Towards Realization of Intelligent Medical Treatment at Nanoscale by Artificial Microscopic Swarm Control Systems

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Quantitative Study

Abstract

Background: In this paper, the novel concept of artificial microscopic swarm control systems is proposed as a promising approach towards realization of intelligent medical treatment at nanoscale. In this new paradigm, treatment is done autonomously at nanoscale within the patient's body by the proposed swarm control systems.

Methods: From control engineering perspective, medical treatment can be considered as a control problem, in which the ultimate goal is to find the best feasible way to change the state of diseased tissue from unhealthy to healthy in presence of uncertainty. Although a living tissue is a huge swarm of microscopic cells, nearly all of the common treatment methods are based on macroscopic centralized control paradigm. Inspired by natural microscopic swarm control systems such as nervous, endocrine and immune systems that work based on swarm control paradigm, medical treatment needs a paradigm shift from macroscopic centralized control to microscopic swarm control. An artificial microscopic swarm control system consists of a huge number of very simple autonomous microscopic agents that exploit swarm intelligence to realize sense, control (computing) and actuation at nanoscale in local, distributed and decentralized manner. This control system can be designed based on mathematical analysis and computer simulation.

Results: The proposed approach is used for treatment of atherosclerosis and cancer based on mathematical analysis and in-silico study.

Conclusion: The notion of artificial microscopic swarm control systems opens new doors towards realization of autonomous and intelligent medical treatment at nanoscale within the patient's body.

Keywords: Intelligent medical treatment, Microscopic swarm control, Medical nanorobotics, Mathematical analysis, Computer simulation

Introduction

Is it possible to manufacture and send

nanoscale agents within the human body to autonomously sense and control the life conditions? In 1966, when the science fiction film of 'Fantastic Voyage' was produced, realization of such scenario was a dream. But in recent years, remarkable advances in

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nanotechnology have made it possible to manufacture and send nanoscale agents inside the human body to move today's medicine towards diagnosis and treatment of complex diseases such as cancer, different types of disability, atherosclerosis, stroke, and dementia. This new interdisciplinary research area is called nanomedicine.

Each nanoscale agent has very limited capabilities. Sense, actuation, and control (computing) are local, distributed and decentralized. The internal environment of human body is very uncertain, dynamic and noisy. Brownian and viscous forces usually dominate the propulsion force and thus the motion of a nano-agent is pseudo-random. Only short-range and local communication is often possible among agents. Generally, many assumptions that are used for simplification in macroscopic and lumped models could not be employed in the nanoscale and thus the models are microscopic and distributed. Fortunately, most applications in nanomedicine have access to large swarms of nanoscale agents in even small volumes of the environment. The central question is: How can a swarm of very simple nano-agents perform complex tasks intelligently in such an uncertain environment? As a practical approach, this paper introduces the novel concept of artificial microscopic swarm control systems to realize artificial swarm intelligence at nanoscale inside human body.

There exist few works in the literature that have directly used swarm intelligence in nanomedicine. Chandrasekaran et al. discussed the application of quorum sensing (the ability of some types of bacteria, immune cells and other biological cells to communicate and coordinate behavior via signaling molecules) to the realization of swarm intelligence in a swarm of bio-nano robots (Chandrasekaran & Hougen, 2006). Martel et al. discussed a micro-assembly process and considered it on several thousand flagellated bacteria acting as micro-workers (Martel & Mohammadi, 2009). He

also described the problems of communication and cooperation in the swarms of sensotaxis-based bacterial microrobots (Martel, André, Mohammadi, Lu, & Felfoul, 2009). Martel et al. compared the aggregates of synthetic microscale nanorobots with the swarms of computer-controlled flagellated bacterial robots for target therapies through the human vascular network (Martel, 2010). Wang et al. demonstrated that like swarming insects drawing crowds to a food source, a system of nanoparticles and engineered proteins can communicate with one another to raise the concentration of systemically administered drugs at the site of a tumor (Wang, Brown, & Xia, 2011). The system harnesses one of the body's own communication pathways, one that coagulates blood, to accumulate drugs where they are needed. The researchers engineered a set of nanoparticles that trigger the body to grow blood clots around tumors. A second set of nanoparticles that recognizes the blood clots then delivers a dose of anti-cancer drug to the tumor.

