J Nanopart Res (2010) 12:1–10
DOI 10.1007/s11051-009-9729-4

PERSPECTIVES

Is there a shift to "active nanostructures"?

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Received: 8 May 2009 / Accepted: 27 July 2009 / Published online: 25 August 2009

Abstract It has been suggested that an important transition in the long-run trajectory of nanotechnology development is a shift from passive to active nanostructures. Such a shift could present different or increased societal impacts and require new approaches for risk assessment. An active nanostructure "changes or evolves its state during its operation," according to the National Science Foundation's (2006) Active Nanostructures and Nanosystems grant solicitation. Active nanostructure examples include nanoelectromechanical systems (NEMS), nanomachines, self-healing materials, targeted drugs and chemicals, energy storage devices, and sensors. This article considers two questions: (a) Is there a "shift" to active nanostructures? (b) How can we characterize the prototypical areas into which active nanostructures may emerge? We build upon the NSF definition of active nanostructures to develop a research publication search strategy, with a particular intent to distinguish between passive and active nanotechnologies. We perform bibliometric analyses and describe the main publication trends from 1995 to 2008. We then describe the prototypes of research that emerge based on reading the abstracts and review papers encountered in our search. Preliminary results suggest that there is a sharp rise in active nanostructures publications in 2006, and this rise is maintained in 2007 and through to early 2008. We present a typology that can be used to describe the kind of active nanostructures that may be commercialized and regulated in the future.

Keywords Active nanostructures · Active nanotechnology · Bibliometrics · Trends · Prototypes · Science and technology trends

Introduction

Research in nanotechnology is anticipated to lead to the development of novel devices and systems with applications in multiple areas including materials,

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energy, defense, aerospace, and medicine (Lux Research 2007; NSET 2007). However, while some early nanotechnology-enabled products are already on the market, there is uncertainty about the trajectories and timing of more advanced phases of nanotechnology commercialization and also about the societal impacts and risks posed by potential nanotechnology applications (Royal Society 2004; Wilsdon 2004; Bennett and Sarewitz 2006; Besley et al. 2008). Efforts to inform discourse about the development pathways of nanotechnology and their societal impacts require an engagement with the technical content of nanotechnology. This paper contributes to this discourse by examining the extent to which nanotechnology research is increasing its focus on "active nanostructures."

The concept of "active nanostructures" was put forward by Dr. Mihail Roco (2004) in his vision of four generations of nanotechnology. This vision defined successive stages in a timeline for nanotechnology prototyping and commercialization, beginning with current first generation passive products (such as nanocoatings, nanoparticles, or nanostructured materials). In Roco's conception, active nanostructures form the basis of the second generation of nanotechnology development beginning around the mid-2000s. As described by Roco in a workshop for the International Risk Governance Council (IRGC), active nanostructures have characteristics such that their "…structure, state and/or properties change during their use; successive changes may occur either intended or unforeseen reactions in the external environment" (IRGC 2007). According to Roco, this evolving functionality may be reversible or irreversible. Targeted drugs, actuators, and adaptive structures were among the examples of applications of active nanostructures. Roco envisaged two further stages of nanotechnology evolution—systems of nanosystems and molecular nanosystems—on a trajectory of development leading through to the 2020s. In this article, we concentrate on exploring the first shift in this model—the transition from passive to active nanostructures. To the extent that this shift is underway, it could signify an important inflexion in the development of nanotechnology, since impacts (including benefits as well as potential risks) may be both greater and different in character in the second phase when compared with the first. The International Risk Governance Council has characterized passive and active nanostructures as possessing distinct risk "frames", in which the risks associated with active nanostructures challenge current risk assessment paradigms and are associated with "system uncertainties" (IRGC 2007). We do not make any additional judgments in this article about these impacts, risks, and implications. Rather, our concern is with the fundamental and critical issue of how to measure whether there is indeed a shift to active nanostructures.

