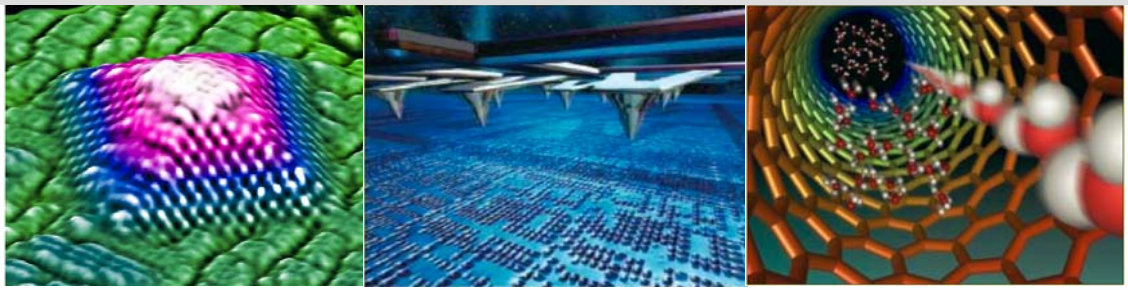
“Enabling and Investigative Tools in Nanotechnology: Measuring, Modeling and Computer Simulation Methods”



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Outline

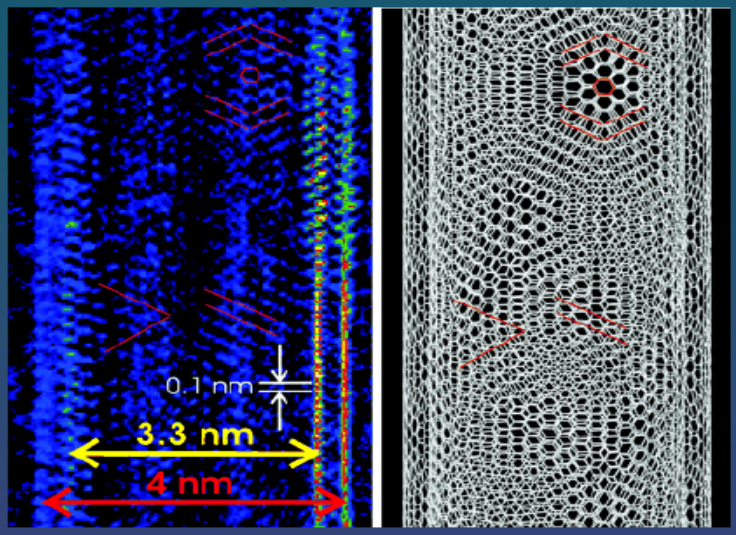
1. Nanoscience and Nanotechnology
2. Research Directions in Nanomaterials and Nanostuctures by Design
3. Research Directions in Nanofabrication Methods
4. Research Directions in Nanotechnology-based Medical Applications

1. Nanoscience and Nanotechnology in Europe

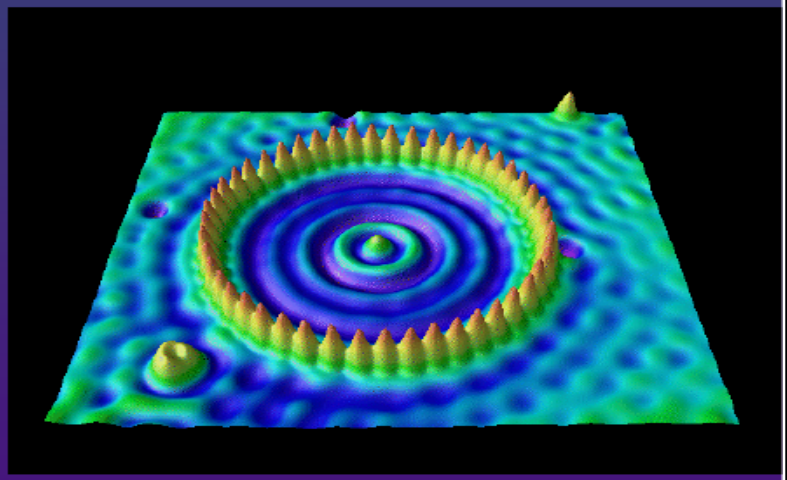
- Nanotechnology Products and Markets
- Nanotechnology R&D Investment
- Nanotechnology R&D Programs in Europe

What is Nanotechnology?

- Ability to understand, create, and use structures, devices and systems that have fundamentally new properties and functions because of their nanoscale structure,1-100 nanometer .
- Ability to image, measure, model, and manipulate matter on the nanoscale to exploit those properties and functions.
- Ability to integrate those properties and functions into systems spanning from nano- to micro- to macro-scopic scales.

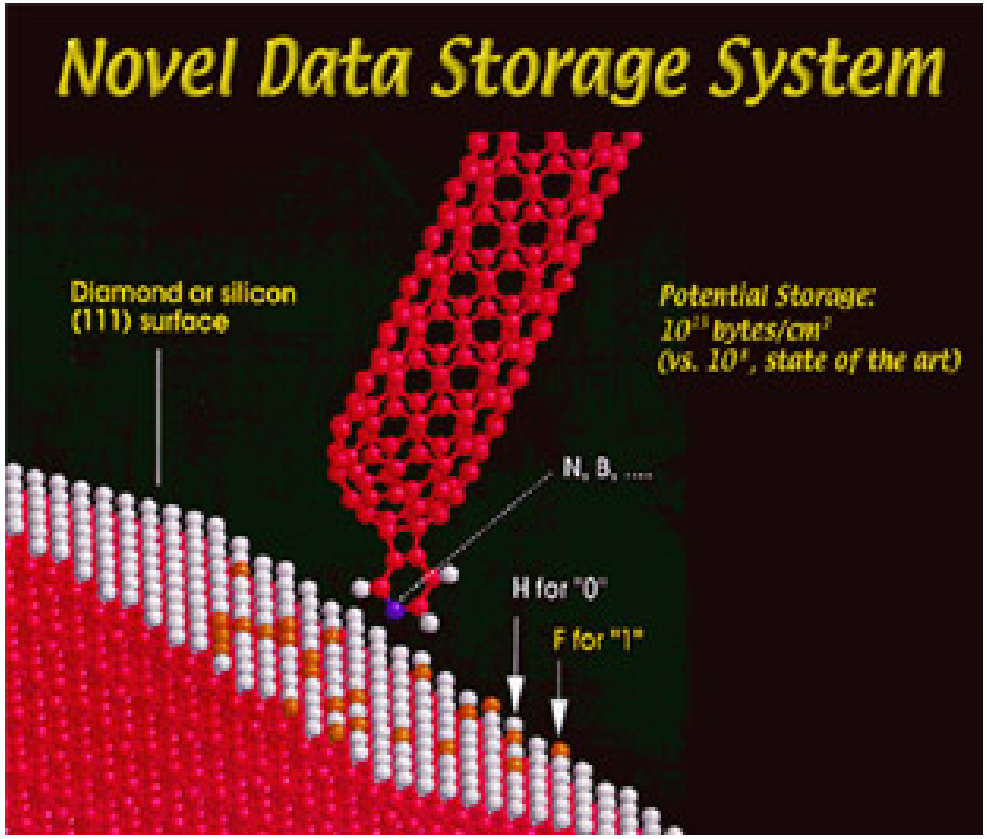


Nanoarea Electron Diffraction of DW Carbon Nanotube - Zuo, et.al



Corral of Fe Atoms - D. Eigler

Impact of Nanotechnology



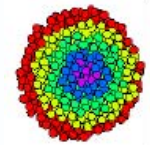
Source: www.ipt.arc.nasa.gov

- Computing and Data Storage
- Materials and Manufacturing
- Health and Medicine
- Energy and Environment
- Transportation
- Security
- Space exploration

- The market size for nanotechnology products amounted to $147 billion in 2007 and is expected to grow to over $1 trillion by 2015.

Four Generations of Products (2000-2020)

Four Generations of Products (200-2020): Timeline for beginning of industrial prototyping and nanotechnology commercialization



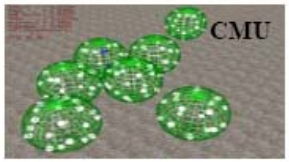
1st: Passive nanostructures (1st generation products)

Ex: coatings, nanoparticles, nanostructured metals, polymers, ceramics

~ 2000

2nd: Active nanostructures Ex: 3D transistors, amplifiers, targeted drugs, actuators, adaptive structures

~ 2005



3rd: Systems of nanosystems

Ex: guided assembling; 3D networking and new hierarchical architectures, robotics, evolutionary

~ 2010

4th: Molecular nanosystems

Ex: molecular devices 'by design', atomic design, emerging functions

~ 2015-2020

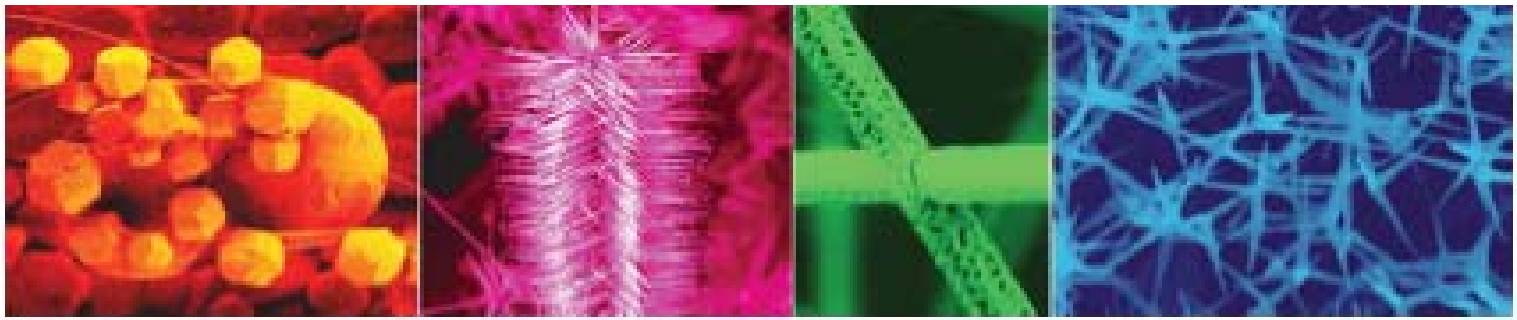
New R&D challenges

	R&D → Broad Use
IT	1960 - 2000
BIO	1980 - 2010
NANO	2000 - 2020

AIChE Journal, 2004, Vol. 50 (5), M. Roco

Commercialization of Nanotechnology Products

- The transition of new and emerging nano-enabled technologies from the laboratory to commercial products is dependent on numerous factors, including:
  - Integrating the nanostructures, nanodevices, and nanosystems into products with characterized and reproducible properties.
  - Scaling-up the manufacturing or fabrication for commercial production; development of related technologies.
  - Market forces and cost.
  - Consumer acceptance of nano-enabled technologies and products.
- All of these factors will determine whether nanotechnologies will move from the laboratory to the market.



Nanotechnology R&D Funding (Global)

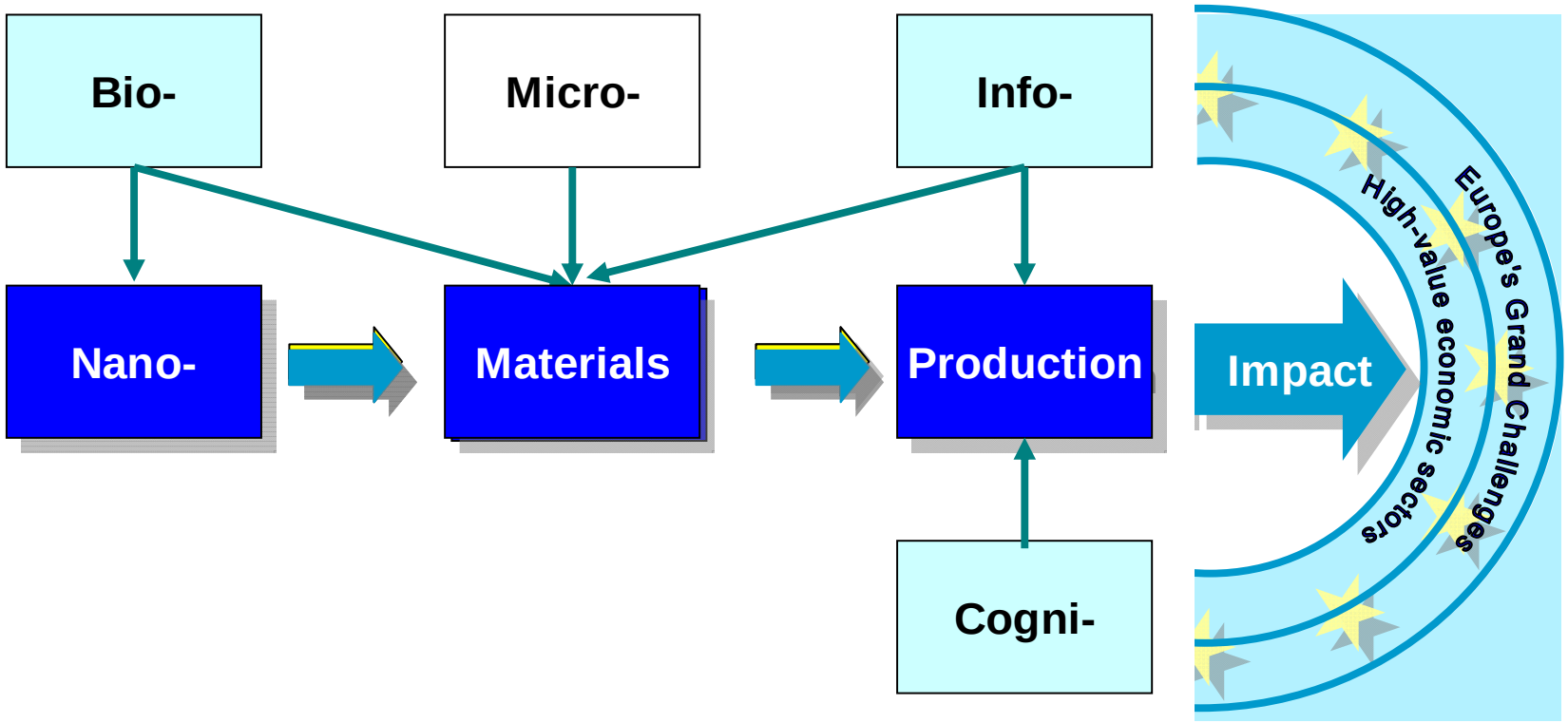
Global Nanotechnology Research Funding (Public and Private)
in 2005-2006 & 2007-2008

	2005 - 2006			2007 - 2008		
	Public (Billion €)	Private (Billion €)	TOTAL	Public (Billion €)	Private (Billion €)	TOTAL
EU	3.4	1.9	5.3	3.8	2.5	6.3
USA	2.8	3.1	5.9	2.6	4.1	6.7
Japan	1.5	2.4	3.9	2.7	4.4	7.1
Russia				0.8		0.8
China	1.5	0.9	2.4	0.8	0.3	1.1
Others				1.5	1.1	2.6
TOTAL	9.2	8.3	17.5	12.2	12.4	24.6

Sources: EC and Lux Research

Interactions Between, Nano-, Bio-, Info- & Cogni-Science

- Nanotechnology is not the only critical technology needed by the high-value manufacturing sectors.
- Biotechnology (bio-) and ICT (info-) technologies together with cognitive (cogni-) science are also important.
- Collectively, they form enabling technologies for product and process technology innovations in other industrial sectors.

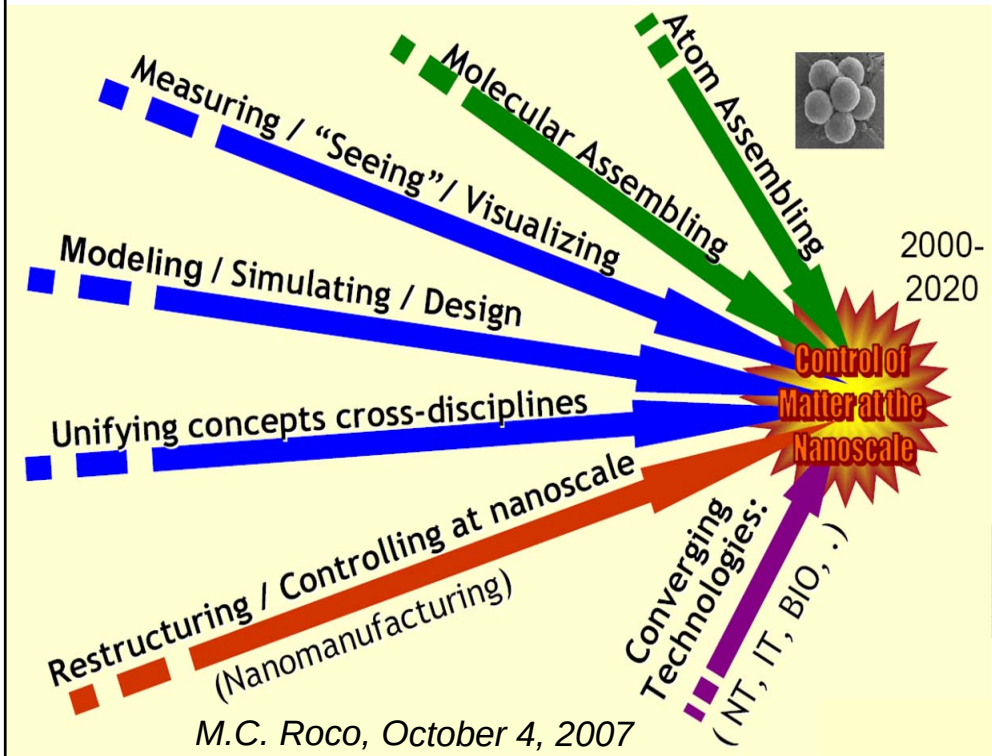


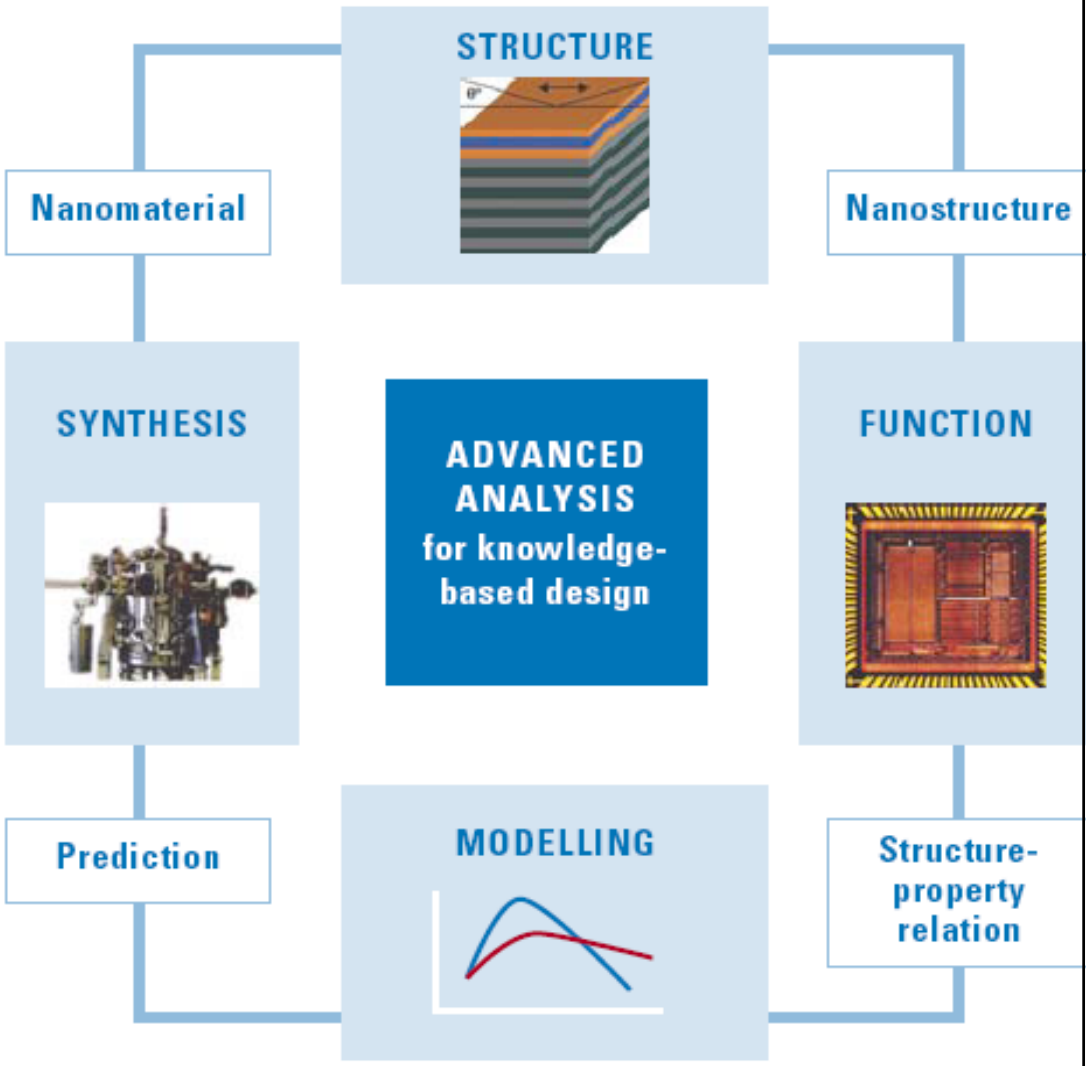
2. Research Directions in Nanomaterials and Nanostuctures by Design

- Fundamental Understanding and Synthesis
- Analytical Nano-tools and Measurements
- Manufacturing and Processing
- Modeling and Simulation

Fundamental Understanding and Synthesis

- The largest barrier to rational design and controlled synthesis of nanomaterials with predefined properties is the lack of basic scientific knowledge regarding the physics, chemistry and biology that limits our ability to predict a priori structure-property processing relationships.