Rowhanimanesh et al. proposed the concept of swarm control systems for nanomedicine and considered its application to the prevention and treatment of atherosclerosis (Rowhanimanesh & Akbarzadeh-T., 2012; Rowhanimanesh & Akbarzadeh-T., 2013; Rowhanimanesh, 2013; Rowhanimanesh & Akbarzadeh-T., 2015). Loscrí at al. desgined an acoustic communication technique of nanorobot swarms for nanomedicine applications (Loscrí & Vegni, 2015). Hajizadeh et al. introduced the concept of swarm learning for autonomous nanoparticles to control drug release rate in treatment of atherosclerosis (Hajizadeh-S., Akbarzadeh-T., & Rowhanimanesh, 2015a & 2015b). Razmi et al. used swarm of autonomous fuzzy nanoparticles for control of tumor growth in cancer (Razmi, Moghaddam, & Rowhanimanesh, 2015).

Methods

An artificial micrsocopic swarm control

system consists of a huge number of very simple autonomous microscopic agents that are able to cooperate and communicate with each other to realize artificial swarm intelligence at nanoscale inside a living tissue. An autonomous microscopic agent utilizes three fundamental units including sensor, controller and actuator units as schematically shown in figure 1. Some sensors and actuators can be used as transceivers for communication. This structure enables the agent to continuously sense its environment, communicate with other agents, and autonomously apply the required actions if any abnormality is occurred. The hardware complexity of these units should be low for more reasonable manufacturing within the existing bounds of technologies.

Although different nanoscale sensors and actuators can be used in an autonomous microscopic agent, chemical concentration is the most common signal for both input and output. Hence, the sensor unit usually includes nanoscale molecular concentration sensors to

sense concentration signals from the interior environment of the tissue and the actuator unit is usually composed of controllable drug pumps/valves that are connected to drug payload to release the drug molecules in the aqueous environment of the tissue with a flow rate determined by the controller unit.

The most important part of an autonomous microscopic agent is controller unit (decision making unit) that determines which concentration signals are sensed by the agent (input) and how drug release rate (output) is changed according to the sensed values. Controller unit should be analytically designed based on the mathematical model of disease dynamics at nanoscale and its performance must be verified through computer simulation before any implementation. In this paper, our insight to the notion of autonomous microscopic agent is abstract and mathematical. For real-world implementation of such agents, the critical assumptions of biocompatibility and biodegradability should be considered carefully.
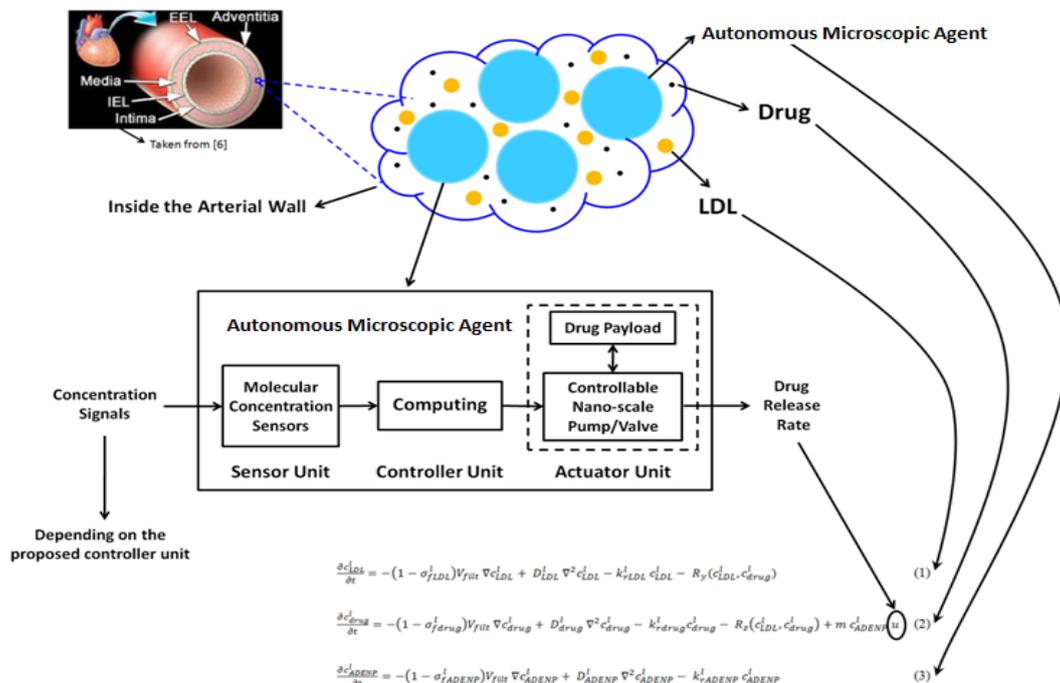