The US National Science Foundation (NSF) (where Dr. Roco is Senior Advisor for Nanotechnology) has been soliciting proposals for "Active Nanostructures and Nanosystems" (ANN) since 2005. The NSF's grant solicitation defines an active nanostructure thus: "An active nanostructure changes or evolves its state during its operation." The NSF's Nanoscale Interdisciplinary Research Team (NIRT) grant gives the following examples of active nanostructures: nanoelectromechanical systems (NEMS), nanomachines, self-healing materials, nanobiodevices, transistors, amplifiers, targeted drugs and chemicals, actuators, molecular machines, light-driven molecular motors, plasmonics, nanoscale fluidics, laser-emitting devices, adaptive nanostructures, energy storage devices, and sensors (National Science Foundation 2006).

Another definition of active nanostructures is offered by James Tour, an organic chemist. Based on research in his laboratory at Rice University, he offers a classification of nanotechnology based on whether the role of the nanoscale entity in a prototype involves passive, active, or hybrid nanotechnology. In the case of active nanotechnology, "… the nano entity does something elaborate such as absorbing a photon and releasing an electron, thereby driving a device, or moving in a specific and definable fashion across a surface" (Tour 2007). The definitions offered by Roco and Tour overlap to a large extent, except that Tour does not include nanostructures with irreversible evolving functionality. These overlapping conceptions of active nanostructures are also discussed in a report by the Project on Emerging Nanotechnologies (Davies 2009).

In the following article, we present analytical methods and results from our ongoing research on the trajectories of active nanostructures. Our aim is to inform nanotechnology dialogue and governance by providing robust approaches to measuring significant shifts in nanotechnology research and applications. We address two research questions in this paper: (a) Is there a shift to active nanostructures? (b) How can we characterize the prototypical areas into which active nanostructures may emerge?

Methodology

There have been multiple approaches to delineating the domain of nanotechnology in publications and patents, all of which encounter choices about what to include or exclude (Huang et al. 2003; Kostoff et al. 2006a, b; Bassecoulard et al. 2007; Porter et al. 2008). Nonetheless, these studies reach a core area of consensus, with all studies incorporating nanoscale materials such as nanoparticles, carbon nanotubes, quantum dots, fullerenes, and dendrimers in their definition of nanotechnology.

However, operationalizing a more complex concept like "active nanostructures" is fraught with additional difficulty, due to following reasons. The term "active nanostructure(s)" is not always used by scientists in publications to describe their study. Moreover, there are few terms that are explicitly associated with active nanostructures, while some examples cited by experts as active nanostructures are not associated with novel keywords. An example of the former is Nanoelectromechanical System. An example of the latter is Roco's example of a "Find–Detect–Treat" dendrimer platform which integrates the formerly separate modalities of a targeting group, detection or imaging group, and the drug. The keywords associated with the publication describing that research are: Folate-binding protein, Positive tumor-cells, In vitro, KB cells, Polyamidoamine dendrimers, Starburst dendrimers, Receptor, Efficacy, Delivery, and Oligonucleotides (Kukowska-Latallo et al. 2005).