Role of advanced analysis for nanomaterials science and nanotechnology (Source:GENNESYS)

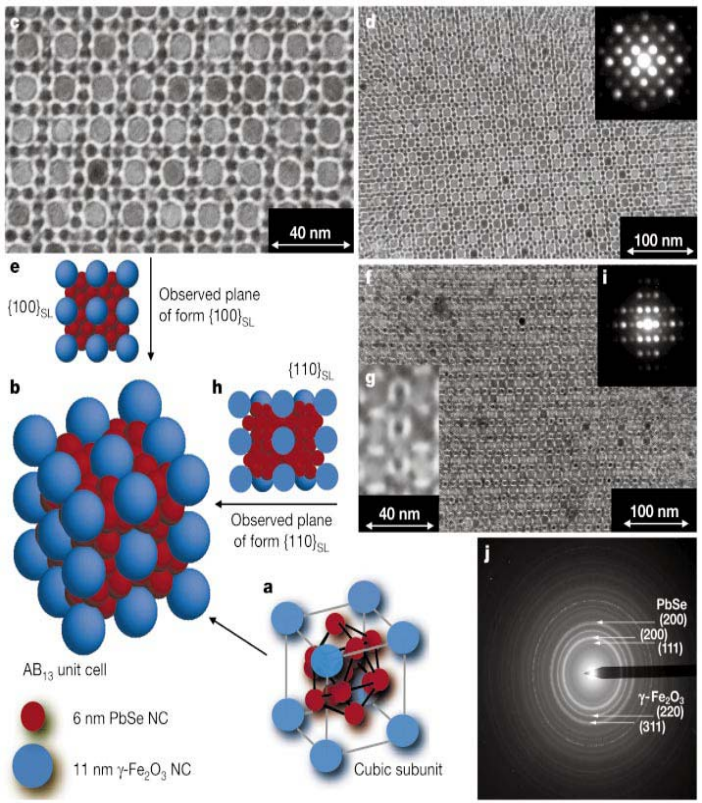
Self-Assembly Processes

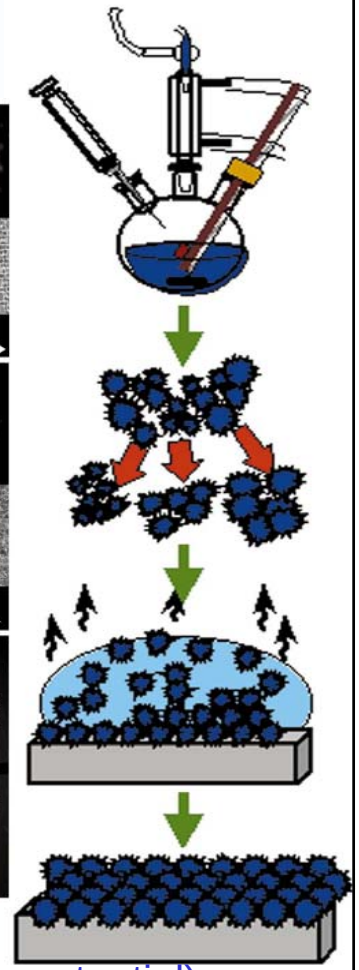
- Exploit self-assembly during processing of molecular and nanoscale systems.
- Self-Assembly Processes
  - Molecular / NP self-assembly
  - Flow and Field Assisted self-assembly
  - Templated (opals, liquid crystals,…)
  - DNA directed assembly
- Self-Assembly of Supercrystals
  - Photonics
  - Sensors
  - Magnetic storage

- Modeling of self-assembly
- Incorporation in multi-scale models
- Scale-up of self-assembly

C.B.Murray 2006

Binary Supercrystals





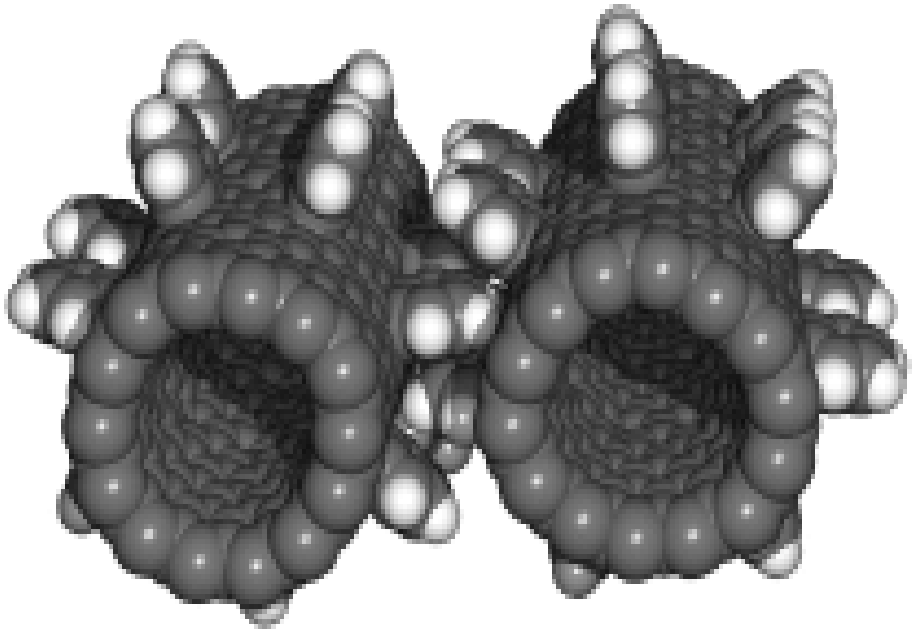
✓Interaction of NPs with field (flow or potential)

✓Controlled particle destabiliztion (aggregation vs. deposition)

✓Binary supercrystal formation (deposition vs. self-organization)

Molecular Machines

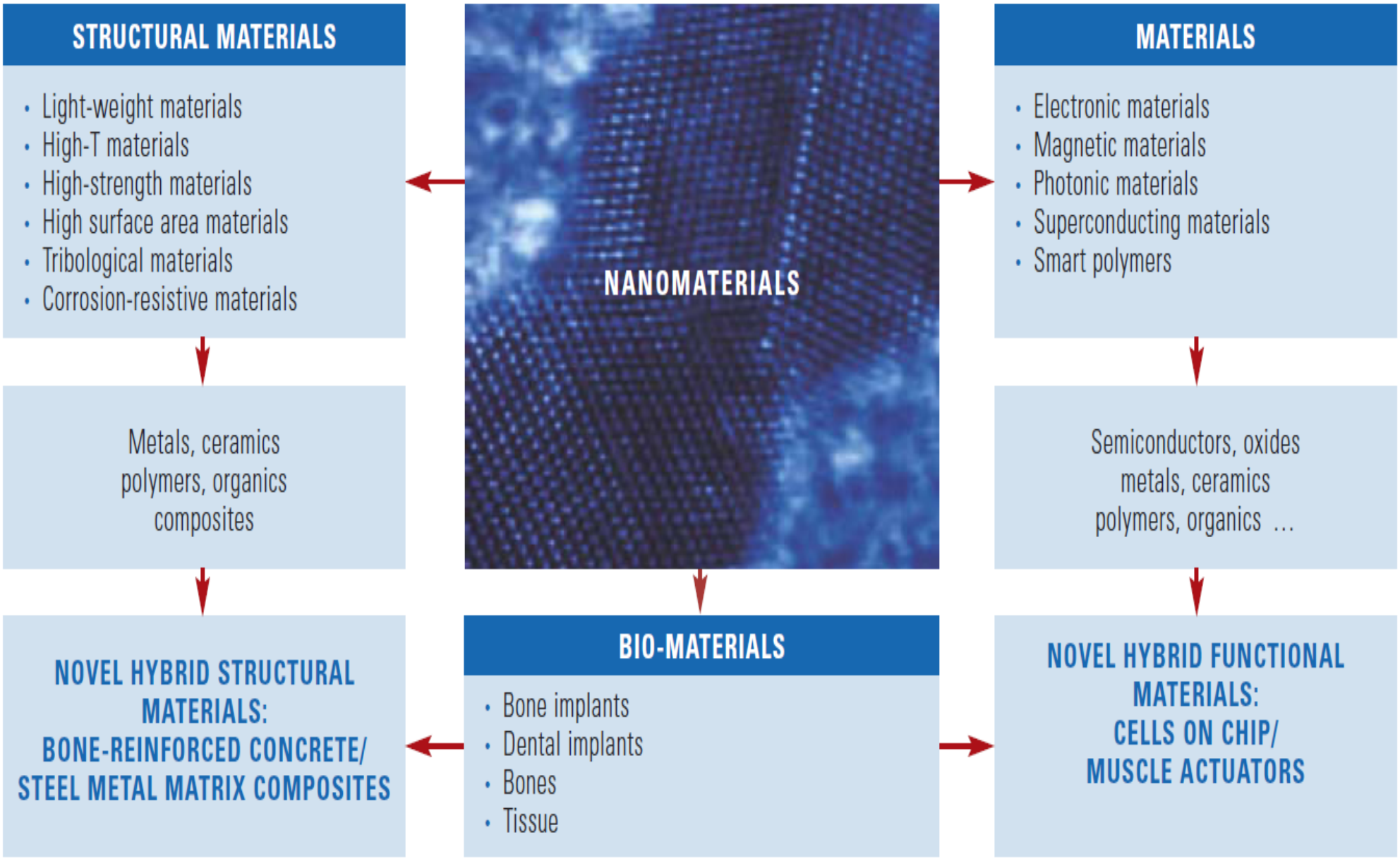
- Supramolecular Assemblies can be used as molecular machines
- NEMS - NanoElectroMechanical Systems
- Molecular Machinery (CNT gears)



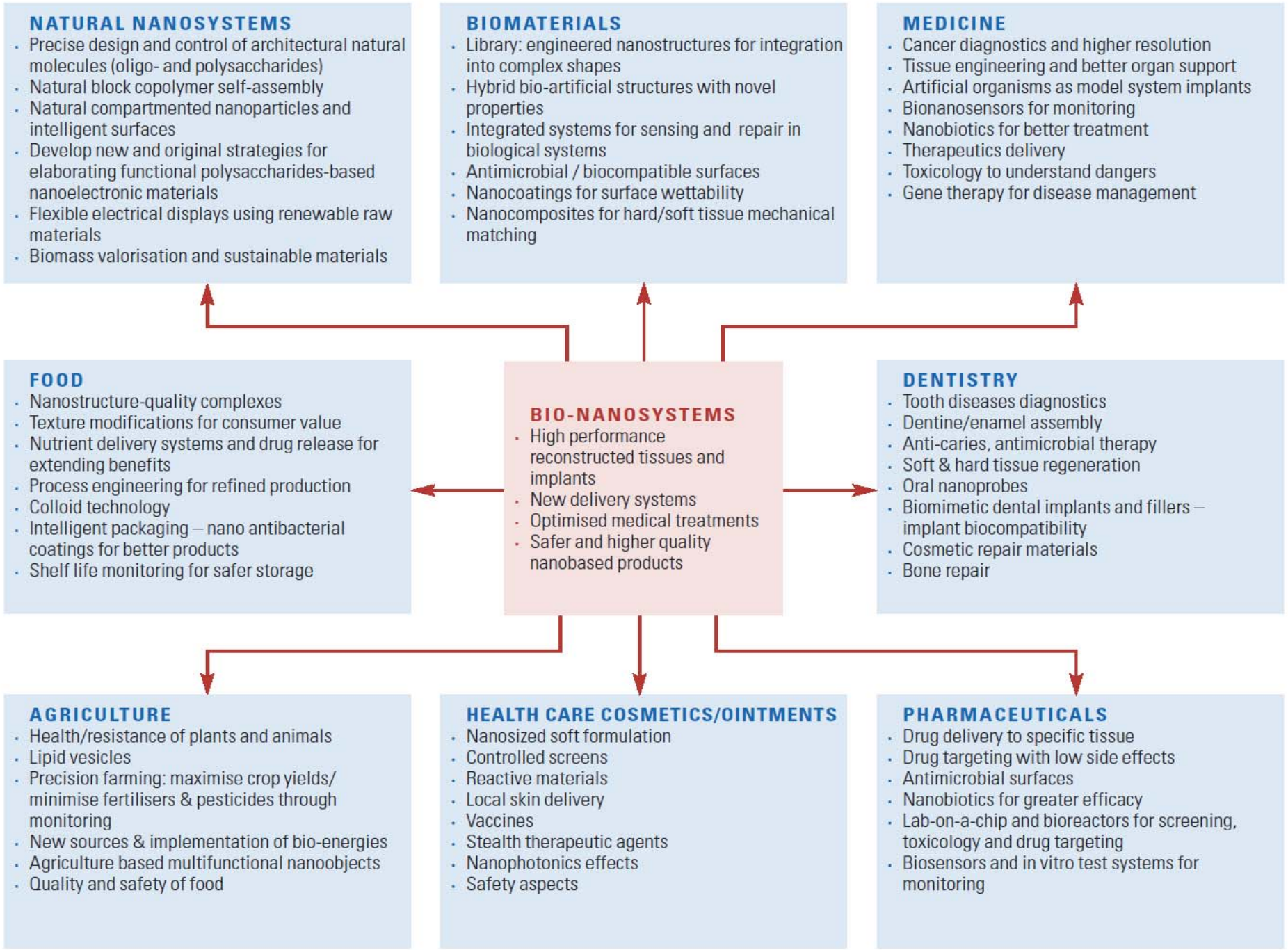
MD is used to investigate the properties and design space of the CNT gears.

Han, J., A. Globus, R. Jaffe, and G. Deardorff. 1997. Molecular dynamics simulation of carbon nanotube based gears. *Nanotechnology* 8:95-102. Bristol, U.K.: IOP Publishing Ltd.

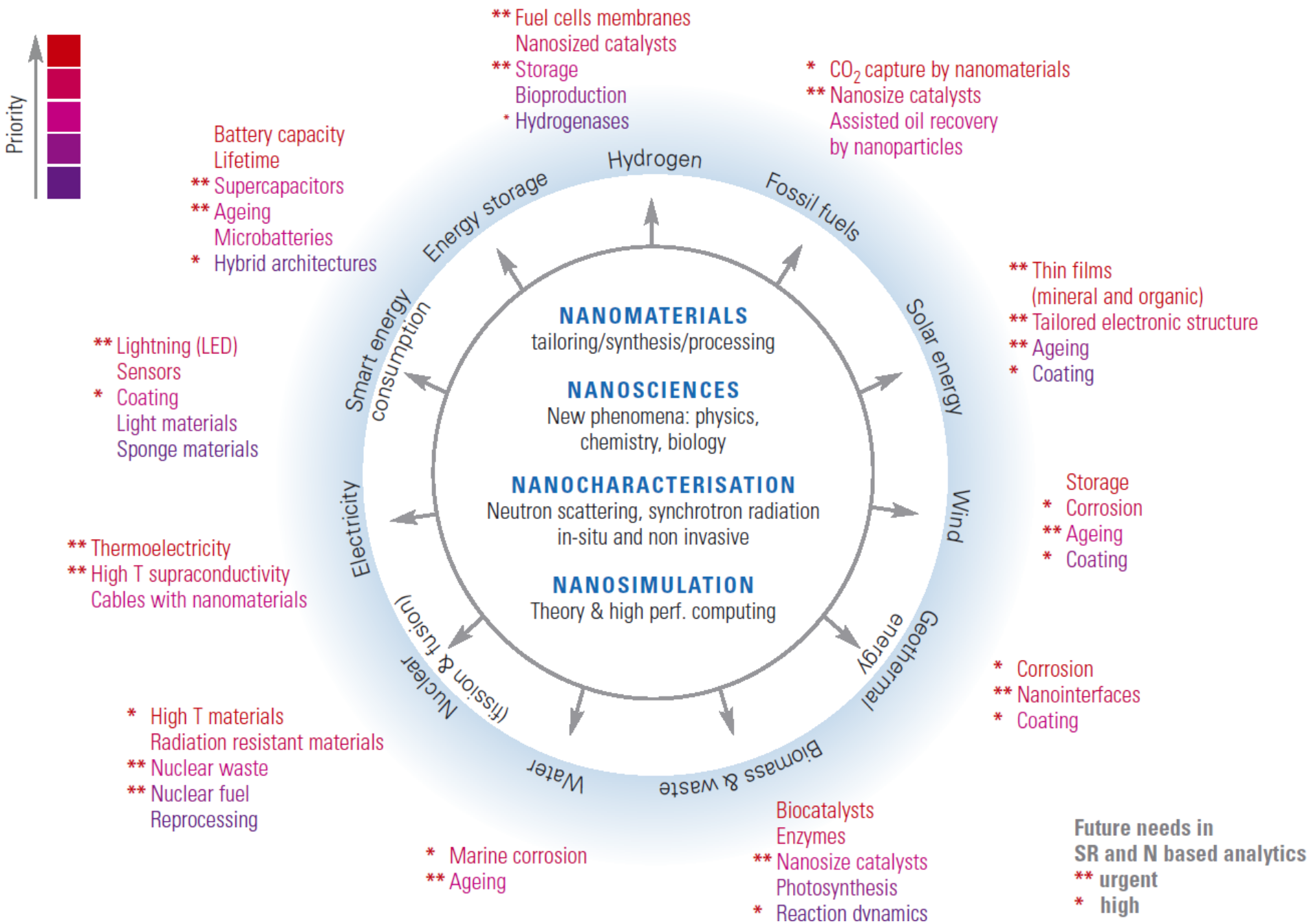
Overview of Nanomaterials



Overview of Bio-nanosystem Technologies



Nanomaterials for Future Energy



Research Priorities in Nanomaterials Synthesis

- Develop models, theories, and experimental validation methods for guiding synthesis and assembly.
- Basic knowledge of self-assembly processes, particularly those governed by non-covalent forces.
- Develop new bottom-up methods based on exploitation of biological principles such as molecular recognition and templated synthesis, as well as supramolecular chemistry.
- Understanding of nucleation, growth, and disassembly mechanisms.
- Development of mechanisms controlling interfacial interactions in the production of nanoparticles (non-agglomeration), and ordered, spatially-resolved nanostructures.
- Develop new design strategies and paradigms for the controlled assembly of nanocomposite and spatially resolved nanostructures with long-range order.

Research Priorities in Nanomaterials Synthesis

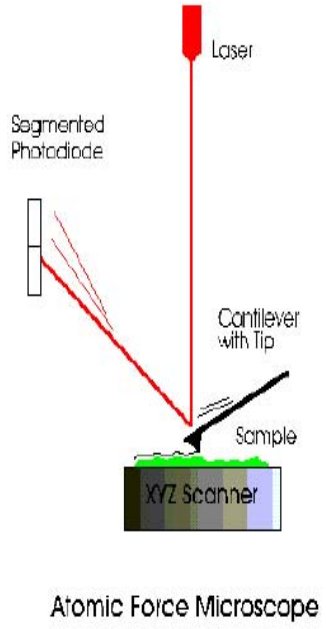
- Understanding of mechanisms controlling heterogeneous integration across time and length scales.
- Understanding of structure-property-processing relationships at the nanoscale and their influence on the macroscale behaviour of materials.
- Understand the origin of unexpected nanoscale behaviour and develop the ability to predict behaviour for nanomaterials properties including:
  - Hardness and ductility,
  - Electronic and optical properties,
  - Mass transport, reactivity, catalytic properties, etc.
- Develop new high-throughput screening methods to determine structure-property-relationships.
- New synthetic strategies for identified building blocks and assemblies that are amenable to combinatorial screening.
- A database of key nanomaterial properties (e.g., physical, chemical, mechanical) that compares performance to bulk materials.
- Develop a systems approach to enable new, paradigm-shifting applications using nanomaterials.

Analytical Nanotools and Measurements

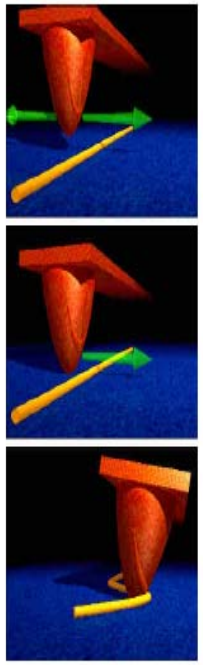
- Observing, correlating and understanding structure and function at the nanoscale is essential to developing reproducible nanomaterials. To do this, analytical tool capabilities must move from static measurements of quenched samples to dynamic, real-time measurements.

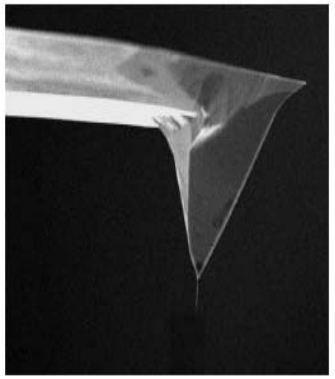
New analytical tools are needed to:

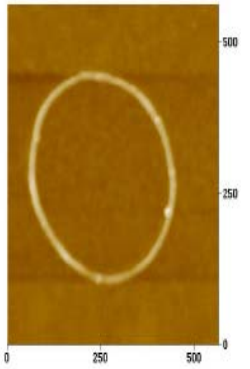
- Evaluate nanomaterials with a spatial resolution 1 nm or less
- Analyze buried interfaces
- Analyze nanoscale biosystems
- Analyze high throughput in real time
- Couple theory/modeling and experiment
- Develop nanostructure / property relationships
- Understand and bridge multiple length scales



Atomic Force Microscope



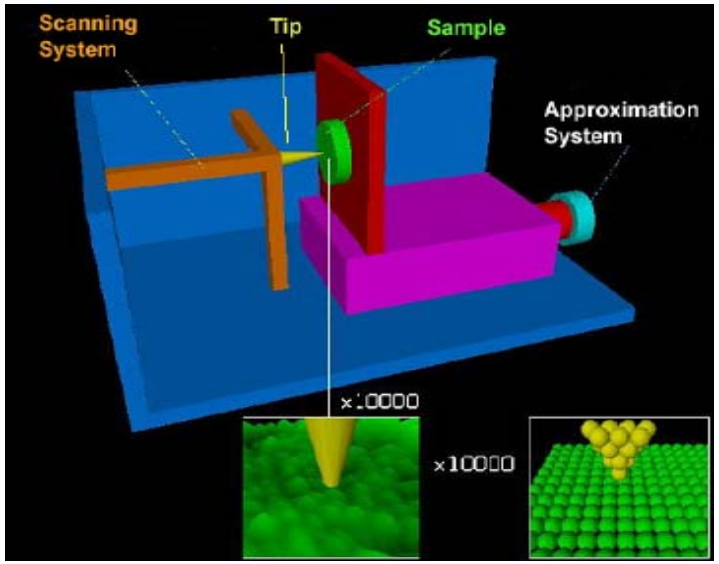


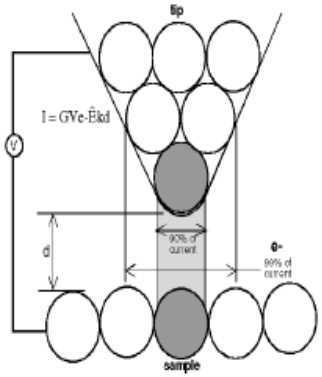


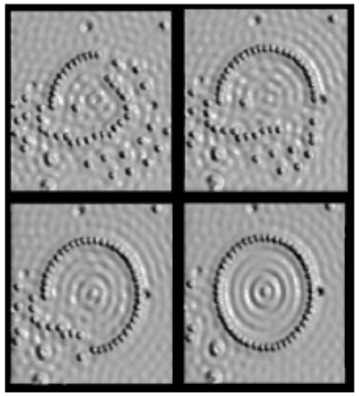
Analytical Nanotools and Measurements

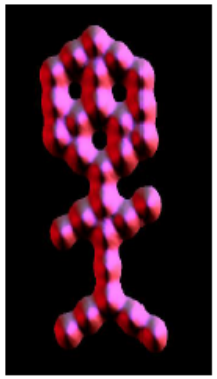
Tool Specifications for Real-time Characterization:

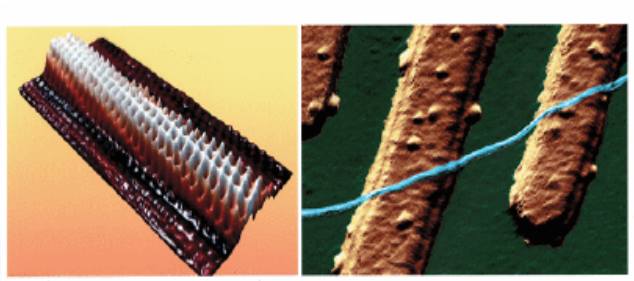
- Three-dimensional tomographic capabilities
- Spatial resolution of 1nm or less
- Applicable to sample volumes of 1μm^3
- Multiple probes for rapid, parallel measurement of identical properties or for simultaneous measurement of different properties







