P. K. Wright, and J. Rabaey, “A study of low level vibrations as a power source for wireless sensor nodes,” *Computer communications*, vol. 26, no. 11, pp. 1131–1144, 2003.

[36] Y. Fu, “Design of a Hybrid Magnetic and Piezoelectric Polymer Microactuator,” pp. 1–231, 2005.

[37] T. Fukuda, F. Arai, and L. Dong, “Nano robotic world–from micro to nano,” in *Proc. IEEE Int. Conf. on Robotics and Automation*, pp. 632–637, 2002.