The complexity of the concept means that there is not a simple one-step bibliometric search strategy to delineate active nanostructures. Rather, our approach relies on the combination of a two-stage bibliometric search strategy with an individual assessment of each abstract. In the development of this strategy, relevant review papers were read to develop an understanding of scientific concepts and discern patterns in the literature. We also drew on the NSF NIRT definition of active nanostructures (National Science Foundation 2006) described earlier. After testing different approaches, the best search strategy to delineate active nanostructures appeared to be an "AND" Boolean operation of two search term categories, the first to define nanomaterials and the second based on an operationalization of the active principles inhenerent in active nanostructures. The nanomaterial search term category is based on the commonly used bibliometric search strategy to bound nanotechnology. This includes terms like nano*, fullerene#, quantum dot#, dendri* (referred in the keywords as dendrimer, dendrimers, dendritic architecture, and dendritic nanostructure), self-assembl* and molecul*. The active principle search term category includes motor, rotor, actuat* (for actuator and actuation), sens* (for sensor and sensing), switch, shuttle, smart, responsive, antenna, wireless, adaptive, memory, plasmon*, device, transistor, valve, "logic gate", "self-healing", and intelligent. Explicit second generation terms like Nanoelectromechanical Systems, NEMS and nanofluidics were also added to the set. The searches were run on SCI EXPANDED Citation Index of Web of Science from 1995 to 2008. In the nano* searches, the exclusion terms nanospray-ESI, Nanog and nanosecond were used. Following this combined nanomaterials and active principle search, and the application of exclusion terms, each resulting publication abstract was read in order to determine if it was actually describing research in active nanostructures, and should be included in the data set. If the bibliographic record (particularly title, abstract, keywords, and keywords plus) mentioned both the material and active principle (or implied it as an application) it was included. Additionally, we did not attempt to resolve gray areas, for example, between microfluidics and nanofluidics. In such a case, if the article described a non-passive application, it was included.

Findings

This section is divided into two subsections: the first one describes our bibliometric findings and the second one describes our bibliographic findings. A more detailed analysis is available in a working paper on our group's website (Subramanian 2009).

Bibliometric analysis

The active nanostructures database comprised 21,868 global publication records. Figure 1 shows the trend

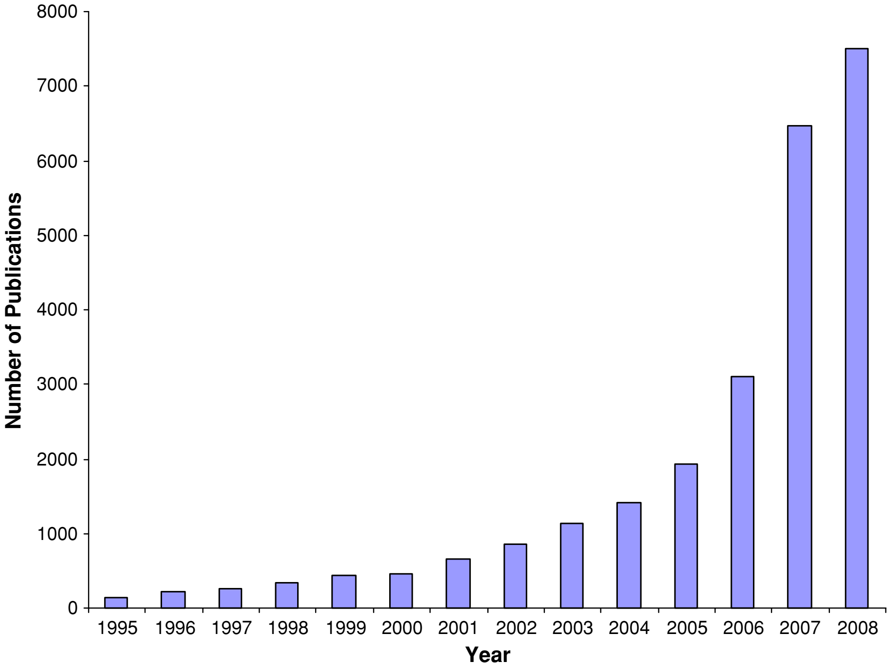

Fig. 1 Publications in active nanostructures from 1995 to 2008. *Source:* Database extracted from the Web of Science, Science Citation Index, 1995–April 2009, using search strategy described in text. Publications for 2008 are estimated, based on data through to April 2008 extrapolated for the full year using a linear trend forecast based on the ratio of active nanostructures publications to all nanotechnology publications for the period 2004–2007

of publications in active nanostructures from 1995 to 2008 (extrapolated). Overall, our exploration suggests that research in active nanostructures is growing. We find that the number of publications increases noticeably from 2005 onwards, which is similar to Roco's prediction. The number of annual publications in 2007 is almost double the 2005 level. The Georgia Tech global database of all nanotechnology publications (using the approach described in Porter et al. 2008) for the same time period contains 530,712 records. A comparison of the two databases shows that the active nanostructures database contains 4,453 unique records, most of which were published in 2007 and 2008. This suggests that the evolving new terms are not fully captured by earlier broad bibliometric definitions of nanotechnology.