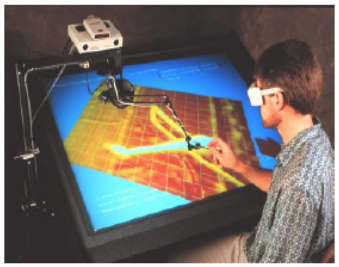


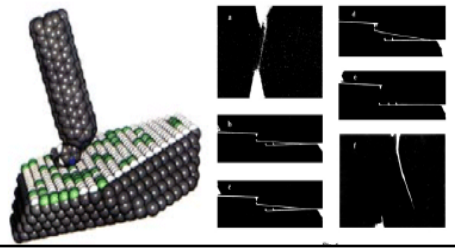


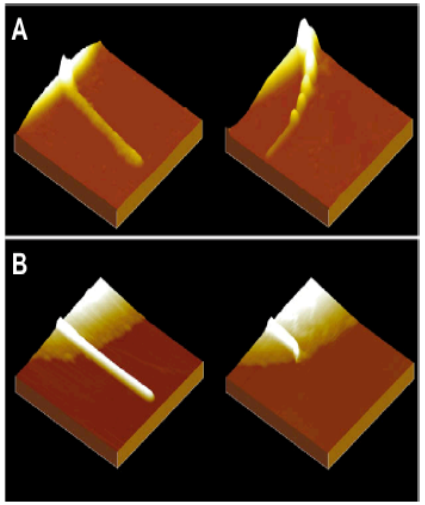
- Fast acquisition speed to monitor kinetic processes in real time
- Function in a manufacturing environment (on-line monitoring)
- Function in different environments (e.g., in-vacuo, in-vivo, and in-vitro)

Research Priorities in Analytical Nanotools

- Develop advanced methods and instrumentation (hardware and software) to provide chemical and physical properties and structural information in real-time, with 1-nm or less spatial resolution—including, but not limited to:
  - Spectroscopies
  - Scattering techniques (Fourier Space)
  - Microscopies (Real Space)
- Integrate individual techniques into 2-D and 3-D, real-time multi-probe systems. (Develop multi-probe systems that integrate imaging, scattering, and spectroscopy functions to enable higher throughput.)
  - Improved sample handling and manipulation
  - Miniaturization capability
  - Vibration isolation capability
  - Reproducible interprobe performance
  - Operation in-vacuo, in-vitro, and in-vivo



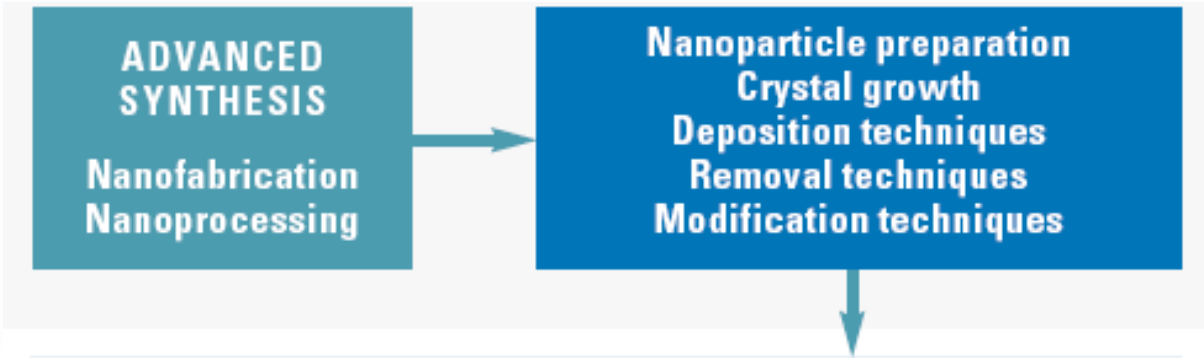




Manufacturing and Processing

- Nanomaterials are manufactured today with traditional manufacturing techniques and unit operations.
- Researchers need to focus more on the the development of scalable, cost-effective, robust and reliable production methods, consistently and correctly controlled at the atomic scale, to significantly expand the commercial use of nanomaterials.
- Biological systems found in nature provide excellent examples of highly controlled and organized architectures that generate complex materials.

Source: GENNESYS Report



KEY CHALLENGES AND GOALS IN SYNTHESIS AND NANOFABRICATION

- New synthesis must include all types of materials (inorganic, organic, bio-)
- Increase reproducibility, precision, control of structural parameter (size, shape, roughness, connectivity, morphology, chemical composition)
- Invent new nanofabrication strategies, develop an in-situ-control of the relevant fabrication parameters
- Synthesis and nanofabrication at the interface to biology
- Synthesis of hybrid materials
- High-throughput screening with spatial resolution in nanoparticle synthesis (particularly for drug production)
- Controlling purity at all synthesis steps
- News ways of self-assembling colloidal particles
- New microfluidic approaches in nanosynthesis
- New interaction between nanosynthesiser and nanoscientists
- Colloidal chemistry: new ways to synthesis in a controlled way non-spherical colloids (rods, pyramids)
- Nanoparticle synthesis (sol-gel gasphase): reduce size variation from 20% to less than 5% (to see quantum effects); use of inverted micelles

Research Priorities in Manufacturing

Develop Robust Scale-Up and Scale-Down Methodologies for Manufacturing.

- Develop models and documented design tools to scale up or scale down processes quickly and effectively
- Design and develop processes to engineer materials at the device level that retain properties of the nanoscale (e.g., retention of nanograins in sintered consolidated material)
- Develop reliable passivation techniques to allow safe handling and preservation of nanomaterial functionality
- Develop purification and classification processes

Develop Novel Manufacturing Techniques for Hierarchical Assembly.

- Develop robust reproducible self-assembly techniques that integrate synthesis and assembly functions of manufacturing and minimize labor and energy input.
- Develop efficient modular tools for building-block assembly

Research Priorities in Manufacturing

Develop Dispersion and Surface Modification Processes that Retain Functionality.

- Develop techniques for direct measurement of dispersion characteristics and surface modification in the manufacturing environment
- Develop the ability to address contamination in the process
- Develop a broad library of scalable surface functionalization and compatibilization techniques for modifying and dispersing all families of nanoparticles while retaining functionality

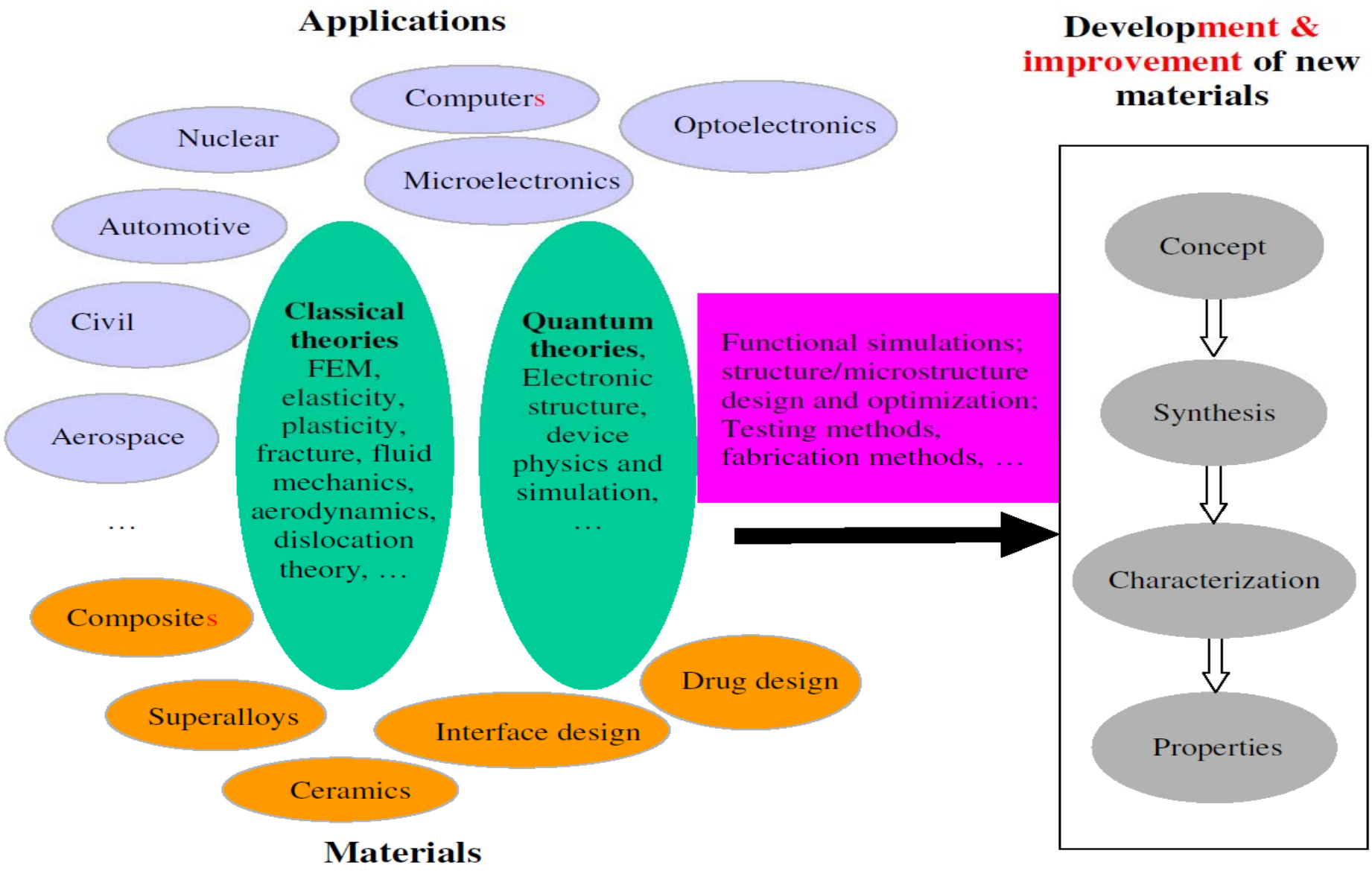
Process Monitoring and Control for Nanomaterial and Product Consistency.

- Develop robust, rapid quality control (QC) tests
- Develop “smart” responsive control systems for real-time processing based on improved analytical tools that provide on-line imaging techniques

Integrate Engineered Materials into Devices While Retaining Nanoscale Properties.

- Develop manufacturing methods that cross material-scale boundaries
- Develop and design processes that integrate engineered materials at the device level while retaining properties of the nanoscale

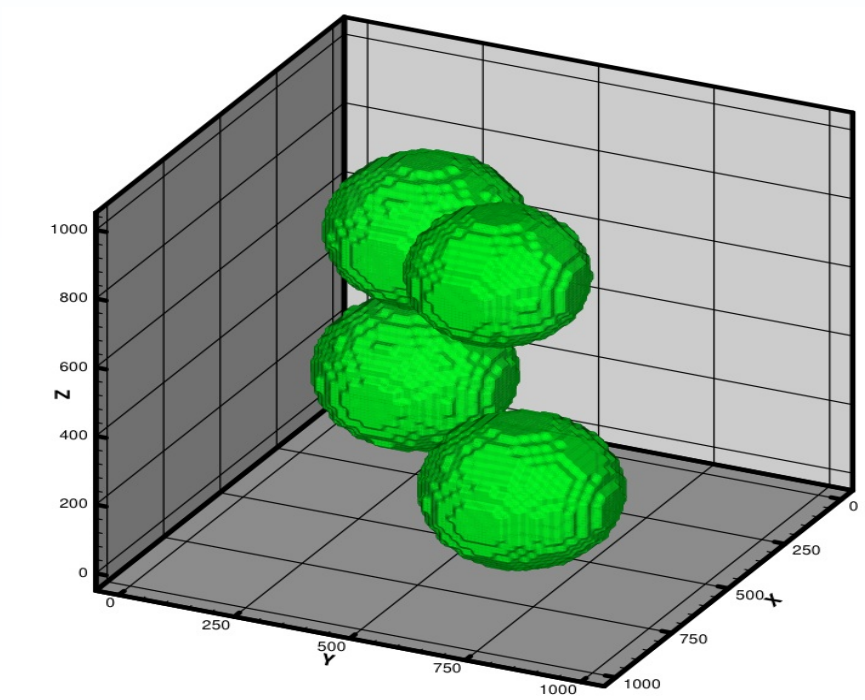
Materials Theory and Simulation

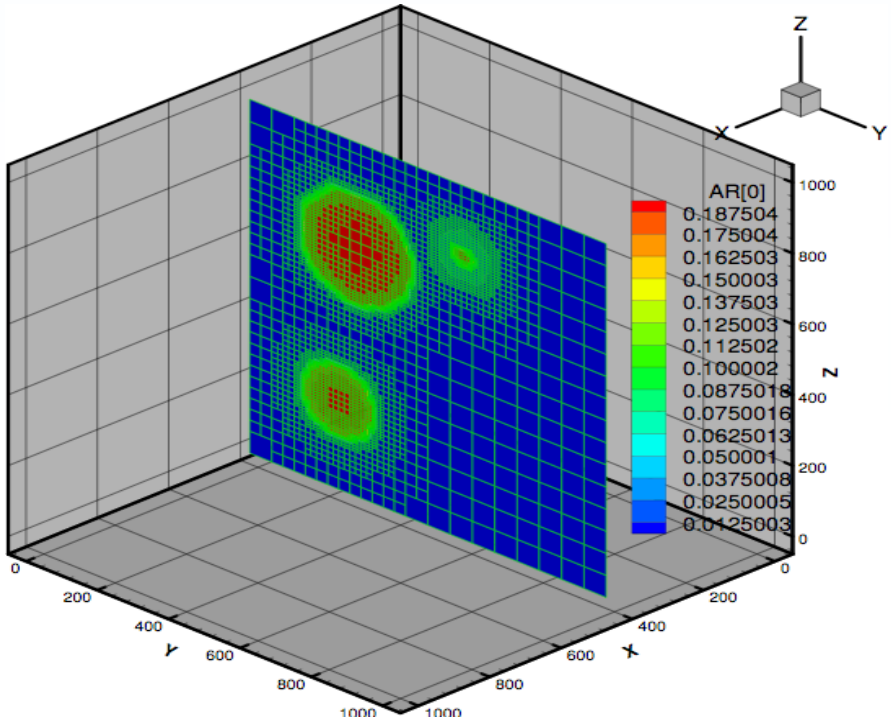


Materials theory plays an indispensable role in the development and improvement of new materials in various industries.

Modeling and Simulation

- Robust, high-confidence models and simulations are needed to predict the properties and behavior of new nanomaterials and assembled systems across scales – from synthesis of particles through their integration into devices, and finally, to their performance in final products.





Nanoparticles & Nanostructured Materials

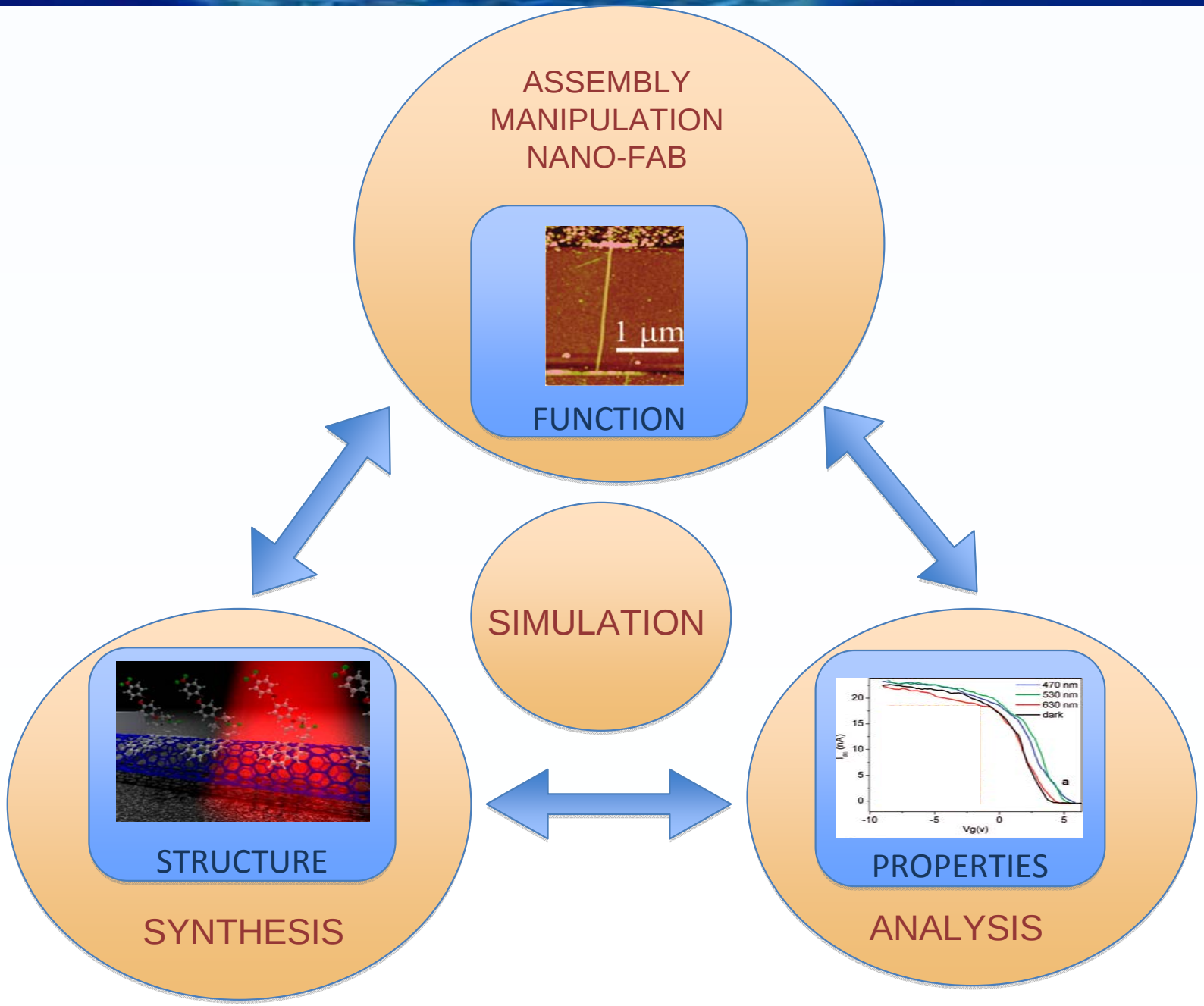
- A unique aspect of nanostructured materials is the diversity of morphologies that can be achieved using various building blocks and processing techniques. Unique enhancements of properties can be achieved but these properties are often difficult to predict.

  - Materials: Metals and metal alloys, ceramics and glasses, semiconductors, polymers and polymer composites, soft solids (liquid crystals, colloidal matter, ice cream)

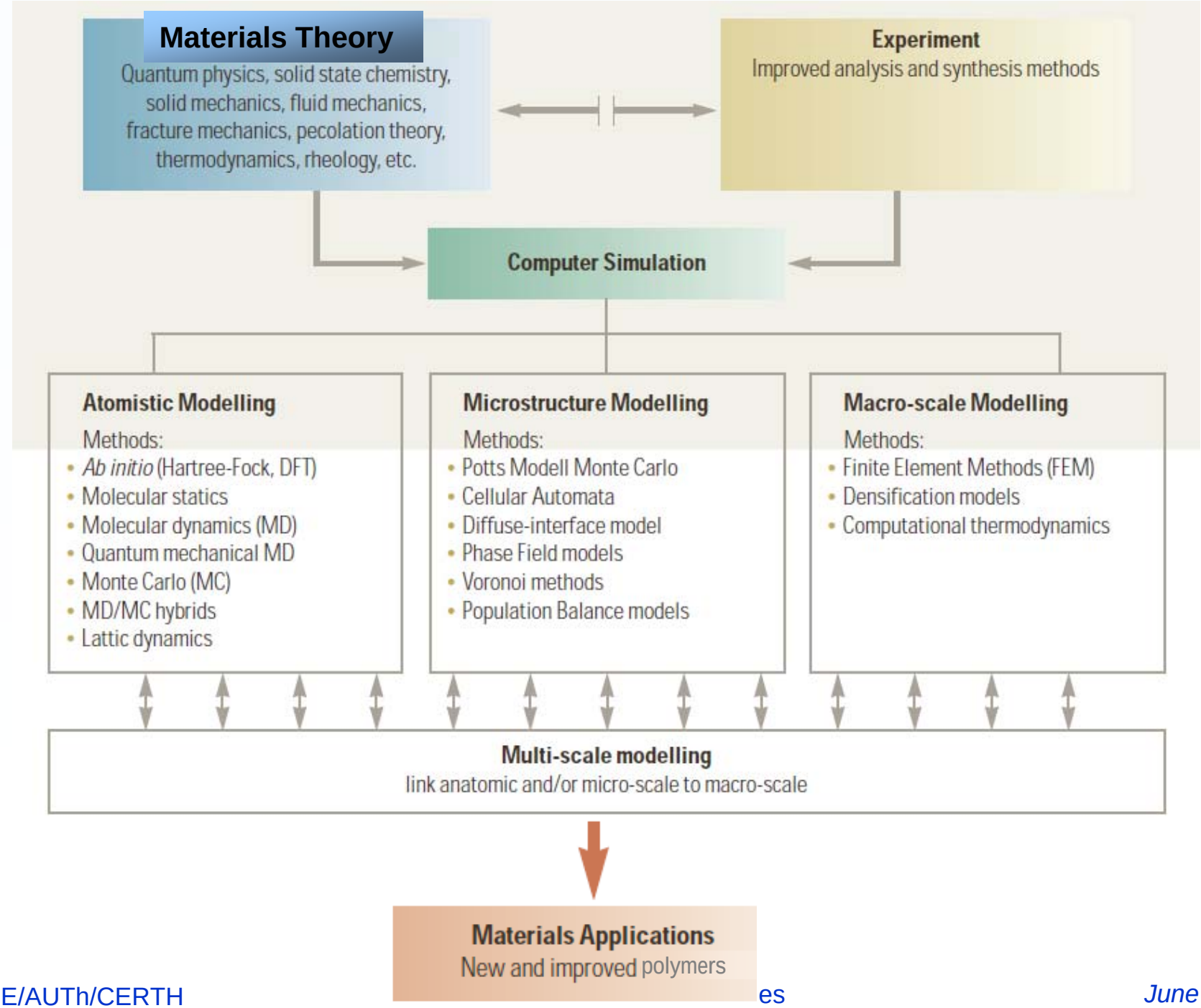
  - Properties: Magnetic, Electrical, Optical, Thermal, Mechanical, catalytic, etc.

- The ultimate goal is to reduce the dependence on experimental measurements and perform at least the preliminary stages of materials selection and design on computer. The aim is to reduce the cost and time of developing materials for new applications.