Figure 1. The general structure of an autonomous microscopic agent (used for the treatment of atherosclerosis (Rowhanimanesh & Akbarzadeh-T., 2013))

Results

In this section, it is demonstrated that how the proposed concept of artificial microscopic swarm control system can be used as a non-invasive targeted treatment method for atherosclerosis and cancer as two of the most complex diseases. The system is analytically designed based on the mathematical model of the dynamics of disease at nanoscale. The performance of the designed control system is evaluated through computer simulation in ADENP Tool, a MATLAB toolbox developed by author in (Rowhanimanesh, 2013) for simulating microscopic swarm control systems in nanomedical applications. These two cases are briefly considered here. Without loss of generality, in both cases the controller unit is designed according to fuzzy control approach.

Case I: Atherosclerosis (Rowhanimanesh & Akbarzadeh-T., 2015): The anatomical structure of arterial wall is schematically illustrated in figure 2. The following equations describe the governing dynamics on LDL, FNP, pheromone, ANP, and drug transport within the arterial wall. The details of model description and physiological parameters are presented in (Rowhanimanesh & Akbarzadeh-T., 2015).

$$\frac{\partial c_{LDL}^l}{\partial t} = -\left(1 - \sigma_{fLDL}^l\right)V_{filt}\nabla c_{LDL}^l + D_{LDL}^l\nabla^2 c_{LDL}^l - k_{rLDL}^l c_{LDL}^l - R_y(c_{LDL}^l, c_{drug}^l) \quad (1)$$

$$\frac{\partial c_{FNP}^{lj}}{\partial t} = -\left(1 - \sigma_{fFNP}^l\right)V_{filt}\nabla c_{FNP}^{lj} + D_{FNP}^l\nabla^2 c_{FNP}^{lj} - k_{rFNP}^l c_{FNP}^{lj} \quad \text{(for } j = 1:q) \quad (2)$$

$$\frac{\partial c_{ph}^l}{\partial t} = -\left(1 - \sigma_{fph}^l\right)V_{filt}\nabla c_{ph}^l + D_{ph}^l\nabla^2 c_{ph}^l - k_{rph}^l c_{ph}^l + m_{ph}\sum_{j=1}^{q} c_{FNP}^{lj}\, u_{FNP}^{lj} \quad (3)$$

$$\frac{\partial c_{ANP}^l}{\partial t} = -\left(1 - \sigma_{fANP}^l\right)V_{filt}\nabla c_{ANP}^l + D_{ANP}^l\nabla^2 c_{ANP}^l - k_{rANP}^l c_{ANP}^l \quad (4)$$

$$\frac{\partial c_{drug}^l}{\partial t} = -\left(1 - \sigma_{fdrug}^l\right)V_{filt}\nabla c_{drug}^l + D_{drug}^l\nabla^2 c_{drug}^l - k_{rdrug}^l c_{drug}^l - R_z(c_{LDL}^l, c_{drug}^l) + m_{drug}\, c_{ANP}^l\, u_{ANP}^l \quad (5)$$

As depicted in figure 3, a swarm fuzzy control approach is applied for intelligent control of Low-Density Lipoprotein (LDL) concentration in the arterial wall by stigmergic cooperation between two distinctive swarms of autonomous microscopic agents called Fuzzy Nanoparticles (FNPs) and Auxiliary Nanoparticles (ANPs).