We are intrigued by the sharp rise in the active nanostructures publications in recent years. We examined the funding awards provided by the National Science Foundation through its ANN solicitation. Using the NSF's Fastlane award search, we found that NSF has awarded $14.3 million in the years 2006–2007 as a part of ANN grants. This comprises 15 awards, of which two were exploratory research grants, while the majority was for interdisciplinary research grants in electronics, bionanotechnology, or other areas. Six were awarded from the Chemical, Bioengineering, Environmental, and Transport Systems (CBET) division of NSF's engineering directorate; six were from the Civil, Mechanical, and

Table 1 Top 10 countries in active nanostructures from 1995 to April 2008

Country	Composition of active nanotechnology database (%)	Composition of Georgia Tech global nanotechnology database (%)
USA	31.7	19.3
China	13.3	12.0
Japan	12.1	10.0
Germany	8.1	8.3
South Korea	6.7	3.8
UK	5.6	4.5
France	4.6	5.4
Italy	3.0	3.1
Taiwan	2.8	2.0
India	2.7	2.6

Source: Active nanostructures publications, in database extracted from Web of Science, Science Citation Index, 1995-April 2009, using search strategy described in text. Total number of publications is 21,686. Georgia Tech global database of nanotechnology publications, 1995–2008, using method described in Porter et al. (2008). Total number of publications is 530,712. Percentages in columns add to more than 100% due to multiple country co-authorships

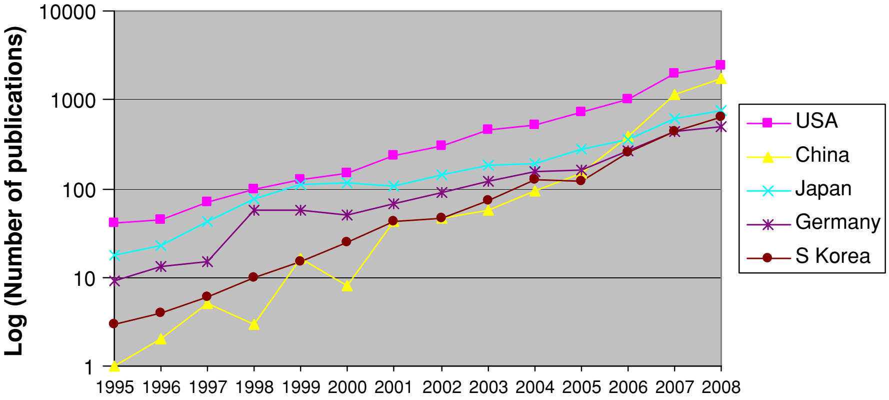

Fig. 2 Publication trends in active nanotechnology in top five countries. *Source:* See Fig. 1

Manufacturing Innovation Division; and three from the Electrical, Communications, and Cyber Systems (ECCS). This is a relatively small amount of funding, and the limited number of awards made cannot by themselves account for the rapid increase (by many thousands annually) in publications related to active nanostructures in recent years.

Table 1 shows the top 10 countries that publish articles in active nanostructures from 1995 to April 2008, and their respective share of publications in the active nanostructures and the Georgia Tech all nanotechnology data sets. The active nanostructures database comprises of 95 countries, with 31 countries having more than 50 publications. The United States, China, and Japan account for 32%, 13%, and 12% of the publications, respectively. The top ranking countries concur with the Georgia Tech database, although the order of the countries in the Georgia Tech database from the fifth country onwards is slightly different.