Design of Nanomaterials and Nanodevices



Computational Materials Research



Challenges in Materials Simulation

Functional Design Current Status:

1. Impressive advances in solving the challenges:
   - Models / Algorithms / Approximations
2. Simulation is allover in nanoscience research
   - To a large extent, it has substituted ‘traditional’ Theory, due to its capacity to give quantitative (not just qualitative) answers to each specific system
   - A large community of groups specialized in simulations in nanomaterials
   - Many experimental groups do simulations to understand and complement their experiments.
3. Huge improvement in computer power

General Computational Tools

Electronic structure/quantum calculations(10^2-10^3atoms, 10ps)

- Quantum chemical methods
- Ab initio Molecular Dynamics (classic nuclei / QM electrons)
- Density Functional Theory (DFT) and Hartree-Fock (HF) Approaches

Local Density Approximation (LDA) is a simplified version of the "parameter-free" DFT and HF approaches. Semi-empirical quantum chemical methods are systematic simplifications of DFT or HF theories. Hybrid approaches link DFT-MD with a full QM treatment of the hydrogen nuclei.

"Classical" calculations (~10^4-10^6 atoms, 1ns)

- Molecular Dynamics (~10^6 atoms)
- Monte-Carlo (critical phenomena / phase transitions)

Can describe generic properties of large collections of model molecules (polymer, colloids, supramolecular assemblies, nanoparticles, etc.). Requires interaction potentials ("force fields") from QM calculations.

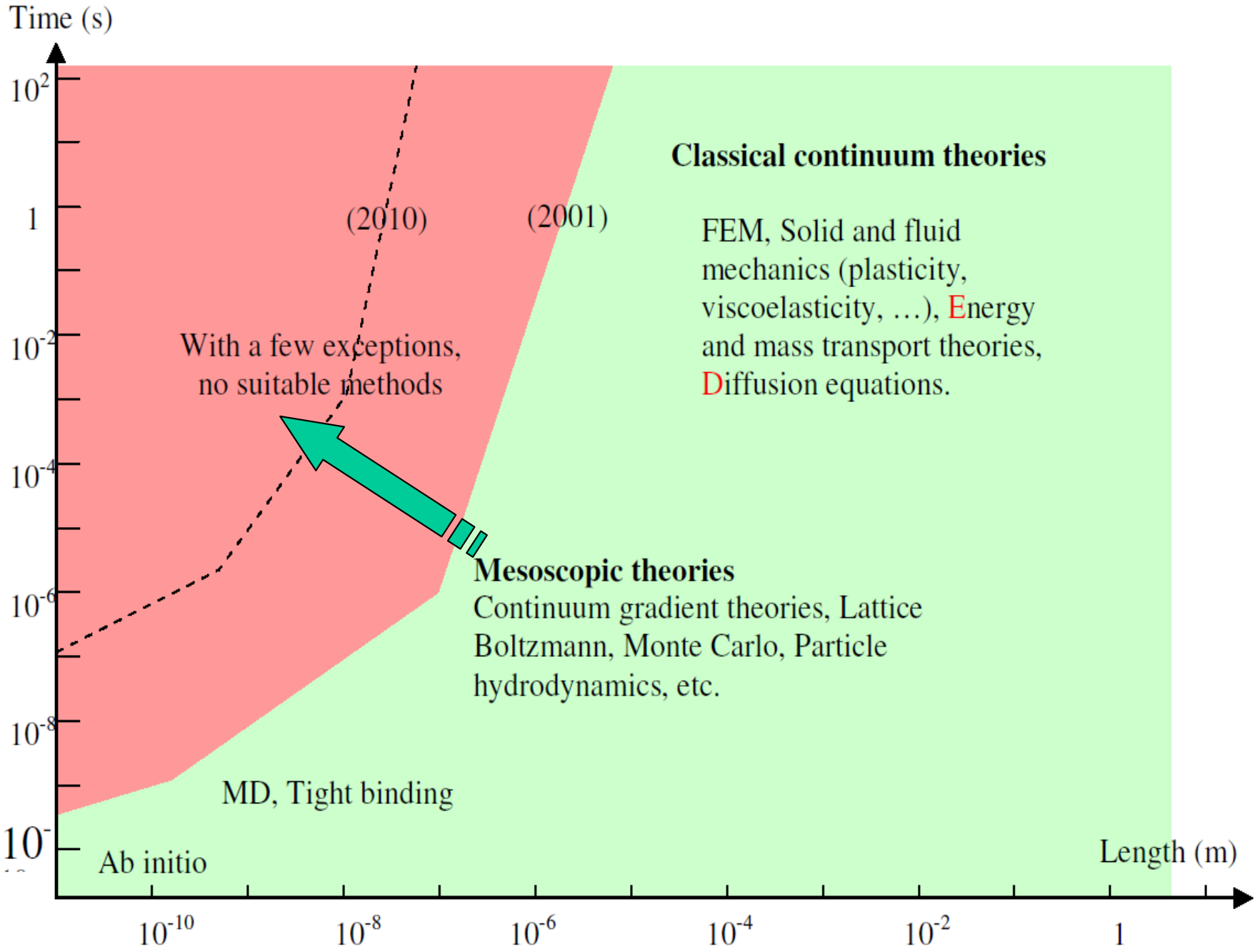
General Computational Tools

Mesoscopic and Macroscopic Methods

- Semi-Macroscopic (Mesoscale) models such as Dissipative Particle Dynamics (DPD), Lattice Boltzmann Hydrodynamics (LBH), Self-Consistent Field Methods (SCF).
- Traditional: FEM, FD, FV, CFD

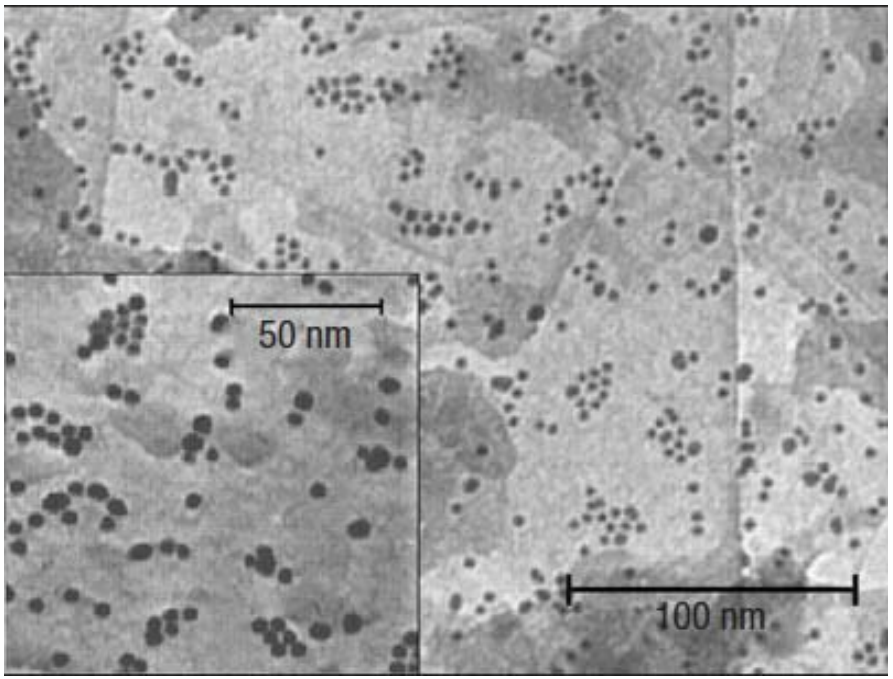
Provide a closer link to molecular properties and Monte Carlo sampling.

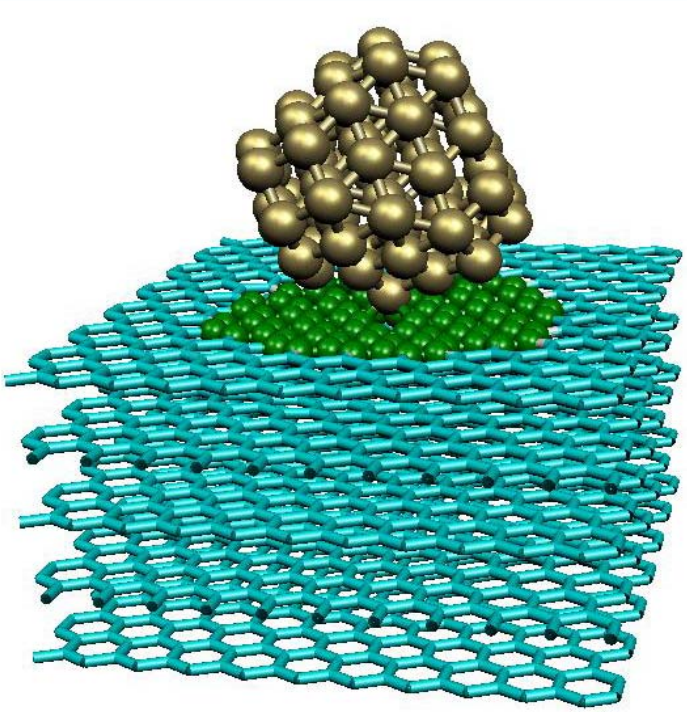
Challenges in Materials Simulation



Multiple length and time scales

- Electronic information with ‘chemical accuracy’
- Large-scale (often macroscopic) environment that fixes boundary conditions





Gold nanoclusters on graphite; R. Palmer‘s group, Birmingham

Multi-Scale Modeling in NanoMaterials

Current Status and Future Directions

- Extension of existing computational techniques to broader length and time scales. Development of new theories and computational tools.
- Integration between completely different computational approaches (e.g., quantum vs. classic mechanics, deterministic vs. stochastic, continuous vs. discrete) remains a challenge.
- Fundamental breakthroughs and new techniques are needed to achieve this integration. Ultimately, Problem solving environments comprised of smart software that will permit an engineer to design nanoscale systems and devices without a detailed understanding of the underlying physics need to be developed.

Multi-Scale Modeling in NanoMaterials

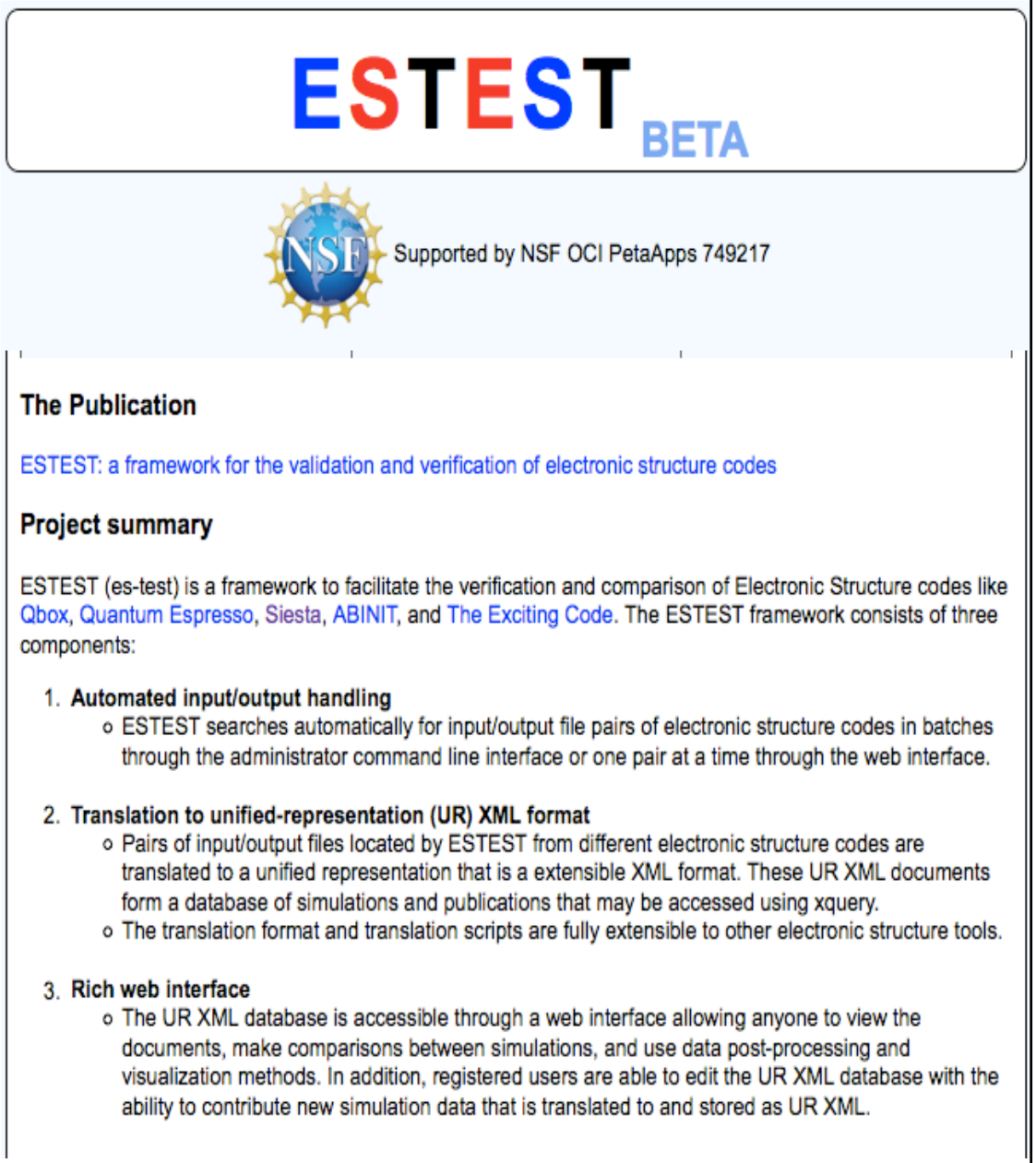
- Data management and computing. Enormous amounts of data are being generated (experimentally and computationally) and need to be “processed”, i.e., consolidated into existing databases and “analyzed”, i.e., identify and extract useful information, in an efficient manner.
- Self-assembly, self-organization, and emergent behavior are characteristics of many nanoscale systems e.g., biological systems. Significant advances and fundamental breakthroughs are needed to understand these processes and utilize them in the design of next-generation nanotechnological systems and devices.

Code Development / Maintenance

- Massively parallel codes are not easy to write ! !
- Issues: distribution of tasks and memory; load balance
- Typical development time: 5 years
- CHALLENGE: Keep up with HARDWARE development through SOFTWARE development. New (collaborative?) paradigms are needed
- Several ‘standard’ codes out in the market (VASP, Castep, SIESTA, Quantum Expresso, CP2K, ...)
- Issues of code consistency - VALIDATION
- Data Bases of Simulation results
- Extracting valuable information from Data Bases

Code Validation and Verification

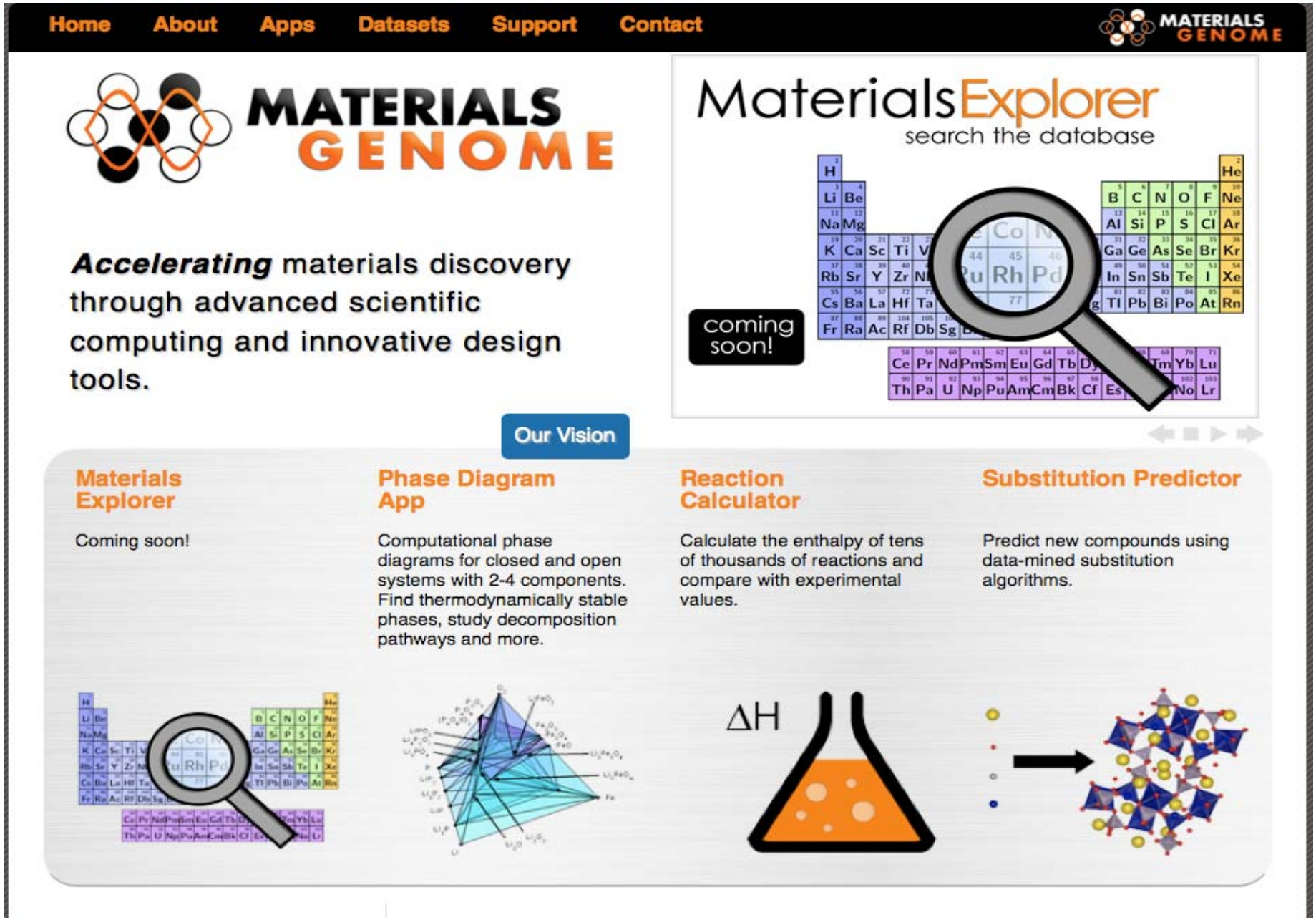
- Codes for electronic structure are not always consistent in results.
- Verification and validation is needed
- Automatic I/O handling
- Input compatibility - XML formats.
- Web-based database
- First step towards code interoperability
- “Open Innovation” strategy is the final goal:
  - Modules, functions, libraries...
  - Warehouse for optimized/specific software



http://estest.ucdavis.edu/

Extracting Valuable Info from Data Bases

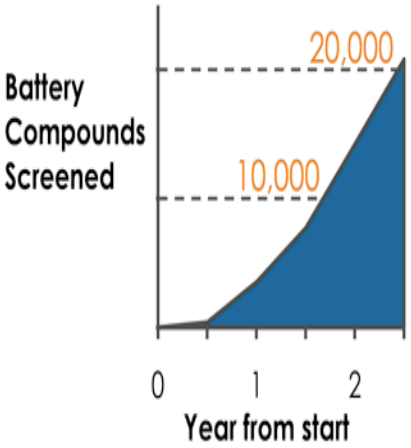
http://www.materialsgenome.org



Extracting Valuable Info from Data Bases

http://www.materialsgenome.org

18 years
to move materials
from **lab** to **market**



The Power of Computation

Computational materials science is now powerful enough that it can predict many properties of materials before those materials are ever synthesized in the lab.

By scaling materials computations over supercomputing clusters, we have computed some properties of over 80,000 materials and screened 25,000 of these for Li-ion batteries.

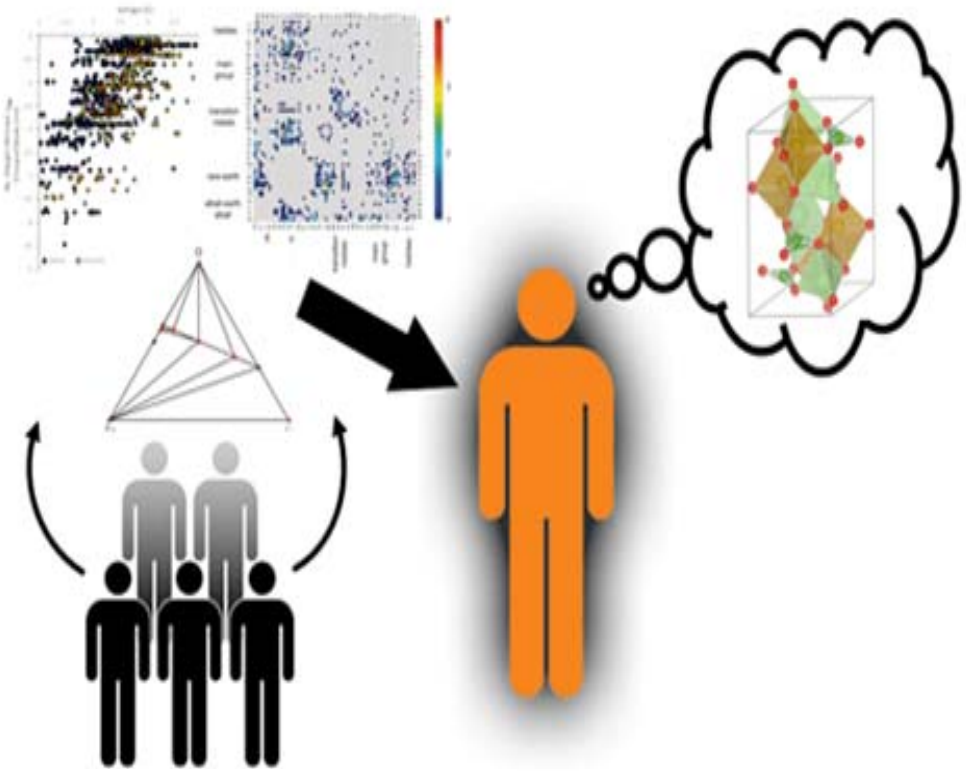
The computations predicted several new battery materials which were made and tested in the lab and are now being patented.