The effect of the proposed control system on the LDL level in the interior of the arterial wall is considered over 48 hours (two days) in two distinguishing situations: unhealthy (abnormal) arterial wall where the peak of LDL concentration is 200 mg dL^{-1}, and healthy arterial wall where the peak of LDL concentration is 60 mg dL^{-1}.
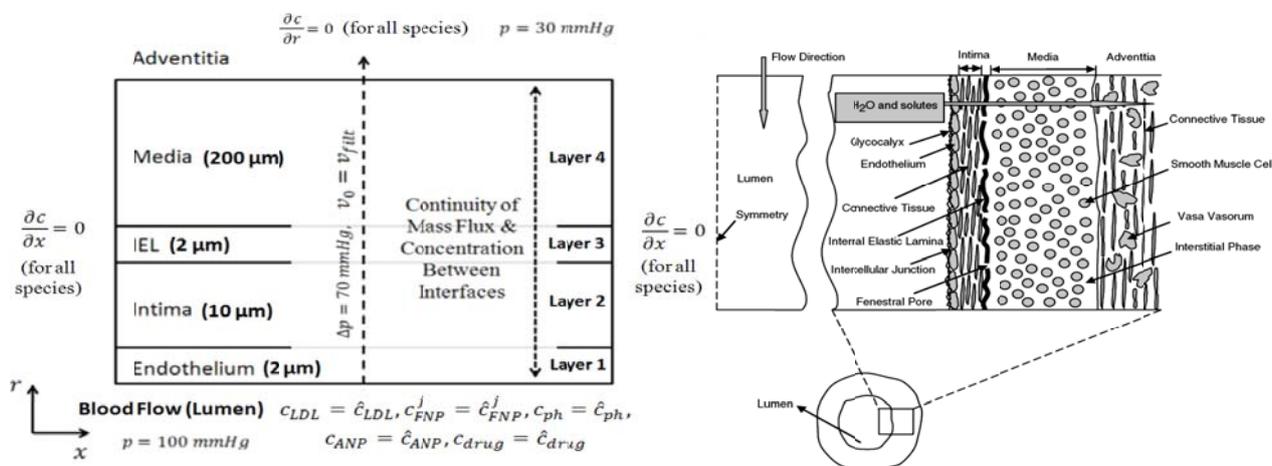

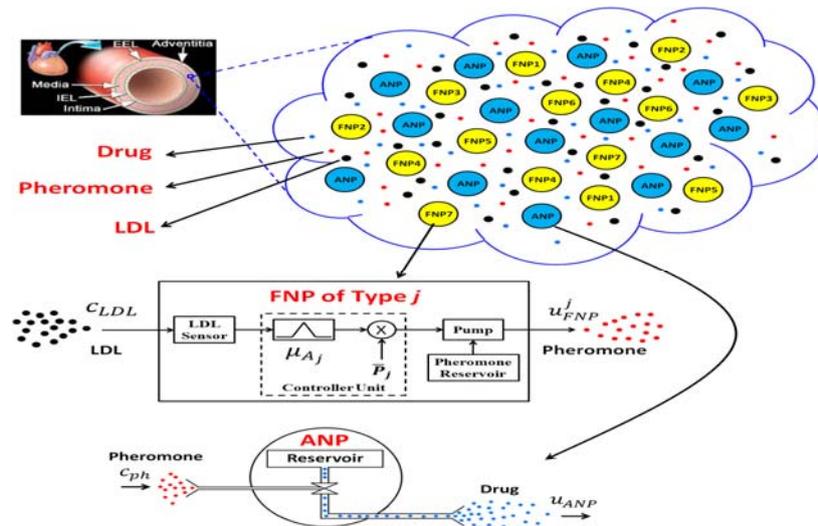**Figure 2.** Transverse section of arterial wall (Rowhanimanesh & Akbarzadeh-T., 2015)

Figure 3. The architecture of the proposed artificial microscopic swarm control system for treatment of atherosclerosis (Rowhanimanesh & Akbarzadeh-T., 2015)