We explore the publication trends in active nanostructures in the top five countries over time, to compare how these countries are contributing to the sharp rise in publications from 2005. Figure 2 shows yearly publication trends in logarithmic scale from 1995 to 2008 for USA, China, Japan, Germany, and South Korea. There is a particularly sharp rise from 2006 for China, with upward increases also seen from 2006 onwards for the United States and South Korea.

Table 2 shows the top 10 ISI subject categories under which articles in active nanostructures are published from 1995 to April 2008. Publications are distributed across 147 subject categories, with 45 subject categories having more than 50 publications during the study period. The three leading categories are materials science, applied physics, and physical chemistry with 25.8%, 22.0%, and 14.6% of all publications, respectively. These top three journal categories occur in the Georgia Tech global nanotechnology database in the

Table 2 Top subject categories in active nanostructures from 1995 to April 2008

Journal Subject categories	Composition of active nanotechnology database (%)	Composition of Georgia Tech global nanotechnology database (%)
Materials Science, Multidisciplinary	25. 8	18.3
Physics, Applied	22.0	15.8
Chemistry, Physical	14.6	12.8
Chemistry, Multidisciplinary	13.0	8.3
Nanoscience and Nanotechnology	12.7	3.3
Physics, Condensed Matter	12.3	12.8
Chemistry, Analytical	9.0	2.4
Engineering, Electrical and Electronic	8.1	3.6
Polymer Science	6.5	5.2
Electrochemistry	5.7	2.3

Source: See Table 1

Table 3 Top 10 journals in active nanostructures from 1995 to April 2008

Journal	Composition of active nanotechnology database (%)	Composition of Georgia Tech global nanotechnology (%)
Applied Physics Letters	4.7	2.9
Nanotechnology	2.7	0.9
Physical Review B	2.4	2.9
Langmuir	2.3	1.6
Journal of Applied Physics	2.2	2.0
Sensors and Actuators B-Chemical	2.2	0.3
Journal of Physical Chemistry C	2.1	0.5
Nano Letters	2.0	0.6
Journal of the American Chemical Society	2.0	1.0
Analytical Chemistry	1.5	0.4

Source: See Table 1

same order. However, the categories of nanoscience and nanotechnology, analytical chemistry, and electrical and electronic engineering, and electrochemistry have greater representation in active nanostructures publications than in the Georgia Tech global nanotechnology database.

Table 3 shows the top 10 journals which publish articles in active nanostructures from 1995 to April 2008. Publications are distributed across 1,436 sources, with 86 publication sources having more than 50 publications during the study period. Applied Physics Letters, Nanotechnology, and Physical Review B comprise of 4.7%, 2.7%, and 2.4% of the database, respectively. These journals occur in the Georgia Tech global nanotechnology database, and their percentage occurrence is shown. Nanotechnology, Sensor and Actuators B-Chemical, Journal of Physical Chemistry C, Nano Letters, and Analytical Chemistry are emphasized more in the active nanostructures database than in the Georgia Tech global nanotechnology database.

Table 4 shows the top 10 journal keywords in the active nanostructure articles from 1995 to April 2008. These keywords are not particularly unique to active nanostructures, and are found in the Georgia Tech global nanotechnology database. The working paper version of our paper contains a more comprehensive list of top author and journal keywords, as well as keywords associated with the research described in the next subsection.