Materials Genome

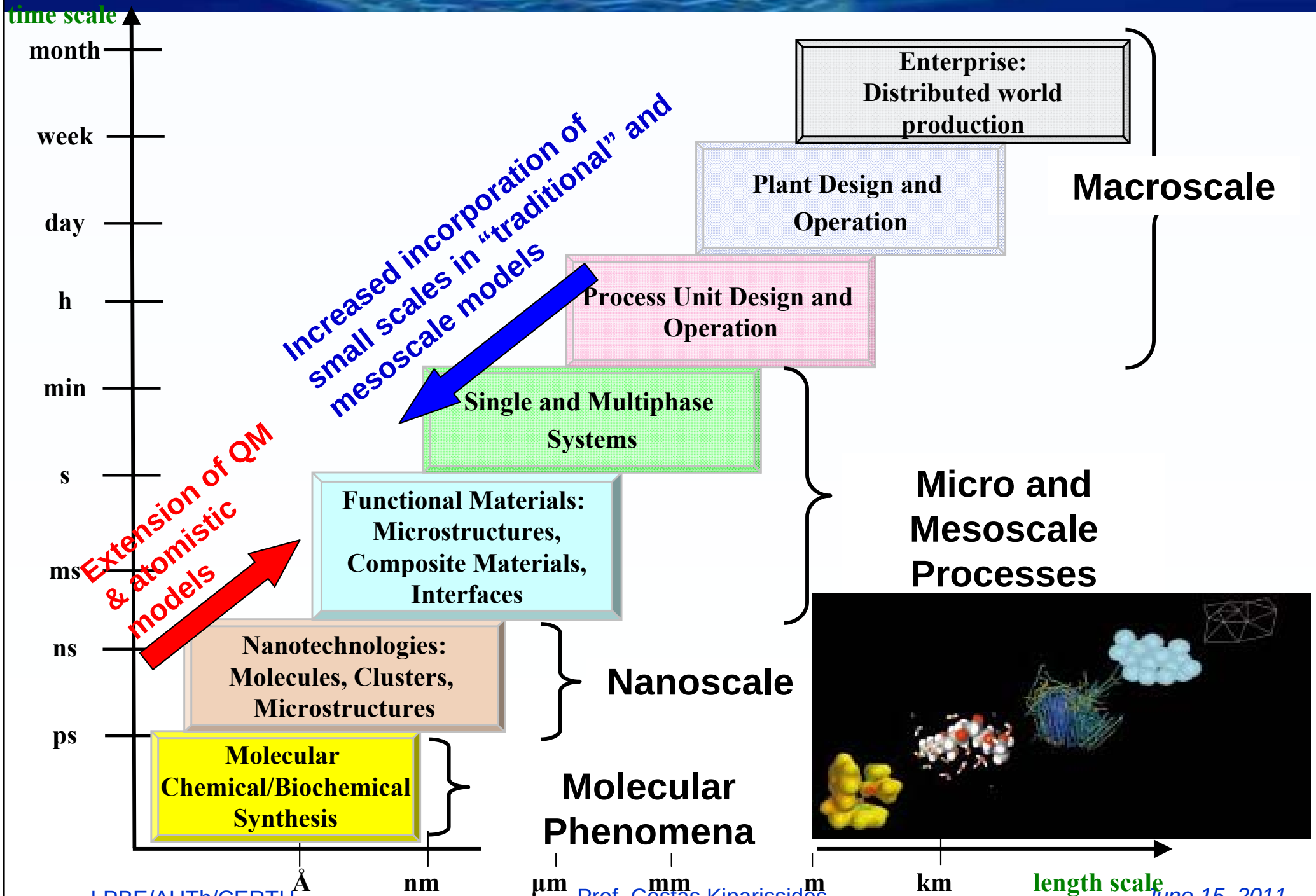
By computing properties of all known materials, the Materials Genome aims to remove guesswork from materials design in a variety of applications.

Experimental research can be targeted to the most promising compounds from computational data sets. Researchers will be able to data-mine scientific trends in materials properties.

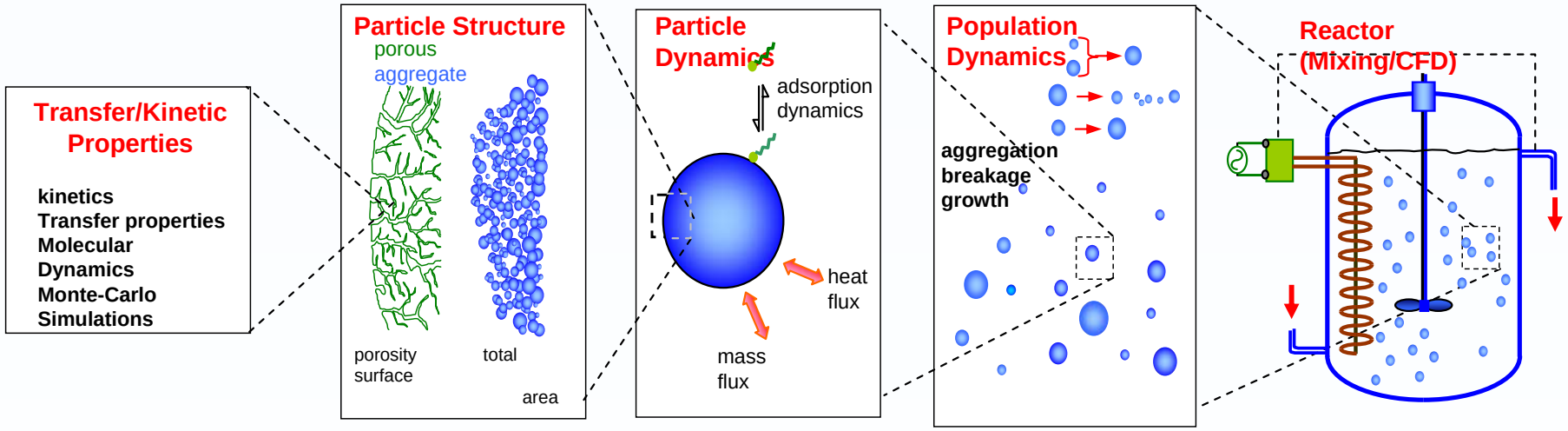
By providing materials researchers with the information they need to design better, the Materials Genome aims to accelerate innovation in materials research.



Multi-Scale "World"



Multi-scale Models of Particulate Systems



Uni-variate Reactor Models → **Multi-scale Uni-variate Reactor Models** → **Multi-scale Multi-variate Reactor Models**

- Wet-phase production of nanoparticles and nano-structured microparticles
- Precipitation processes in aqueous and organic phases
- Multi-scale approach is comprised of completely different models which are not easily integrated (e.g., because of coupling between scales).
- Inverse problem, i.e., recipe and process that generate NPs with desired properties, is not easily solved.

LDPE Manufacturing Technologies

Tubular Process Characteristics

- Lower operating costs than autoclaves
- Optimization of reactor heat removal
- Conversions up to 20-35% per pass.
- Low EVA copolymers (<10%) and polar ethylene acrylate copolymers (EMA, EBA, EEA)
- Tubular reactor technology is used for films, wires, cables and sack grades.

Autoclave Process Characteristics

- Higher operating costs than tubular
- Adiabatic conditions limit conversion to 20-25% per pass.
- Low and high EVA specialty copolymers and polar ethylene acrylate copolymers (EMA, EEA, EBA)
- Autoclave reactor technology is used in the production of extrusion coating resins and hot-melt adhesives.

Tubular Reactor

Autoclave Vessel

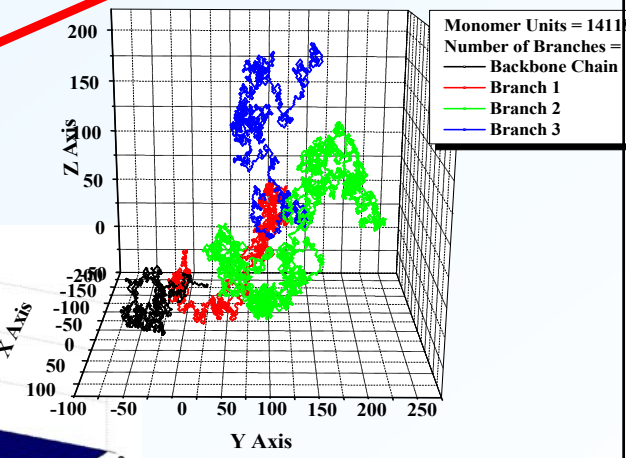
Modeling Complexity

MOM
OCFE
Galerkin
2-D FPT
Monte Carlo

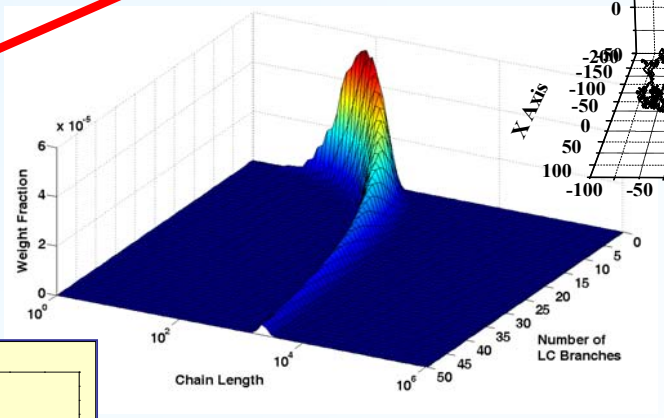
OCFE
Galerkin
2-D FPT
Monte Carlo

2-D FPT
Monte Carlo

Monte Carlo

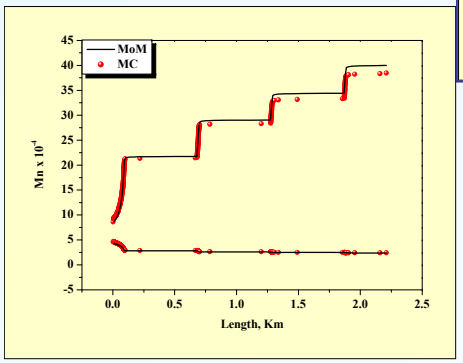


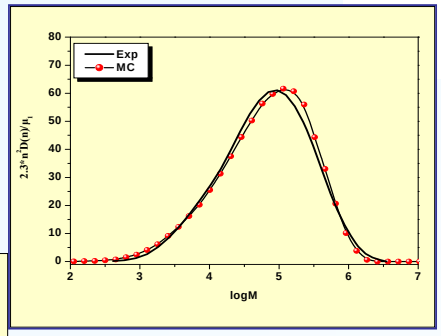
Chain Architecture



Bivariate MW-LCB Distribution

Average Properties





MWD

Molecular Properties using Different Numerical Methods

Macromolecular Architecture Details

The Monte Carlo Method

In MC simulations the properties of a population (i.e., molecular species) are inferred by tracking the corresponding properties of a finite sample.

Basic principles of the formulation (Gillespie 1977):

- Net formation rates for all the chemical reactions in the system

$$R_j = k_j X^c \quad ; \quad j = 1, 2, \ldots, N_R$$

X^c *is the total number of possible combinations of the molecules involved in a reaction step*

- Time interval between two successive reaction events

$$\Delta t = \left(\sum_{j=1}^{N_R} R_j \right)^{-1} \ln\left(rn_i^{-1} \right)$$

rn *is a random number in the range (0, 1)*

- The reaction step, 'j', from the set of all possible reaction events that will take place within the infinitesimal time interval (t+Δt → t+Δt+dt)

$$\sum_{i=1}^{j-1} P_i < rn_k \le \sum_{i=1}^{j} P_i$$

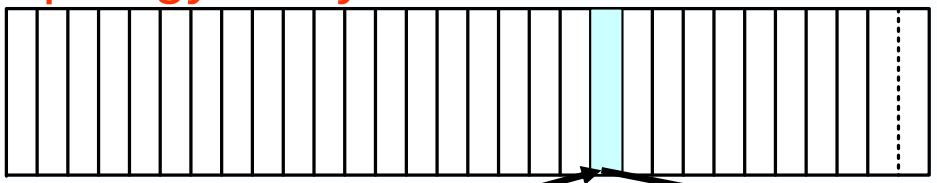
where:

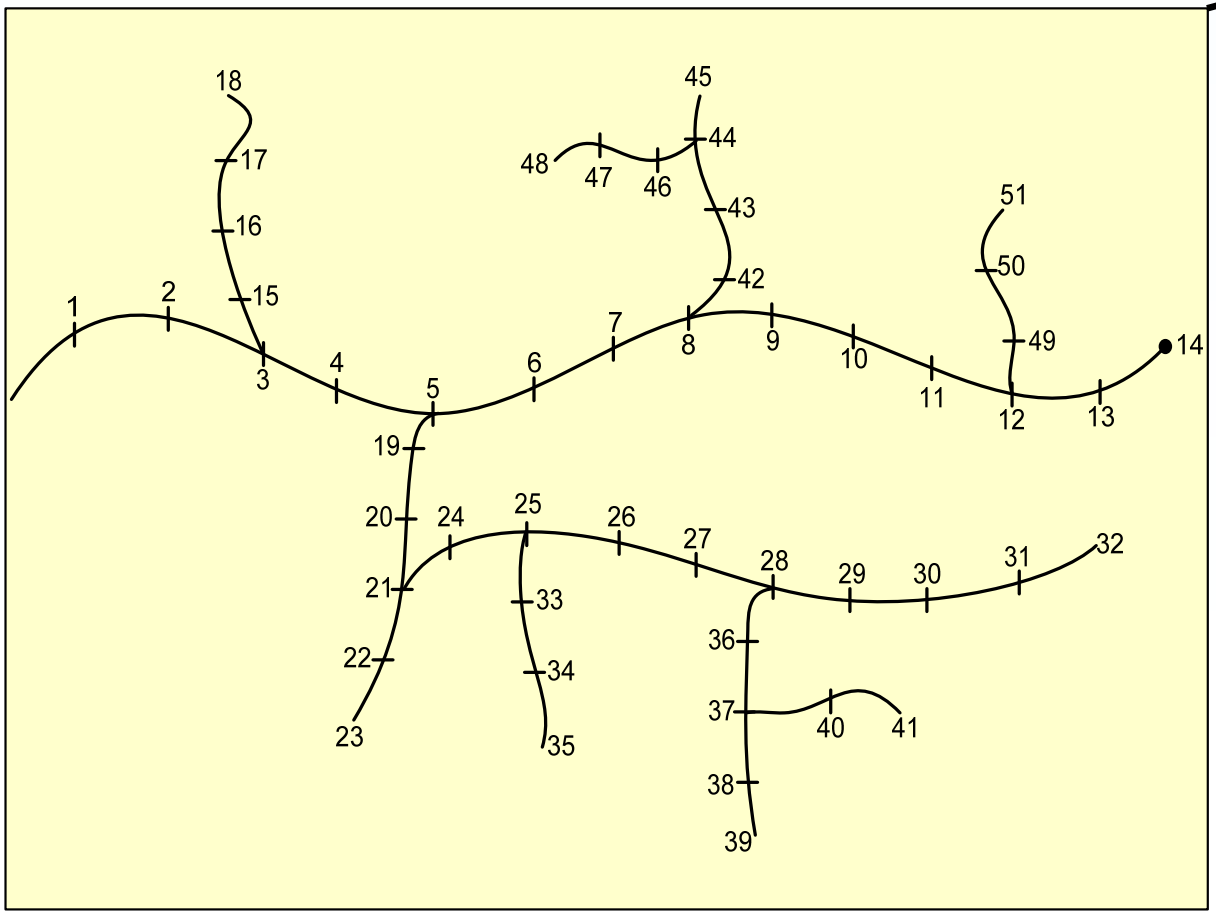
$$P_i = R_i \Big/ \sum_{z=1}^{N_R} R_z$$

Topology MC Algorithm

- The topological information regarding a polymer chain is stored in a topology column of the total topology array.

Topology Array

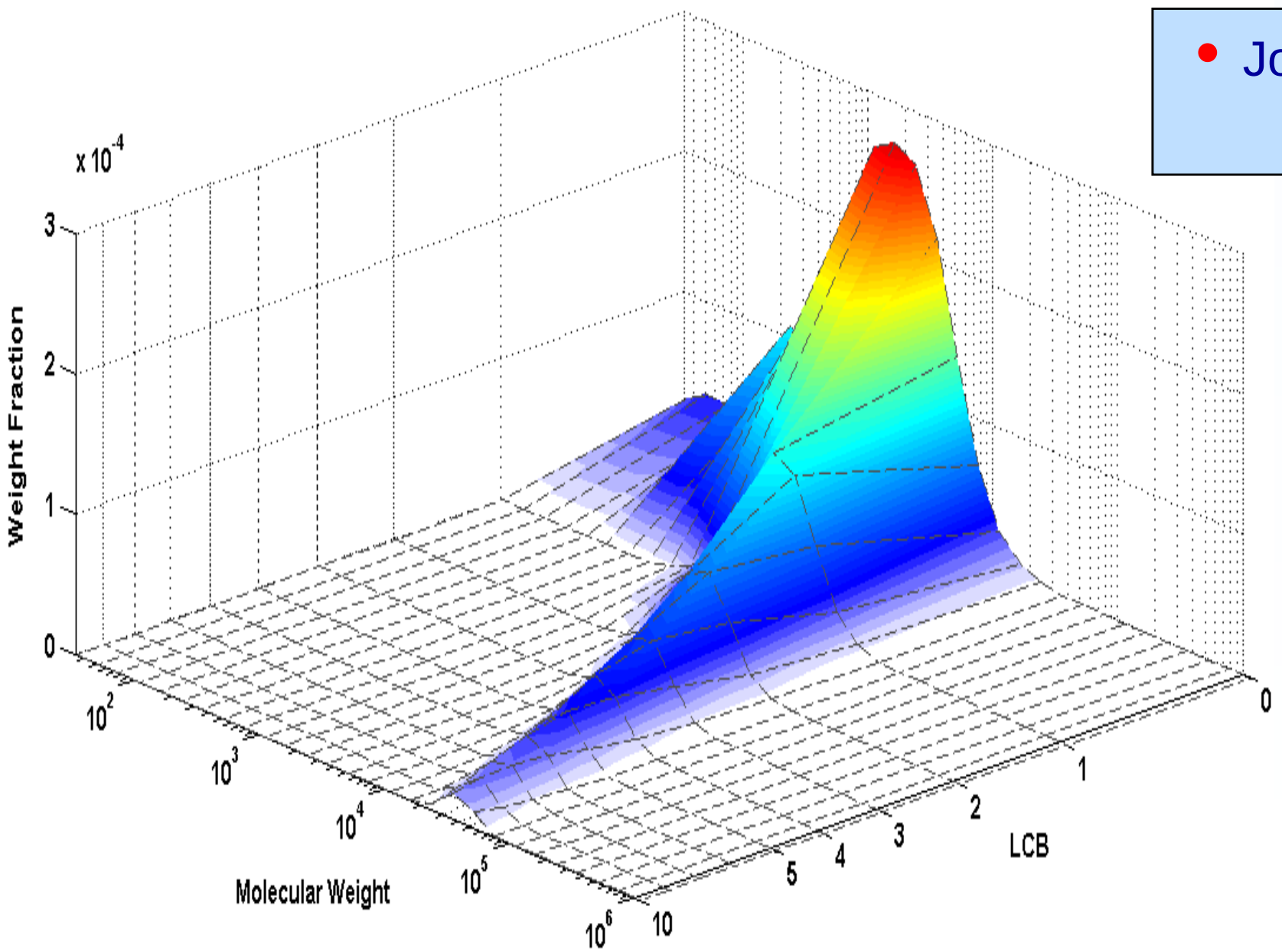




Position	Topological Information	Value
1	Total chain length	**51**
2	Size of backbone chain	**14**
3	Total number of branches (=b)	**9**
4	Size of branch Nº 1	**4**
5	Position of branch Nº 1	**3**
6	Size of branch Nº 2	**5**
7	Position of branch Nº 2	**5**
8	Size of branch Nº 3	**9**
9	Position of branch Nº 3	**21**
...	...	**...**
20	Size of branch Nº 9 (=(2b+3)-1)	**3**
21	Position of branch Nº 9 (=(2b+3))	**12**

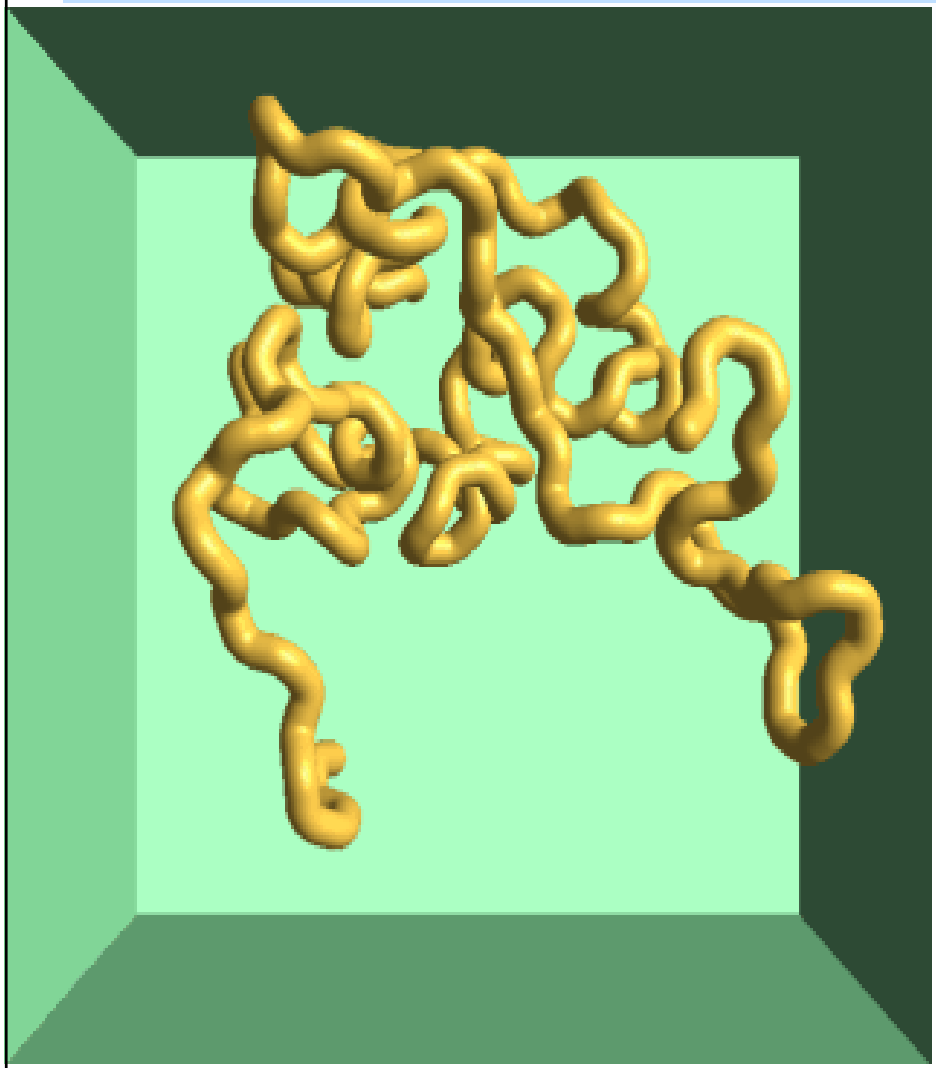
Kinetic/Topological MC Simulation of LDPE