Figures 4 and 5 represent the final (controlled) profile of LDL concentration in the arterial wall at the end of 48 hours and compares this profile with the desired (normal) and uncontrolled (without drug) LDL levels for both healthy and unhealthy cases. Simulation results demonstrate that although the LDL concentration in lumen is very high ($200 \, \mathrm{mg \, dL^{-1}}$), the proposed approach could successfully reduce the LDL level in all layers of an unhealthy arterial wall with reduction rate of 37.33%, 75.31%, 75.35%, and 73.67% in Endothelium, Intima, IEL and Media,

respectively. In figure 5.(b), the proposed method could successfully understand that the arterial wall is healthy, where the LDL reduction rate is trivial and 3.16%, 7.27%, 7.41%, and 7.68% in Endothelium, Intima, IEL and Media, respectively. The mass of the released drug by the proposed technique in a healthy wall is 16 times less than its corresponding value in the unhealthy wall which demonstrates the efficiency of the new method in distinguishing between unhealthy and healthy tissues which could significantly reduce the unwanted side effects of drug.
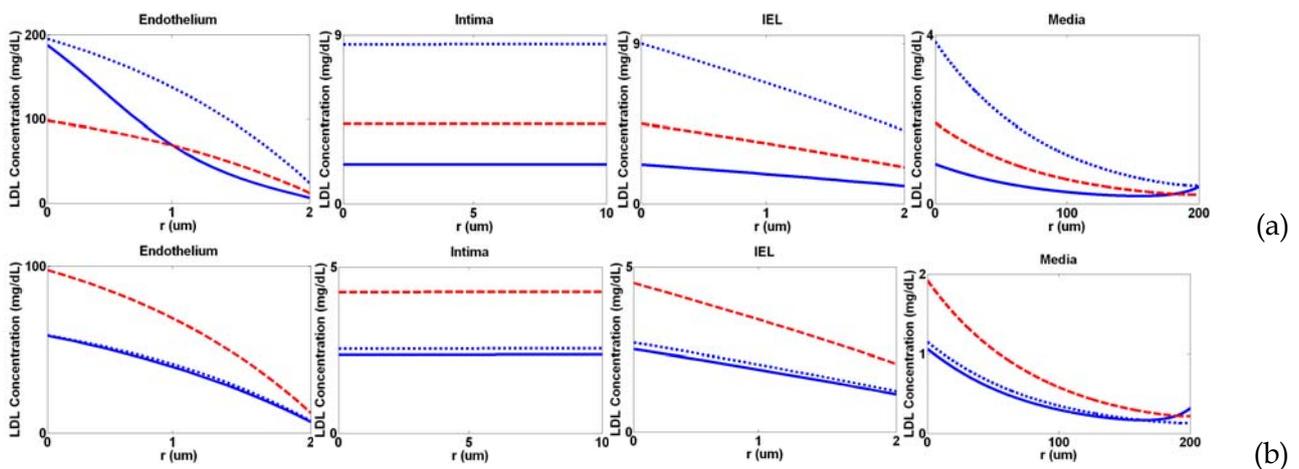

Figure 4. Final LDL concentration profiles (solid) after two days in contrast to desired LDL level (dash) and uncontrolled LDL level (dot). a) Unhealthy arterial wall, b) Healthy arterial wall.
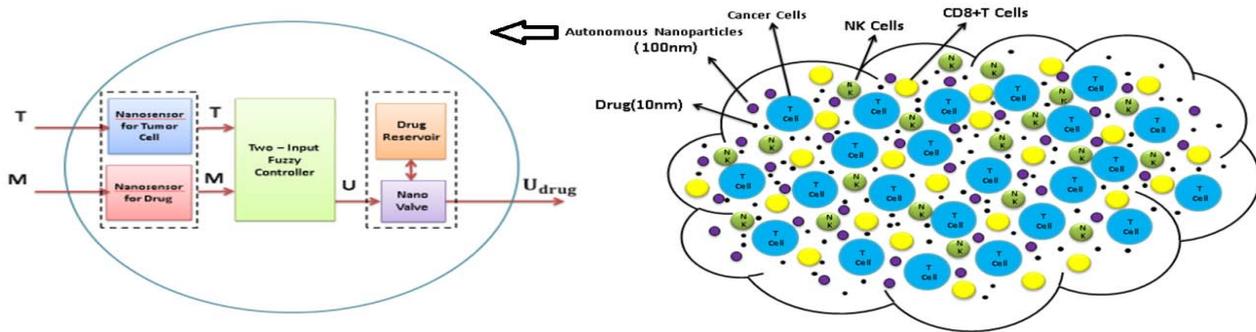
Figure 5. The architecture of the proposed artificial microscopic swarm control system for treatment of cancer (Razmi, Moghaddam, & Rowhanimanesh, 2015).