Table 4 Top 10 journal keywords in active nanostructures from 1995 to April 2008

Keyword	Number of records
Film	1,094
Device	880
Fabrication	656
Sensor	648
Array	587
Nanoparticle	580
Surface	544
Adsorption	499
Carbon nanotube	477
Biosensor	454

Source: Database extracted from the Web of Science, Science Citation Index, 1995-April 2009, using search strategy described in text. Total number of publication is 21,686

Bibliographic analysis

We have shown that research activity in active nanostructures has increased significantly in recent years. However, active nanostructures comprise multiple areas of research, and a typology will be useful in describing them further. Classification by material, technology, or architecture yields too many categories and does not capture the salient features of the research. Classification by applications is also problematic because a single prototype (or slightly modified versions of it) can be used for many applications. For example, similar polymeric encapsulation technologies are used for drug delivery in nanomedicine, nutrient delivery in agriculture, and corrosion inhibitor delivery in anti-corrosion technology.

We suggest the following categories are emerging from the research literature.[1] It is important to note that active nanostructure prototypes are not meant to fall into exclusive categories. In fact, overlapping categories may suggest greater complexity and dynamic behavior. A brief description of each category as follows.

(1) *Remote actuated active nanostructure*: Nanotechnology whose active principle is remotely activated or sensed.
(2) *Environmentally responsive active nanostructure*: Nanotechnology that is sensitive to stimuli like pH, temperature, light, oxidation–reduction, certain chemicals etc.
(3) *Miniaturized active nanostructure*: Nanotechnology which is a conceptual scaling down of larger devices and technologies to the nanoscale.
(4) *Hybrid active nanostructures*: Nanotechnology that involves uncommon combinations (biotic–abiotic, organic–inorganic) of materials.
(5) *Transforming active nanostructures*: Nanotechnology that changes irreversibly during some stage of its use or life.

Remote actuated active nanostructures

Remote actuated active nanostructures include magnetic, electrical, light, and wireless tagged nanotechnologies. Nanotechnology enables the use of more regions of the electromagnetic spectrum, and in unique devices for activation, sensing, and communications.

The integration of the sensing with a wireless modality is important in embedded sensors for biomedical, environmental, agricultural, and surveillance applications. For example, one sensor uses tin oxide nanoparticles integrated with a patch antenna for wireless detection of ethylene gas emitted from over-ripened fruits. Similarly, actuation and drug delivery may be coupled with the wireless modality.

Light is a salient "remote actuator" in the active nanostructures literature. An innovative light-based application is the artificial light harvesting antenna, which mimics its analog in photosynthetic plants and microorganisms. The basic concept involves a light sensitive species, which absorbs light and gets excited, and transfers this energy to other species. Artificial light harvesting antenna may be used in solar energy conversion devices. Nanotechnology has also continued the progress in "active layers" based on photovoltaic phenomena and room temperature photoluminescence and, which can be applied sensors, catalysts, and solar cells. Optoelectronics provides materials for telecommunication, information processing, and radars. Plasmonics is also a growing area for sensors based on spectroscopic signatures and optical data transfer. High frequency (gigahertz or terahertz) oscillators based on fullerenes and carbon nanotubes are also an active area of research that will yield nano-antennae for wireless applications.

Environmentally responsive active nanostructures

An environmentally responsive active nanostructure is one which undergoes its change of state in response to a specific environmental cue. Examples of environmentally responsive active nanostructures include sensors, light-driven molecular motors, responsive drug delivery, and environmentally responsive actuators. A brief description of some of these follows.

Sensors are one of the most prominent areas of active nanostructures research in the literature. Detection principles of these sensors are numerous: electrochemical, acoustic, optical, mechanical etc. There is a recent increase in the research on label-free sensors that detects changes in intrinsic properties of the sensing interface due to the presence of the analyte. For example, a biosensor based on magnetoelastic materials senses the binding of a bacterium with a bacteriophage bound on a sensor as a change in the resonant frequency. The transduction principle may also enable integration of previously distinct components of the sensor architecture. For example, nanowires and carbon nanotubes often integrate the sensing and electrical interface of sensor devices. Detection can also be based on more than one criterion. For example, a molecular imprinted polymer

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[1] This section draws on a reading by Vrishali Subramanian of journal research publication abstracts and review literature included in the active nanostructures database described in the first part of this paper.