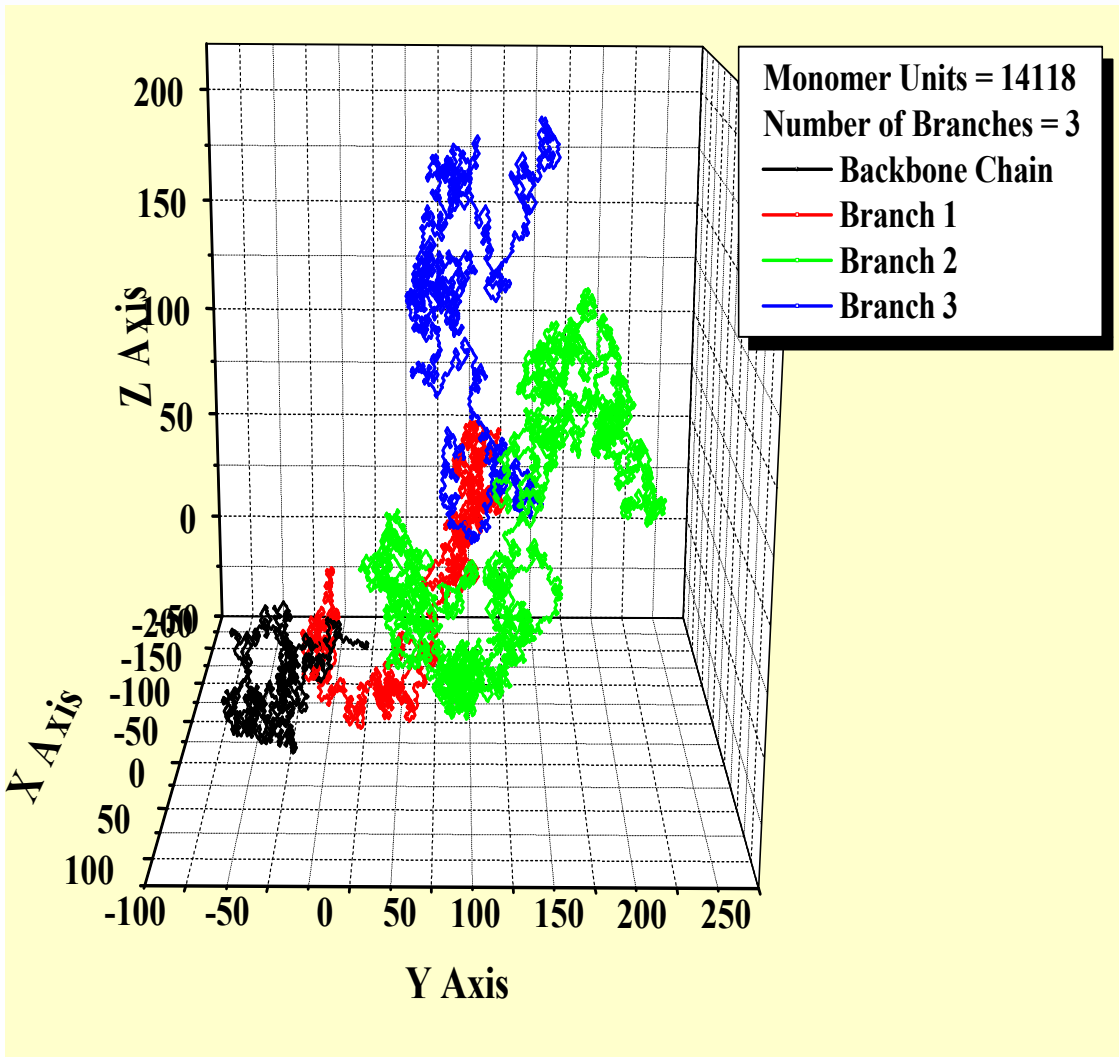
- Joint LCB-MW Distribution



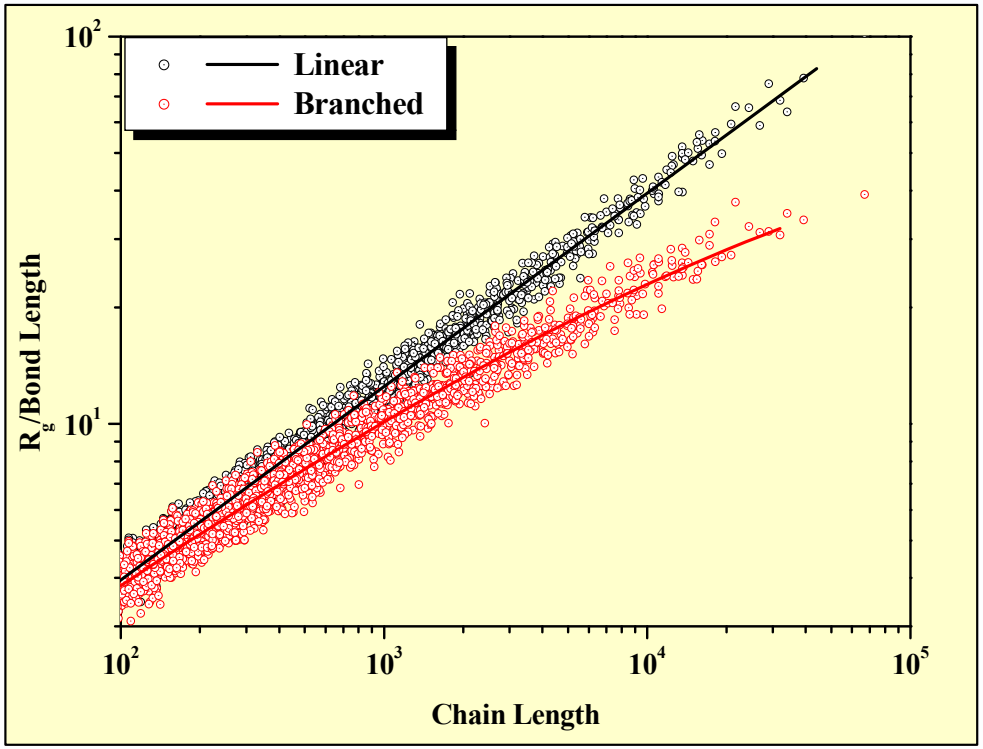
Molecular Dynamics Simulations

- Via the MD simulations, a series of random 3D configurations is obtained for every polymer chain.

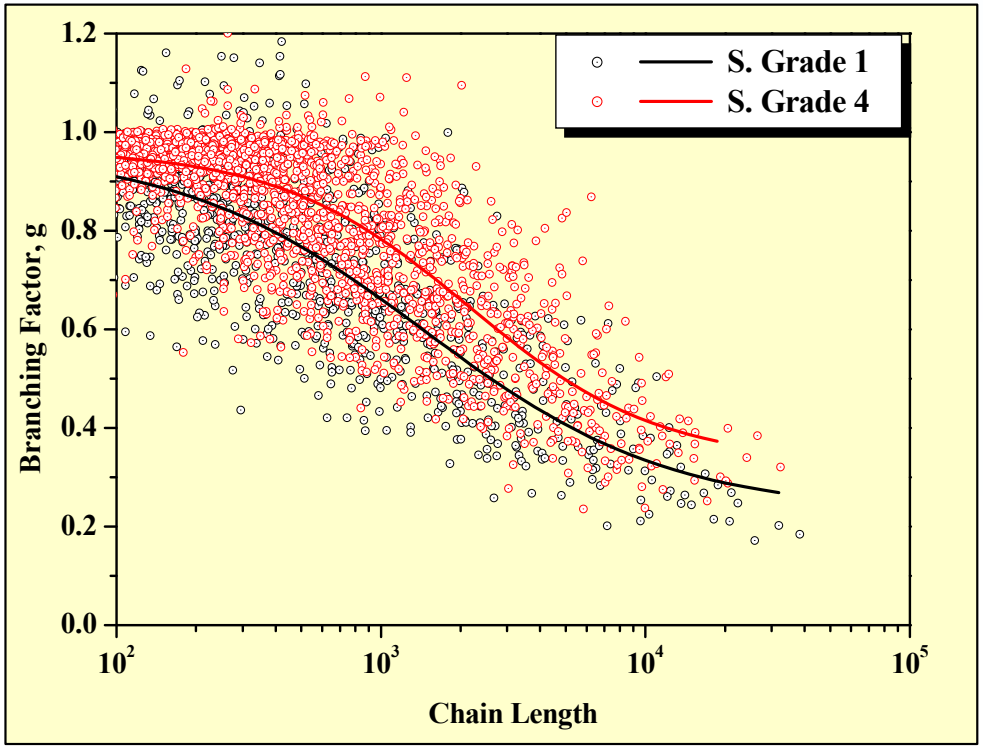




MC Simulation of LDPE

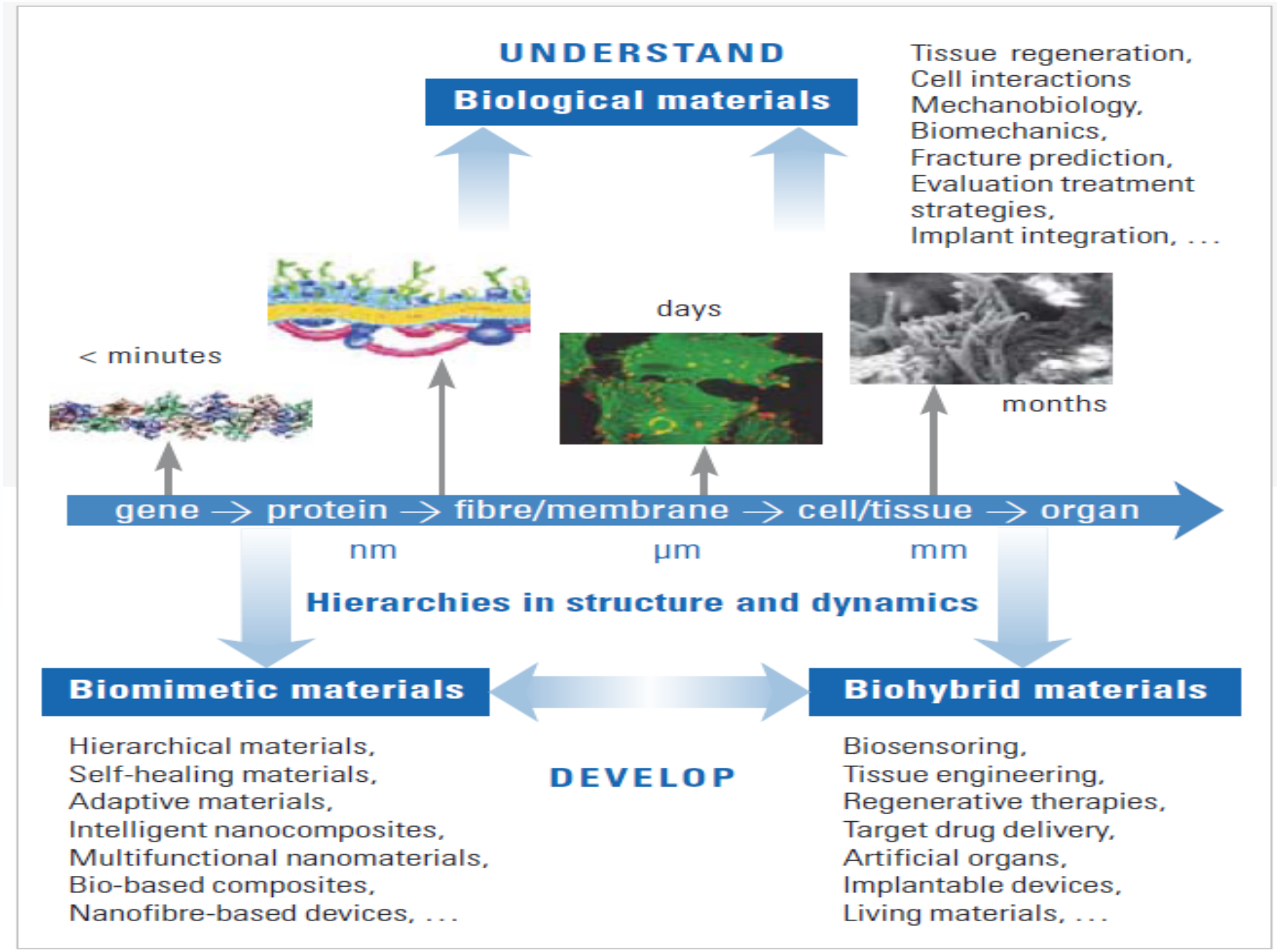


- Radius of Gyration

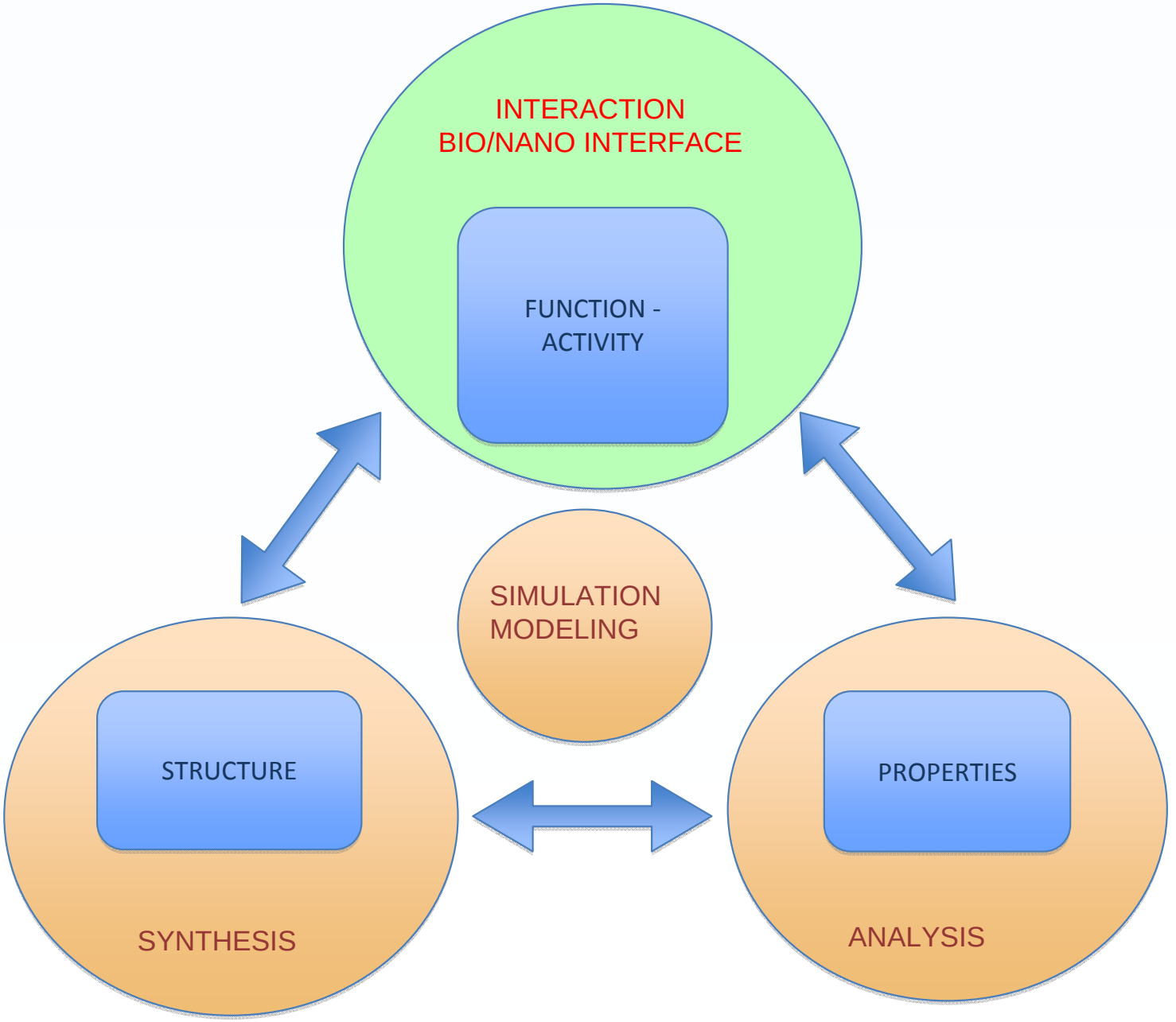


- Branching Factor, g

Biological Materials



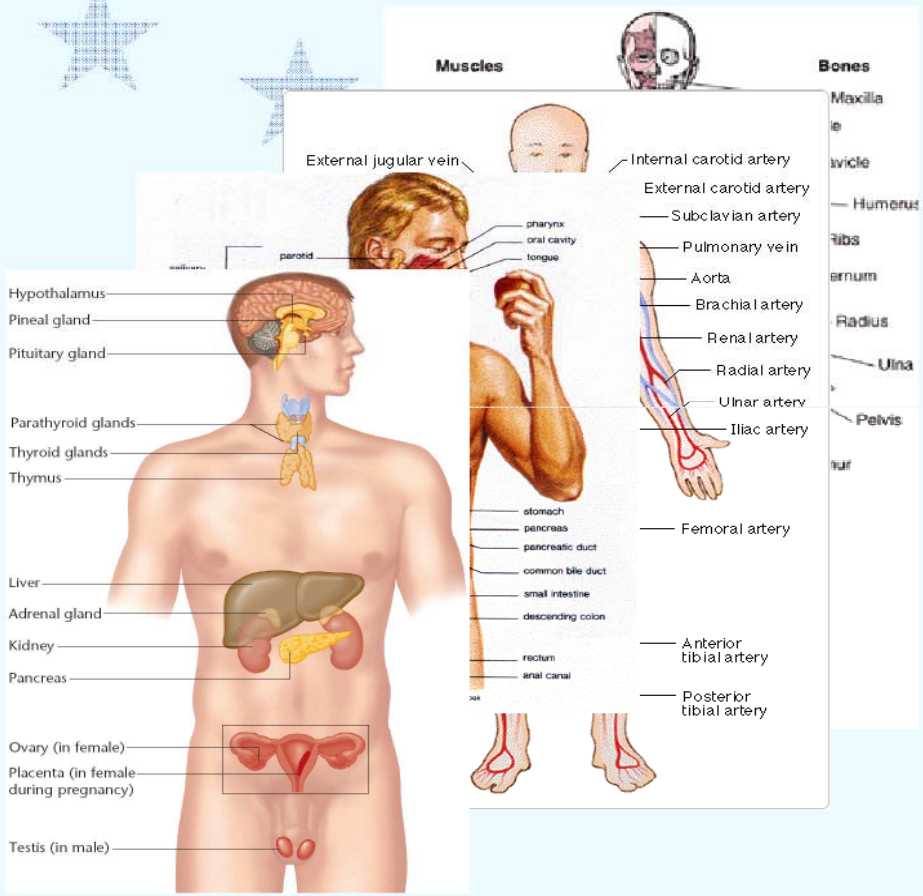
Safe Design of Nanomaterials



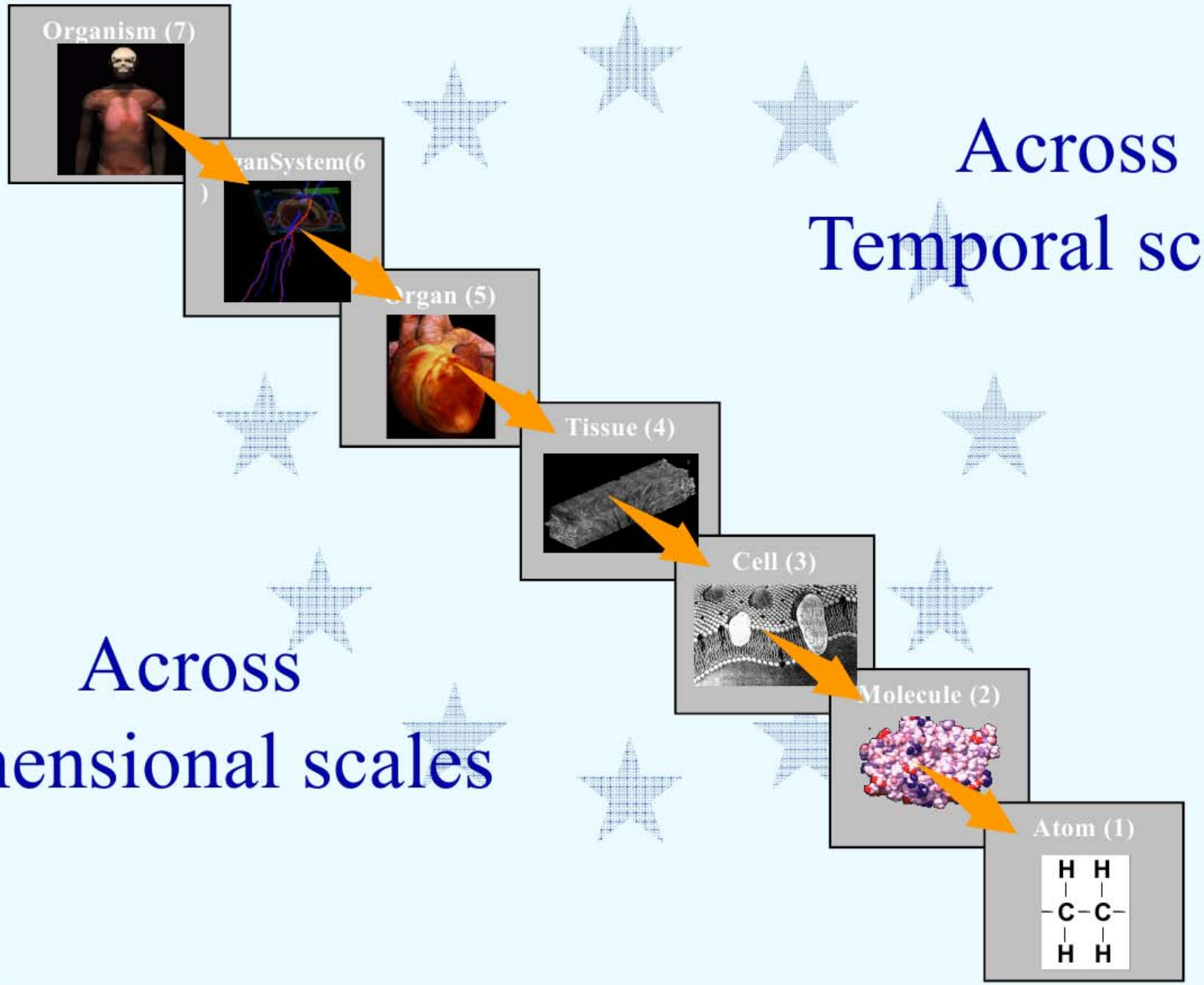
Virtual Physiological Human

Integration across ....

Across sub-systems



Integration across ….



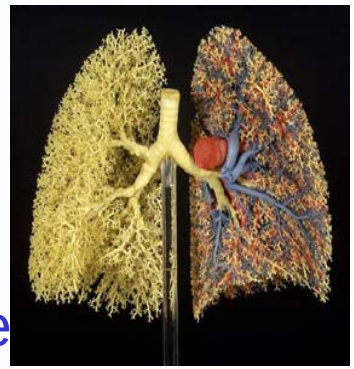
Across
Temporal scales

Across
dimensional scales

EuroPhysiome

Biomedical Particle Transfer & Drug Delivery

Nasal and Pulmonary Drug Delivery

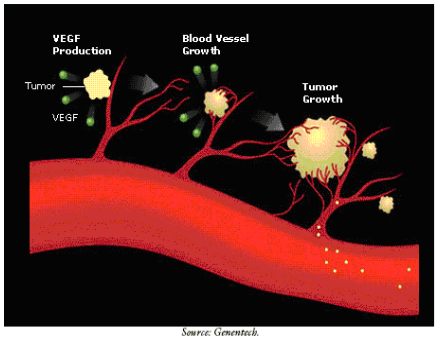


- Deposition and Drug Release in Nasal Cavity
- Targeted Drug Delivery to the Pulmonary Syste
- Deposition and transfer of toxic nanoparticles and nanofibers

Cardiovascular Disease and Atherosclerosis

- Flow Dynamics
- Lipoprotein Particle Dynamics and Plaque Formation

Modeling of Angiogenesis



- Tumor Growth and Metastasis
- Capillary Network Formation

Issues in Safe Design of Nanomaterials

It is an extremely complex problem !