Case II: Cancer (Razmi, Moghaddam, & Rowhanimanesh, 2015): The following equations describe the governing dynamics among tumor cells (T), different families of immune cells (N, L, C), and biochemical molecules (M, I) including drug. The details of model description and physiological parameters are presented in (Razmi, Moghaddam, & Rowhanimanesh, 2015).

$$\frac{dT}{dt} = aT(1-bT) - cNT - DT - K_T(1-e^{-\delta_T M})T \tag{1}$$

$$\frac{dN}{dt} = f(\frac{e}{f}C - N) - pNT + \frac{p_N NI}{g_N + I} - K_N(1-e^{-\delta_N M})N \tag{2}$$

$$\frac{dL}{dt} = -\frac{\theta mL}{\theta + I} + j\frac{T}{k+T}L - qLT + (r_1N + r_2C)T - \frac{u\dot{L}CI}{k+I} - K_L(1-e^{-\delta_L M})L + \frac{p_I LI}{g_I + I} + v_L(t) \tag{3}$$

$$\frac{dC}{dt} = \beta(\frac{\alpha}{\beta} - C) - K_C(1-e^{-\delta_C M})C \tag{4}$$

$$\frac{dM}{dt} = -\gamma M + C_{denp} U_{denp}(t) \tag{5}$$

$$\frac{dI}{dt} = -\mu_I + \phi C + \frac{\omega LI}{\xi + I} + v_I(t) \tag{6}$$

$$D = d\frac{(L/\tau)^l}{s + (L/\tau)^l} \tag{7}$$

Figure 5 shows the architecture of the proposed artificial microscopic swarm control system. As depicted in this figure, autonomous microscopic agents continuously take feedback from both tumor cells population and local concentration of drug in the interior of the cancerous tissue. The goal of this system is damping of the tumor growth and optimal release of drug to minimize the drug side effects. Simulation results in figure 6 demonstrate that the designed control system could reach these goals successfully.
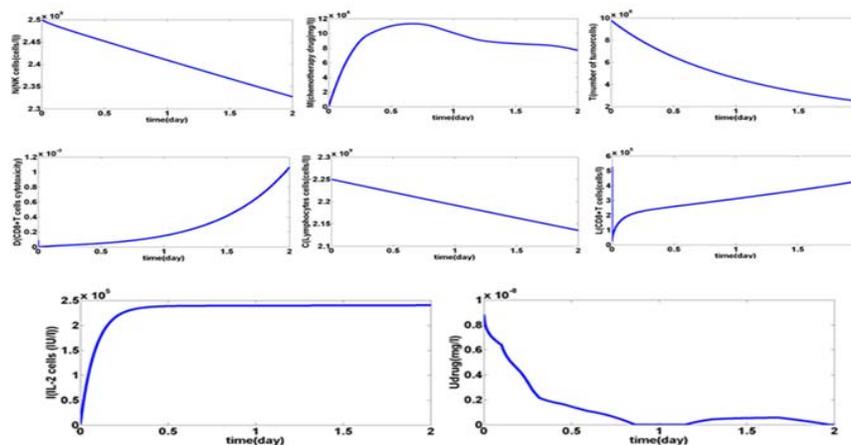

Figure 6. Temporal profile of concentration signals during two days (Razmi, Moghaddam, & Rowhanimanesh, 2015).

Discussion

Recent advances in medical high technologies show that treatment of complex diseases is highly dependent to the ability of control at cellular and molecular scales. As a promising approach towards realization of this crucial need, this paper proposes the novel concept of artificial microscopic swarm control systems. Using this paradigm, intelligent medical treatment can be done autonomously at nanoscale within the patient's body. An artificial microscopic swarm control systems consists of a huge number of autonomous microscopic agents that exploit swarm intelligence to realize sense, control (computing) and actuation at nanoscale in local, distributed and decentralized manner. In this paper, it is demonstrated that how the proposed swarm control system can be used for treatment of atherosclerosis and cancer based on mathematical analysis and in-silico study.