with an “enzyme sensitive groove” mimics the enzyme–substrate “lock and key” interaction in biology. Detection is based on a structural fit as well as chemical recognition. Higher surface areas of nanostructures provide an increased sensing area, and some nanoscale sensors tout a “near molecular scale” detection limit. Sensors are also improving manipulation tools by providing sensing probes for piezoresistive cantilever structures in microscopy. For example, molecular absorption of an analyte on a probe functionalized with nitrogen-rich carbon nitride film can be sensed as a change in stiffness of piezoresistive cantilever. Similarly probes for sensing temperature and other chemical and biological stimuli have also been designed. Improvements in nanoelectronics and artificial intelligence are also improving stochastic sensors such as electronic nose and electronic tongue.

Actuators are used in microfluidic chips and other devices to achieve functions like specific movements, movement of “cargo” and sorting. Materials making up composites include sol–gels, ionic polymer–metal composites, carbon nanotube–polymer composites, deformable polymer-based systems (like dielectric elastomers, liquid crystal elastomers, ferroelectric polymers, conducting polymers etc.), thermal and ferroelectric shape memory alloys, biological components, such as microtubules and (biological) molecular motors, magnetoelastic materials, and supramolecules.

Environmentally sensitive drug delivery includes carrier designs that are sensitive to local microenvironments, such as pH, temperature, enzyme, ionic strength, redox etc. Design of an environmentally sensitive drug delivery system makes use of a physiological environment (including a pathological state) that provides the “stimulus” for the functionality. For example, tumors have a higher temperature (by 2–5 °C) and lower pH (by 0.5–2.5 units) than the rest of the body and this may be used to design carriers to deliver anti-cancer drugs to the tumor site. A carrier of peptide-based drugs has been used to remain inert in the stomach and release the peptide in the intestine, making use of the pH difference between these organs. Environmentally sensitive drug delivery can greatly enhance delivery efficiency of therapeutic molecules like drugs, genes, and polypeptides (e.g., insulin, small interference RNA, peptide nucleic acids etc.), and also reduce the side effects due to incidental interactions. Sensitivity to more than one stimulus has also been achieved with block copolymers.

Hybrid active nanostructures

Hybrid active nanostructures are one of the most novel categories that emerge from the research and include a combination of organic and inorganic materials. Two classes, which will be discussed here, are biotic–abiotic hybrid and silicon–organic hybrid nanostructures.

A biotic–abiotic hybrid device is one that mobilizes biological nanoscale components, such as DNA, protein, membrane, membrane channel pore, photosystem, and enzymes in an abiotic environment to perform an active function. It is important to reiterate the latter part: the novelty of a biotic–abiotic hybrid device is not only due to the unusual combination of materials but also the active functionality. Examples include (a) an enzyme responsive hydrogel which comprises of an enzyme immobilized in a three-dimensional polymer network which shrinks on enzyme catalysis, and (b) motor proteins or whole organisms containing functional motor proteins can be tethered to surfaces to produce linear and rotary motions (that they produce in living systems) in hybrid devices. The possibility of “engineering” living systems is novel. The general advantages to using biological components in hybrid devices are: (a) elegant and fault tolerant architecture (including self-assembly) (b) abundant availability (c) possibility of self-replication, and (d) existing functionality.

Silicon–organic hybrid nanotechnology represents a class of materials, mainly in electronics, where silicon chip technology is coupled with nanoscale organic components (e.g., a film) to obtain a hybrid device. Silicon–organic hybrid nanotechnology are fabricated by a combination of lithography and existing techniques of self-assembly. Some of the materials being used in this area include carbon nanotubes, carbon and silicon nanowires, organic polymers, and supramolecules.