- Many length/time scales - from microscopic to macroscopic
- Many external (uncontrolled) variables: bio-environment

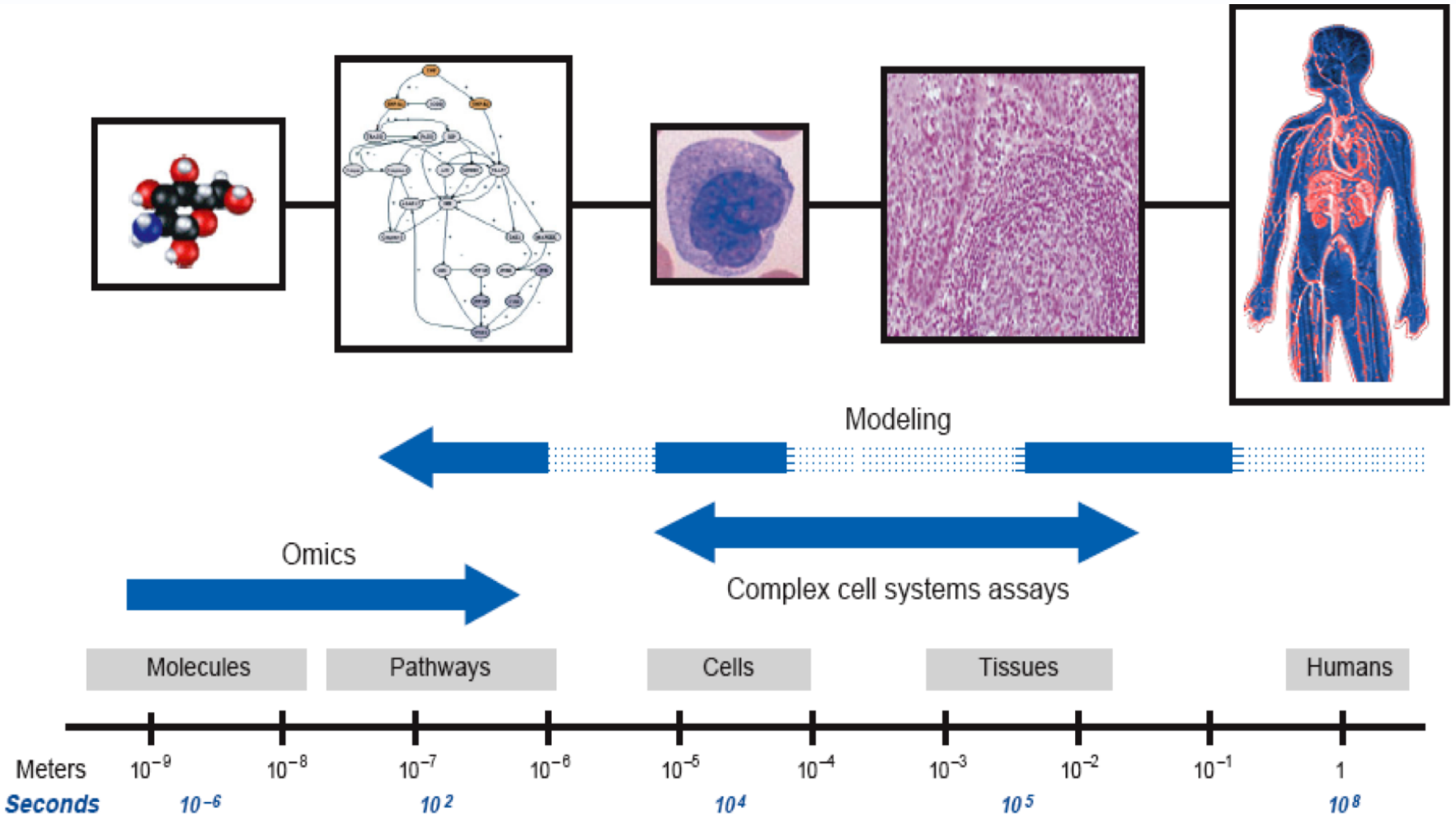
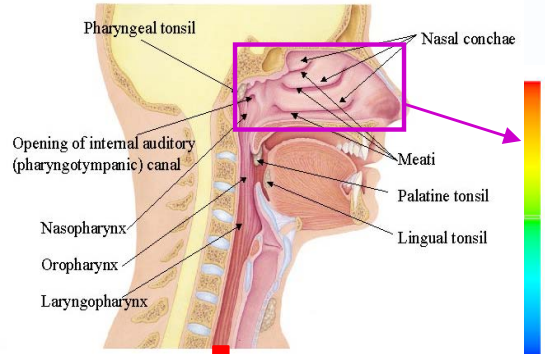
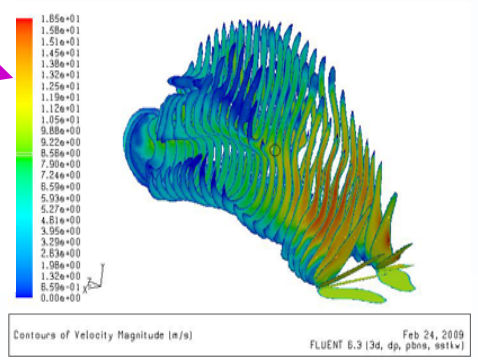


Fig. taken from Butcher et al., Natutre Biotech, 2009

Virtual Physiological Model of Respiratory

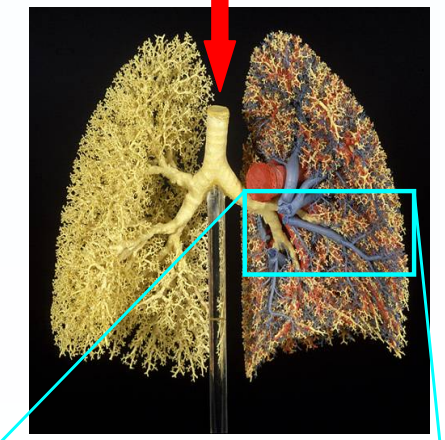
- Includes: nasal cavity, pharyngotrachea, and pulmonary tract (bronchi, bronchioli, and alveoli).
- CFD simulations of each compartment are performed and connected together through the inlet and outlet boundary conditions.
- Eulerian/Lagrangian simulations of particle motion and deposition are performed.
- Delivery models provide the amount of drug/toxin released from deposited particles and droplets.



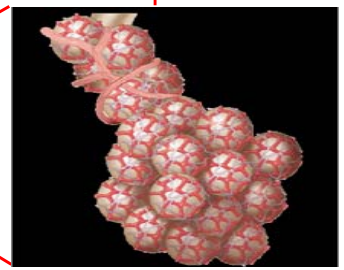


CFD Simulation of Nasal Cavity

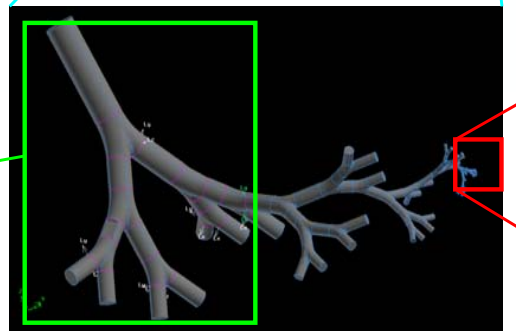
Nasal Drug Delivery Model



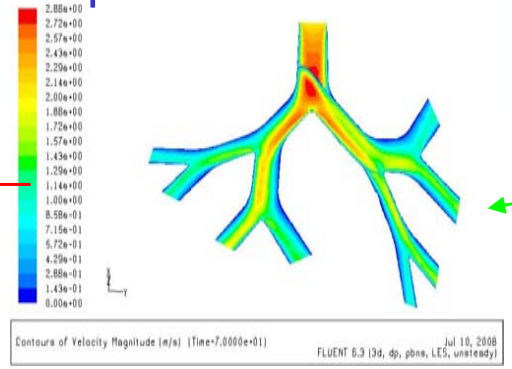
Alveoli Drug Delivery Model



Alveoli Model



Multi-block Pulmonary Model

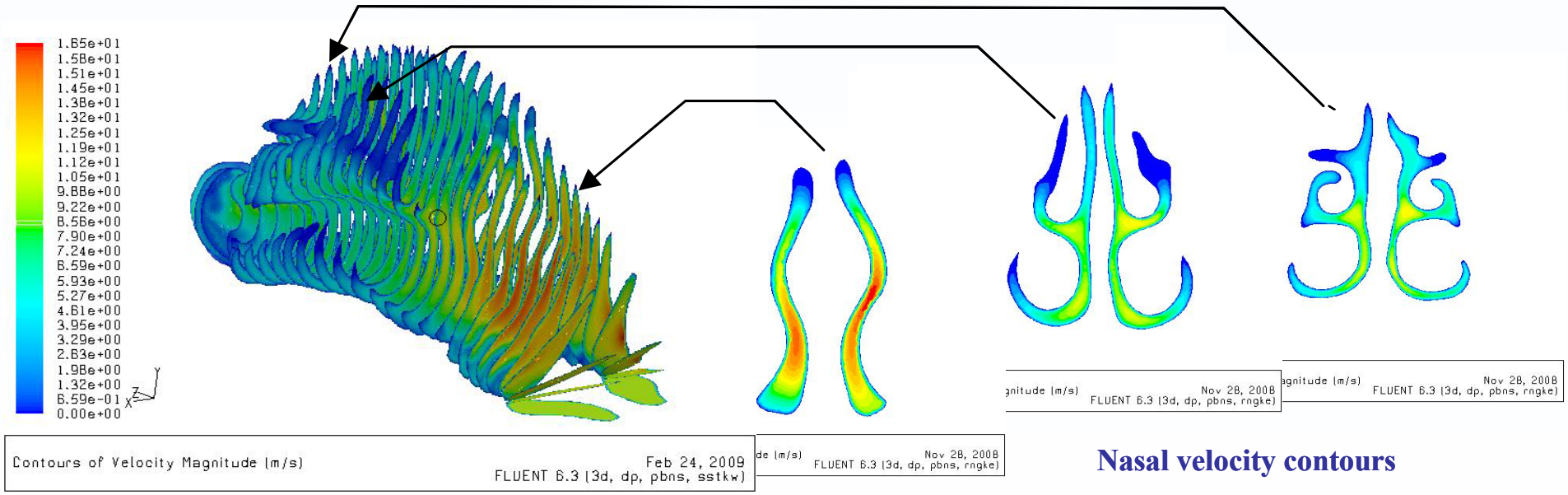


CFD Simulation of Pulmonary Block

Local Drug Delivery Model

CFD Results: Velocity Contours

- Simulations were performed for different inlet velocity magnitudes, profiles, and directions, different outlet conditions, different inlet turbulent intensities as well as different viscous models (e.g., laminar, k-ε, RNG k-ε, k-ω)

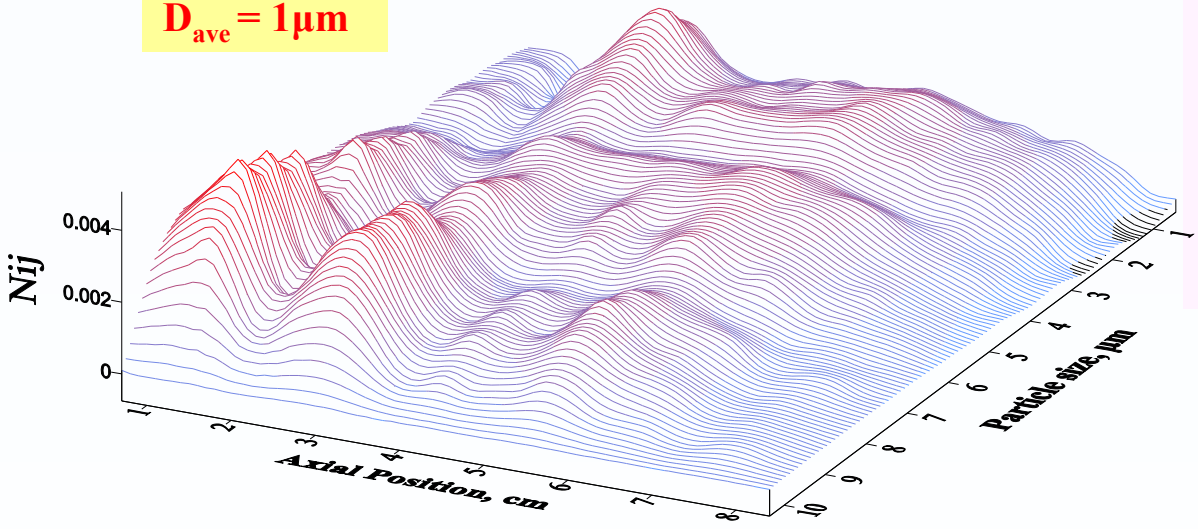


Nasal velocity contours

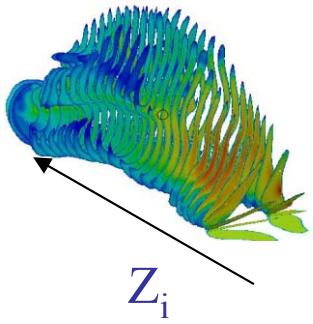
- The flow varies from laminar to turbulent. For inflow velocities vin=1-2m/s (typical of regular breathing) and Re = 900-1800, respectively.
- The flow is strongly non-homogeneous. Largest velocity magnitudes occur in the region near the nasal valve. Flow is directed towards the regions where the nasal cavity meatuses intersect.
- Only limited flow reaches the outer tips of the meatuses and the olfactory region.

Bivariate Deposition Distribution

$D_{ave} = 1\mu m$

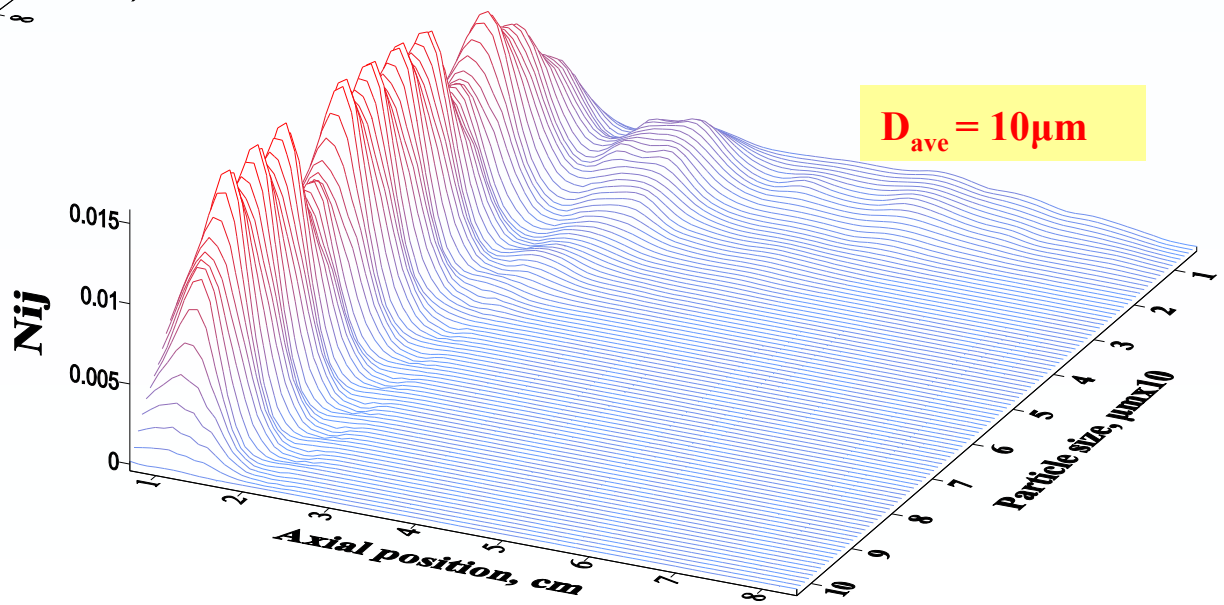


Bivariate deposition distribution, N_{ij}:
Number of particles in the size range $[D_j, D_{j+1}]$ which deposited between Z_i and Z_{i+1}.



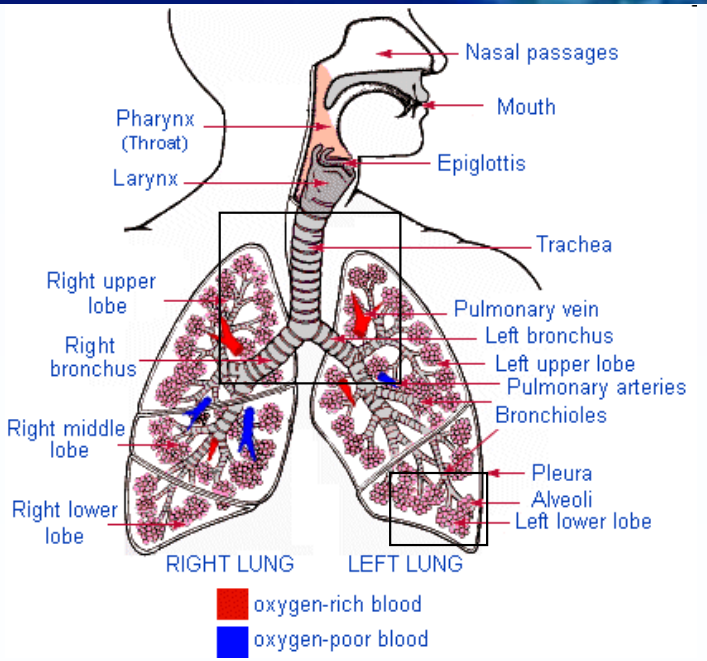
- ✓ k-ω model
- ✓ Zero turbulent dispersion and zero roughness
- ✓ V_{in}=10m/s inlet velocity
- ✓ Rosin Rammler distribution:
  Dispersion parameter =3.5
  Mean Size = 1 and 10μm
- ✓ Mean Axial Deposition
  10μm : 1.44cm : 1μm : 3.23cm

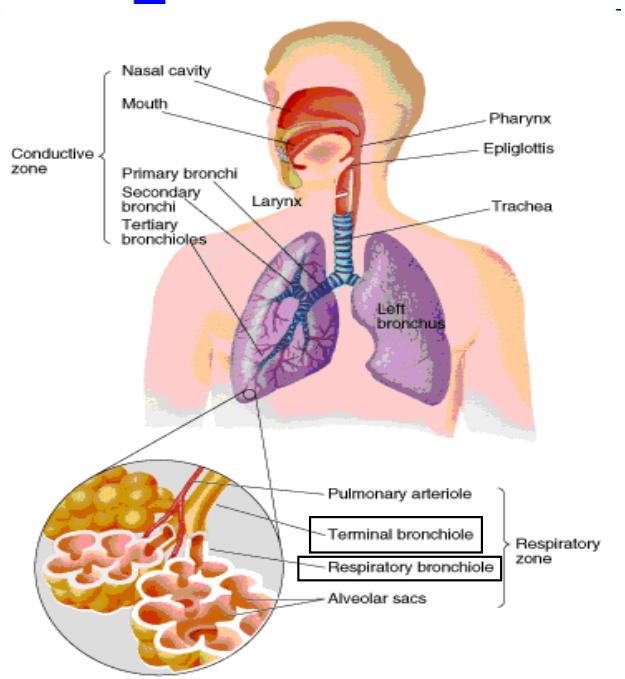
$D_{ave} = 10\mu m$



➢ Small particles (i.e., 1μm) deposit less than large particles (i.e., 10μm) but their deposition is much more uniform.

Geometry and Physiology of the Lungs





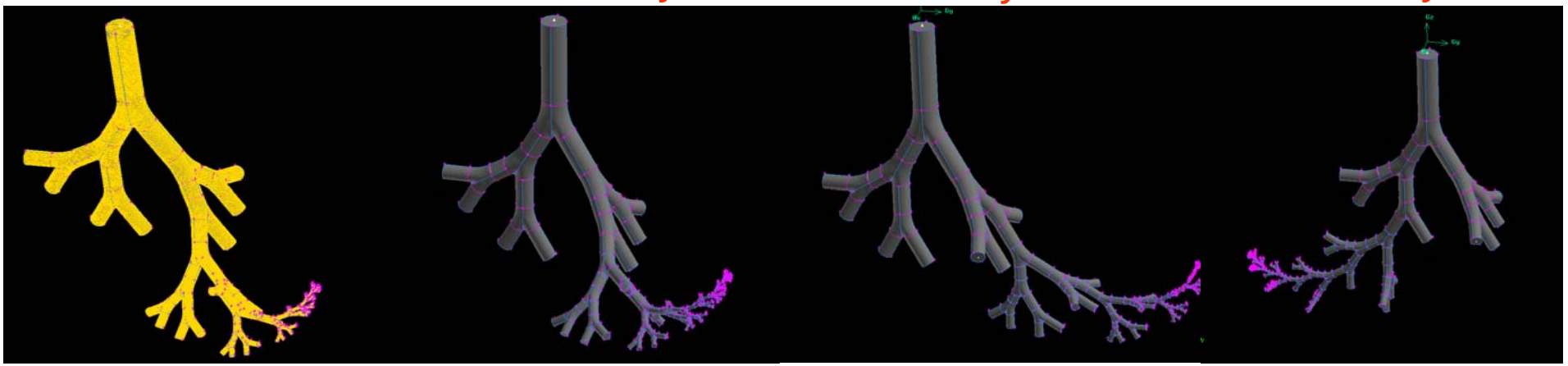
The lungs consist of the Tracheo-bronchial region (TB) and the Alveolar region (A). The first region starts at the larynx, and extends via the trachea, bronchi and brochioli and ends at the terminal bronchioles. The second region consist of the respiratory bronchioles, alveolar ducts and alveoli.

- The tracheobronchial airways consist of a series of symmetrical and asymmetrical branches.
- Each pulmonary branch corresponds to a “generation”.
- The lung consists of 23-24 generations. The first (i.e., “generation 0”) corresponds to the trachea and the last generations (i.e., 17 to 23) represent the bronchioles and alveoli regions.
- The pulmonary system is represented by a sequence of seven computational blocks each consisting of three generations and seven branches.

Pulmonary Geometry and Grid

Simulations were performed for three different geometries (P1,P2,P3) and different inlet velocities.

Grid P1 Geometry P1 Geometry P2 Geometry P3



- Different respiratory system geometries were constructed by assembly of seven computational blocks.
- Each computational block consists of 3 generations of branches – 7 total branches.
- Computational grids were comprised of 200-500,000 tetrahedral elements (per block).
- CFD simulations for the first block were performed by taking as inlet boundary conditions the outlet flow of the nasopharynx (i.e., airflow and particles).
- For the remaining computational blocks the inlet boundary conditions are taken from the outlet flow of the preceding computational blocks.

Research Priorities in Modelling and Simulation

Develop Fundamental Models to Accurately Predict Nanostructure Formation.

Models of fundamental material properties at the nanoscale are needed, as well as models to screen formation and synthetic pathways.

- Develop methods to include chemistry (reaction and degradation) in force-field modeling to understand nanostructure formation
- Modeling of the chemistry of deformable interfaces
- Integrate the chemical functionality of nanomaterials into models
- Link molecular simulation to constitutive models
- Develop methods for comparing equilibrium, non-equilibrium, and kinetically trapped systems

Bridging Models Between Scales, from Atoms to Self-Assembly to Devices.

Accurate predictive models and simulations linking nanoscale properties across time and length scales to specific macroscopic properties are needed. These models will help enable the design and engineering of nanomaterials.

Research Priorities in Modelling and Simulation

Bridging Models Between Scales, from Atoms to Self-Assembly to Devices.