In general, the proposed notion of artificial microscopic swarm control systems can revolutionize medicine especially for intelligent prevention, early and accurate diagnosis, and efficient treatment with least invasion, pain, side effects, recovery time, hospital-acquired infection and cost especially in complex diseases. Also, it can greatly help upcoming medical high technologies such as medical nanorobotics, molecular and cellular medicine, tissue engineering, nanomedicine, engineered microorganisms, targeted therapy, immunotherapy, DNA robotics, and Internet of nano things.

Conflict of Interests

Authors have no conflict of interests.

Acknowledgments

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References

Chandrasekaran, S., & Hougen, D. F. (2006). Swarm intelligence for cooperation of bio-nano robots using quorum sensing. Paper presented at the Bio Micro and Nanosystems Conference, San Francisco, CA.

Martel, S., & Mohammadi, M. (2009). A robotic micro-assembly process inspired by the construction of the ancient pyramids and relying on several thousand flagellated bacteria acting as micro-workers. Paper presented at the IEEE/RSJ International Conference on Intelligent Robots and Systems, USA, 426-427.

Martel, S., André, W., Mohammadi, M., Lu, Z., & Felfoul, O. (2009). Towards swarms of communication-enabled and intelligent sensotaxis-based bacterial microrobots capable of collective tasks in an aqueous medium. Paper presented at IEEE International Conference on Robotics and Automation, Japan, 2617-2622.

Martel, S. (2010). Aggregates of synthetic microscale nanorobots versus swarms of computer controlled flagellated bacterial robots for target therapies through the human vascular network. Paper presented at IEEE International Conference on Quantum, Nano and Micro Technologies, 14-17.

Wang, Y., Brown, P., & Xia, Y. (2011). Nanomedicine: Swarming towards the target. Nature Materials, 10, 482-483.

Rowhanimanesh, A., & Akbarzadeh-T., M.R. (2012). Control of low-density lipoprotein concentration in the arterial wall by proportional drug-encapsulated nanoparticles. IEEE Transactions on Nanobioscience, 11(4), 394-401.

Rowhanimanesh, A., & Akbarzadeh-T., M.R. (2013). Autonomous drug-encapsulated nanoparticles: Towards a novel non-invasive approach to prevent atherosclerosis. Iranian Journal of Medical Physics, 10(2), 118-132.

Rowhanimanesh, A. (2013). Swarm control systems for nanomedicine and its application to the prevention of atherosclerosis. PhD Dissertation of Control Engineering, Faculty Advisor: Prof. M.R. Akbarzadeh-T., Ferdowsi University of Mashhad, Mashhad, Iran.

Rowhanimanesh, A., & Akbarzadeh-T., M.R. (2015). Stigmergic cooperation of nanoparticles for swarm fuzzy control of low-density lipoprotein concentration in the arterial wall. Applied Soft Computing, 34, 799-812.

Loscrí, V., & Vegni, A.M. (2015). An acoustic communication technique of nanorobot swarms for nanomedicine applications. IEEE Transactions on Nanobioscience. 14(6), 598-607.

Hajizadeh-S., A., Akbarzadeh-T., M.R., & Rowhanimanesh, A. (2015a). Swarm learning of interval nanoparticles to estimate the drug release function in atherosclerosis. Paper presented at 4th Iranian Joint Congress on Fuzzy and Intelligent Systems.

Hajizadeh-S., A., Akbarzadeh-T., M.R., & Rowhanimanesh, A. (2015b). Dynamic swarm learning for nanoparticles to control drug release function using RBF networks in atherosclerosis. Paper presented at International Symposium on Artificial Intelligence and Signal Processing.

Razmi, F., Moghaddam, R.K., Rowhanimanesh, A. (2015). Control of cancer growth using two input autonomous fuzzy nanoparticles. Nano. 10(4), 1550062.