Miniaturized active nanostructures

Miniaturized active nanostructures involve a conceptual scaling down of larger technologies and devices, and are an emergent area for technomimetic architectures and bottom-up construction. They include assemblies of functional molecules which can perform specified functions, based on phenomena such as redox, isomerization, chirality light-activated phenomena etc. These phenomena are not novel, and have been observed in solutions for a long time, but the most useful applications of nanotechnology in molecular machines require them to be expressed on a surface (e.g., film, monolayer etc.) or a three-dimensional structure (e.g., gel). The applications include informational (e.g., logic gate), electronic (e.g., single electron transistor), and mechanical (e.g., molecular motor). Examples include synthetic molecular motors, molecular machines, and molecular electronics structures. Many synthetic molecular motors are based on supramolecules. These include molecules, such as cyclodextrin and cyclophanes, as well as mechanically interlocked molecular architectures, such as rotaxanes, pseudorotaxanes, and catenanes.

Transforming active nanostructures

Transforming active nanostructures change irreversibly during their life cycle, and thus require consideration of risks before, during, and after the transformation. Many examples mentioned until now transform irreversibly; usually at the end of their life. This category also includes adaptive structures which transform irreversibly. Self-healing materials are an example of active nanostructures that almost always transform irreversibly. Self-healing materials include metal and plastic coatings which on specific triggers, repair damage caused by corrosion, mechanical damage etc. Common architectures of self-healing materials include composite passive–active layered structures and nanoscale containers with active (repair) chemicals in a passive matrix. Often, repair is initiated with a stimulus trigger such as crack (or deformation), light, pH etc. Varying thermal and electrical properties at the defect may also be used as the stimulus to initiate repair, and facilitate "controlled" release of repair chemicals.

Conclusions

This exploration of the bibliometric data and the research literature on active nanostructures provides important evidence but also raises many new questions. We assess our bibliometric and bibliographic evidence to make a preliminary assessment of two questions: (a) Is there a "shift" to active nanostructures? (b) How can we characterize the prototypical areas into which active nanostructures may emerge?

Early results do suggest that there is a sharp rise in active nanostructures publications in 2006, and this rise accelerates in 2007, and early 2008. The initial inflexion point in the trajectory seems to coincide with the early NSF ANN solicitations in 2005; though, as we have mentioned, this funding has been relatively small, and clearly researchers in active nanostructures have accessed other programs and sources of funds in the US and elsewhere to sponsor their research. The different profile of impacts and risks associated with active nanostructures means that this growth may have implications for societal and health, safety, and environmental considerations, although these need to be addressed in other studies.

The bibliographic section of our findings describes the kind of active nanostructures that may be applied and commercialized in the near future. We have not done a comprehensive assessment of risk, therefore, we can only echo the concern (as raised by IRGC, 2007) that some active nanostructure prototypes may pose new challenges for regulation, both in vivo and in the environment. An example is environmentally sensitive drug delivery systems which are likely to be used for in vivo applications and require a thorough consideration of the transport and fate of the drug delivery system in the body. Stimuli like temperature and pH are "generic" and vary considerably in the body and it must be ensured that unintended interactions do not occur. The fate of the carrier after drug delivery, i.e., whether it is excreted from the body or it concentrates in certain parts of the body is also a concern. The paradigms of toxicology have to be thoughtfully applied, particularly, the notion of "biocompatibility". These criteria are not used in current risk assessments. The Royal Commission on Environmental Pollution (2008) suggests that it is functionality and not nanoscale size that matters for risk, and our bibliographic analysis offers an emphasis on functionality. Further study needs to be done to develop and improve this typology, to measure research trajectories and the introduction of applications of these functional types, and to assess their impact and risk profiles.

Acknowledgments This research was undertaken at the Project on Emerging Nanotechnologies (PEN) and at Georgia Tech with support by PEN and the Center for Nanotechnology in Society at Arizona State University (sponsored by the National Science Foundation Award No. 0531194). The findings contained in this article are those of the authors and do not necessarily reflect the views of Project on Emerging Nanotechnologies or the National Science Foundation.

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