- Simultaneously incorporate atomistic and mesoscale techniques in ab initio methods to predict properties or extract atomistic contributions from observed properties.
- Develop advanced molecular dynamics (MD) simulation methods.
- Develop models of properties that apply to industry and consider unique scaling laws from nano to meso to macroscale (e.g., mechanical, electrical, magnetic, optical, convective transport (heat, momentum, mass), diffusion, thermodynamic equilibria, including adsorption, surface-surface interaction, and chemical reaction).
- Extend models to recognize and predict new and unexpected emergent properties of self-assembled systems
- Expand models to understand and predict toxicology and environmental impact of nanomaterials.
- Combine simultaneous effects (e.g., flow dynamics and thermodynamic driving forces) to provide powerful tools for evaluating potential new technologies.

Outline

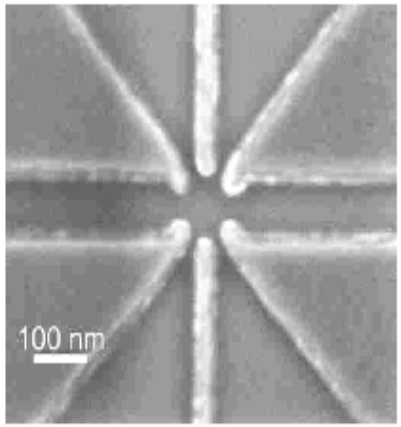
3. Research Directions in Atomically Precise Fabrication Methods

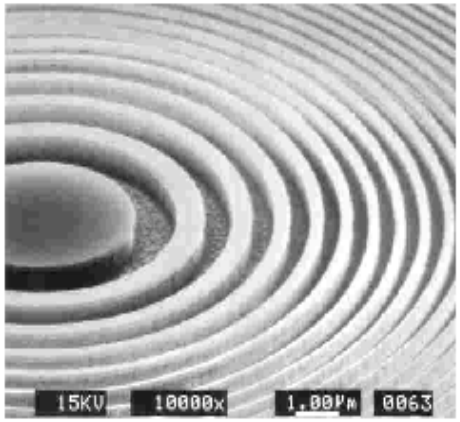
- Atomically Imprecise Fabrication Methods
- Atomically Precise Self-Assembly
- Scanning-Probe Based Nanofabrication
- Atomically Precise Manufacturing
- Hybrid Nanofabrication

Atomically Imprecise Fabrication Methods

- Nano fabrication techniques may be loosely divided into two camps: a top-down approach based on lithography, and a bottom-up approach where structures are built one molecule at a time.
- The first camp favors methods that can extend the existing planar, deposit-pattern-etch paradigm.
- Lithography is used to pattern features of complex geometries as small as 50 nm. Non-optical methods of lithography are being pursued to overcome this size limitation. But as the shrinking length scales continue, new imaging materials may be required to meet manufacturing constraints.

  - Electron Beam Lithography
  - Block Copolymer Lithography
  - Nano-imprint Lithography
  - Dip-Pen Nanolithography
  - Dielectrophoretic Assembly
  - Plasmon Assisted Chemical Vapor Deposition (CVD)
  - Partially Ordered Chemical Self-Assembly



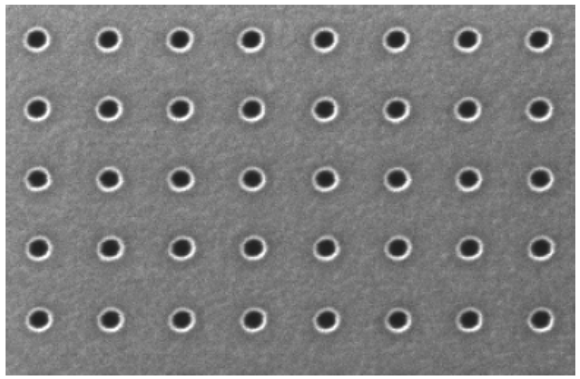


Top-down Nanomanufacturing

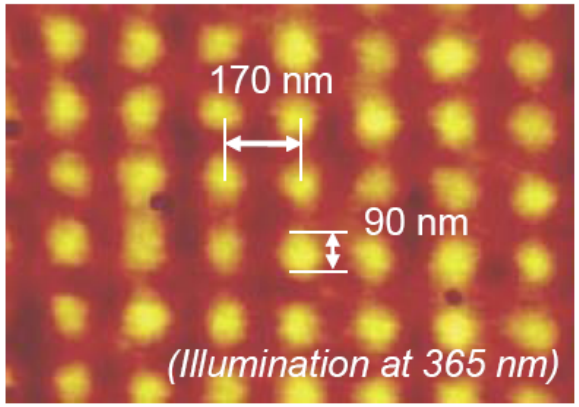
- Critical Challenges:
  Semiconductor Manufacturing at a Crossroads
  - 50 nm resolution limit
  - Lacking 3D capability
- Goal*: 3D Nano-manufacturing with*

  1-20 nm resolution
- Approaches
  - Plasmonic Imaging Lithography (PIL)
  - Ultra Mold Imprinting Lithography (UMIL)

Mask fabricated by FIB



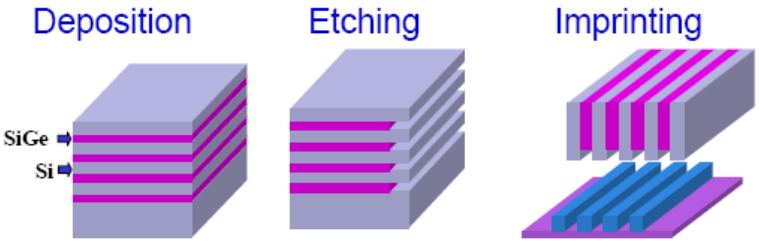
90nm features

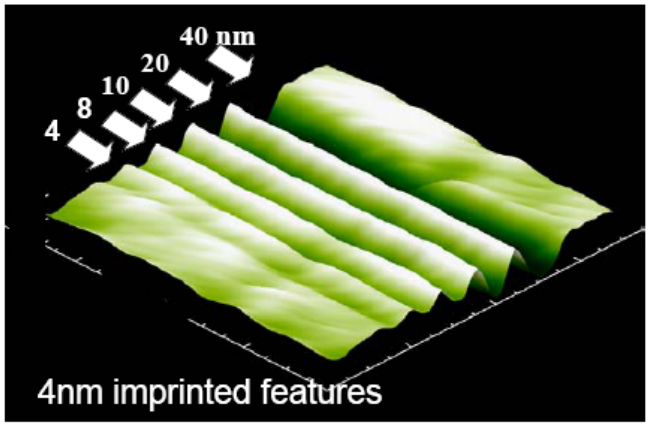


Source: Cheng Sun, Xiang Zhang, SINAM Univ. of California

Ultra Molding Imprint Lithography

Sub-10 nm mold fabricated using Superlattice of alternating SiGe and Si multilayers.





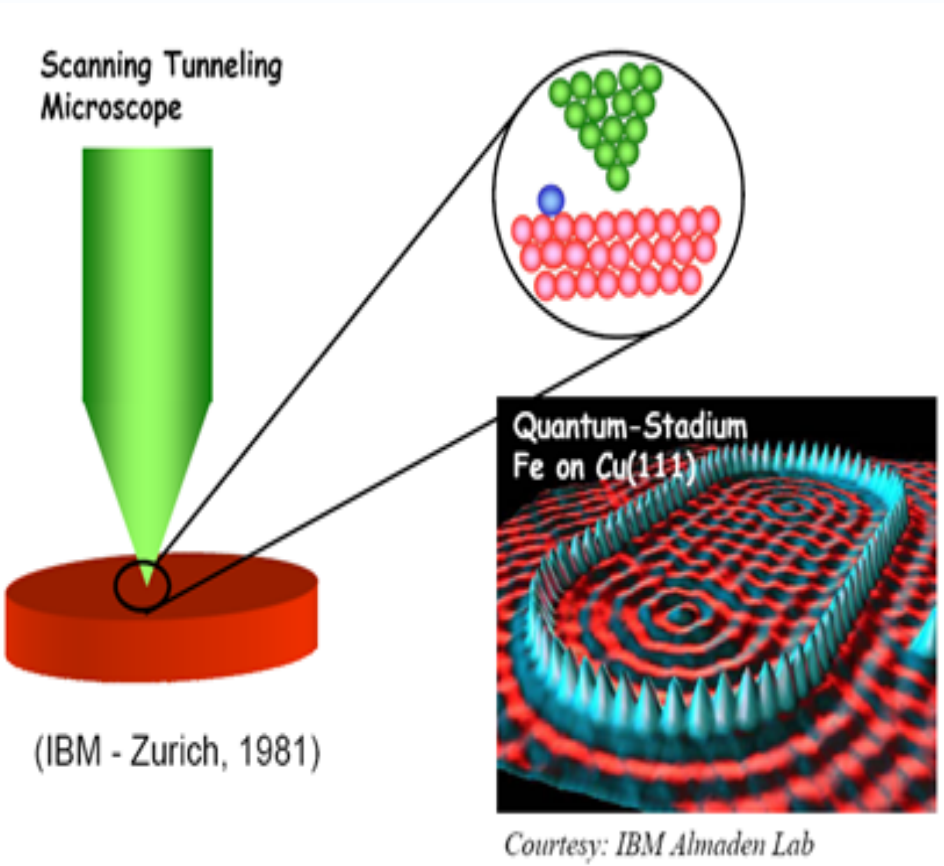
[Chen, Hahn, Tsao, UCLA; Wang, HP; Hocken, UNCC]

Atomically Precise Fabrication Methods

- Atomically precise structures consist of a definite arrangement of atoms . Current examples include:
  - Self-assembled DNA frameworks
  - Engineered proteins
  - Crystal interiors and surfaces
  - Scanning Tunneling Microscopy (STM)-built patterns on crystal surfaces
- The only large structures are simple and regular—crystals; the only complex, 3D structures are polymers—proteins and DNA.
- Atomically precise, STM-built patterns are at a very early stage of development.
- ***What is lacking is a systematic way to combine components to build complex systems***.

Scanning-Probe Based Nanofabrication

- Scanning probe microscopes can image individual atoms and molecules, manipulate them, and effect chemical reactions between them to form atomically precise structures. They offer a basis for atomically precise manufacturing (APM) of several kinds.
- These operations use mechanical positioning to direct the making and breaking of strong bonds, and thus provide examples of mechano-synthesis.



- In order to construct three-dimensional atomically precise structures, a top-down nanopositioning system would have to direct bond making and bond breaking processes with atomic precision. The range of approaches that has been considered includes placement of reactive molecules of various kinds in various environments.

Research Directions

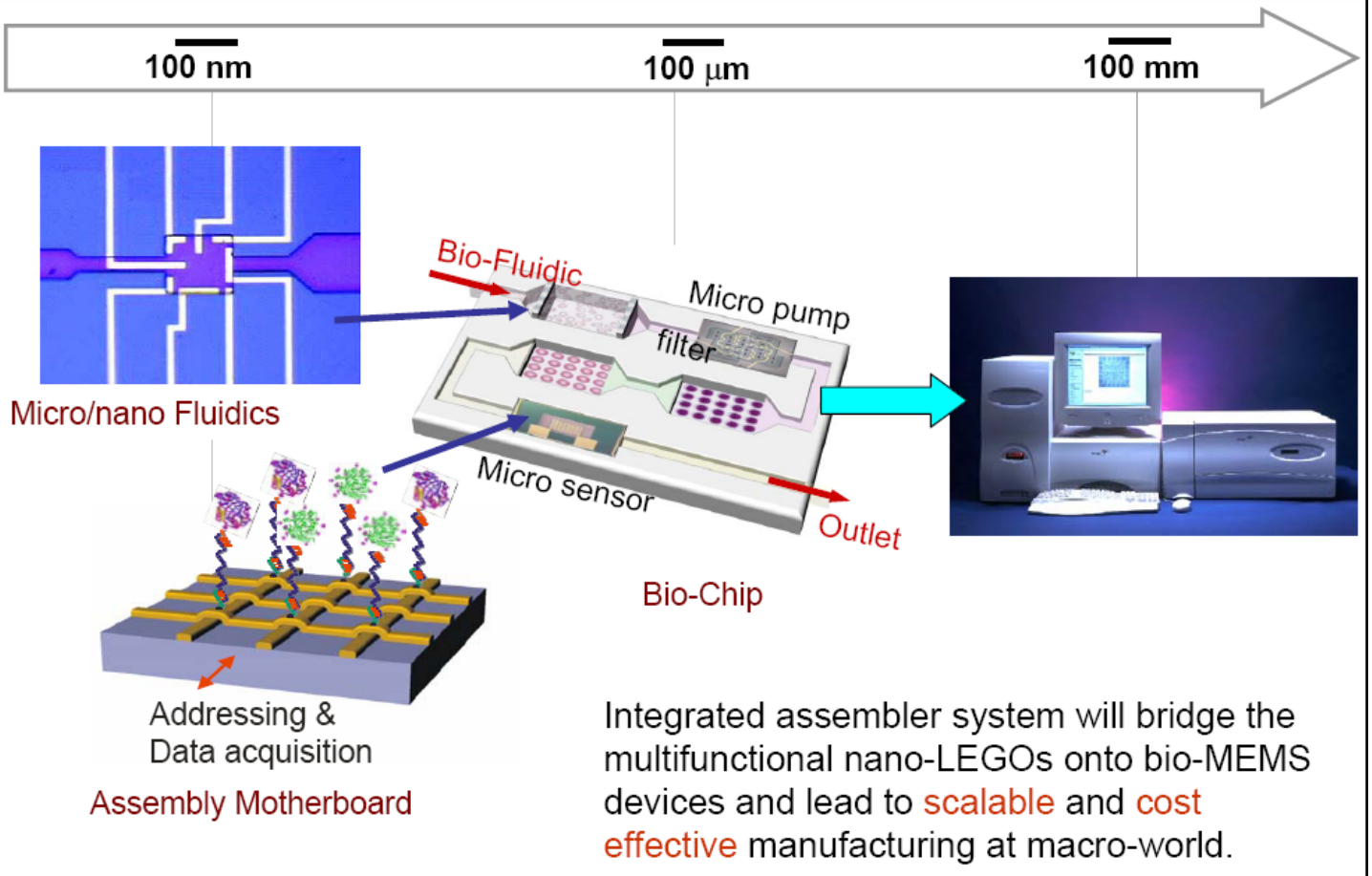
- Scanning probe fabrication is one of many viable pathways to productive nanosystems. For progress to be made in these approaches to APM, improvements in the automated systems that provide accuracy and stability of positioning, and improvements in atomically precise control of probe tip structures, will be of central importance.
  - Atomically precise tooltips
  - Multiple degree of freedom nanopositioning
  - Improved repeatability and reproducibility of positioning devices
  - Increased total area over which higher precision repeatability and reproducibility limits can be met
  - Manipulator tip designs for improved positioning of individual molecules and nanostructures (including gripping ability or selective stickiness, more degrees of freedom and wider ranges of motion)
  - Multi-tip manipulators.

Hybrid Top-down & Bottom-up Nanomanufacturing

- Critical Challenges
  Self-assembly cannot:
  - Heterogeneously assemble pattern for devices
  - Avoid “defects” due to thermodynamic nature

- Goal
  Massive and parallel integration of hetero-geneous nano-LEGOs into devices

- Approaches
  - Hybrid Top-down and Bottom-up technologies



Integrated assembler system will bridge the multifunctional nano-LEGOs onto bio-MEMS devices and lead to scalable and cost effective manufacturing at macro-world.

Source: Cheng Sun, Xiang Zhang, SINAM Univ. of California

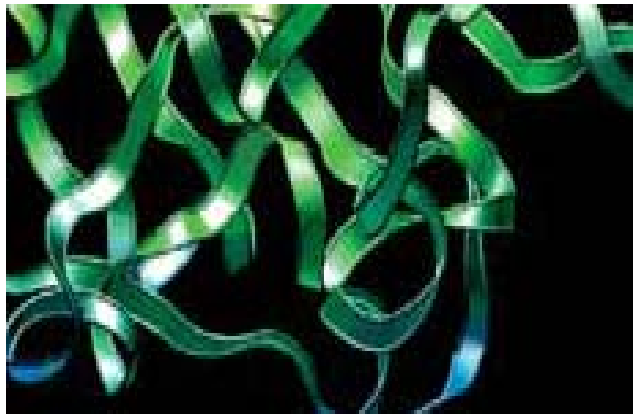
Outline

4. Nanotechnology Research Directions in Life Sciences and Health Care

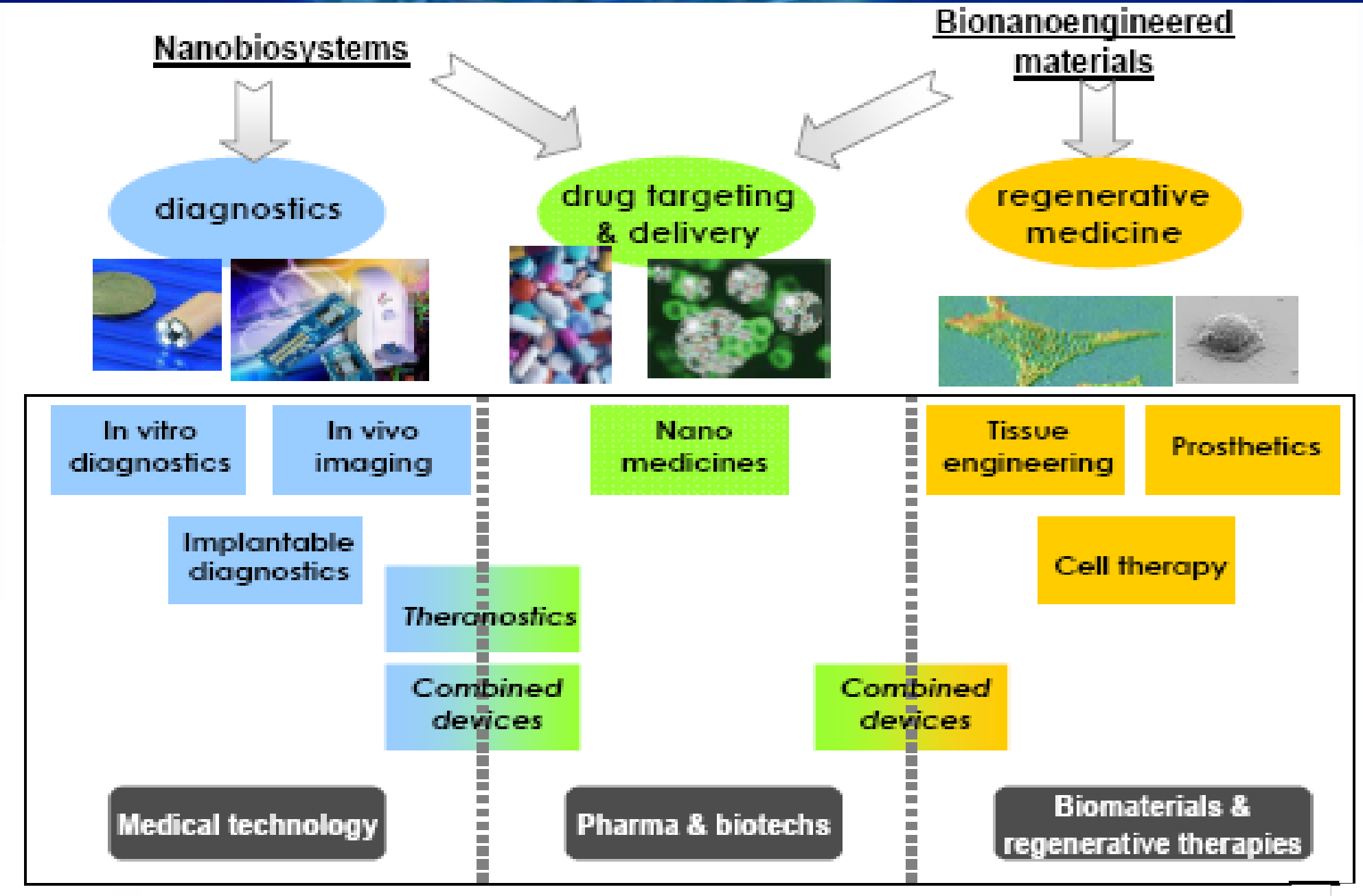
Nanomedicine

The term Nanomedicine refers to the application of nanotechnologies to diagnosis and treatment of diseases.

- ✓ It deals with the interactions of nanomaterials (surfaces, particles, etc.) or analytical nanodevices with “living” human material (cells, tissue, body fluids).
- ✓ It is an extremely large field ranging from in vivo and in vitro diagnostics to therapy including targeted delivery and regenerative medicine.

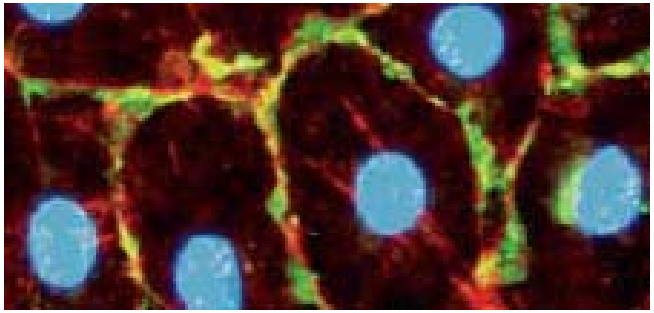
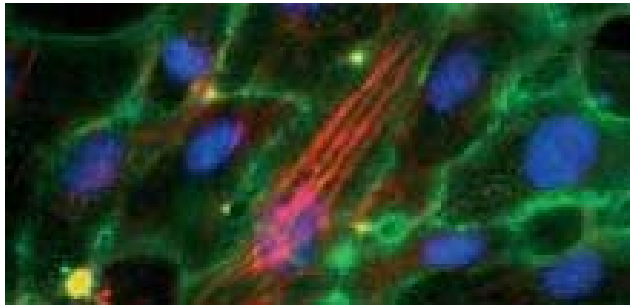
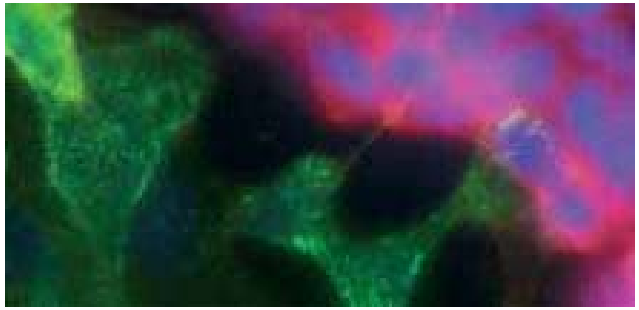


Nanotechnology for Medical Applications

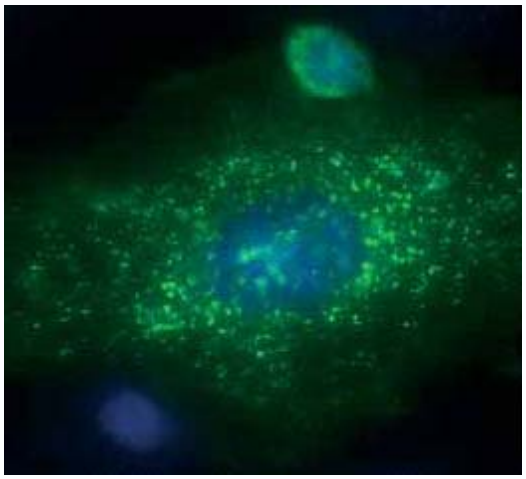


R&D Priorities - Diagnostics

- In the long term the capacity of central lab diagnostics will probably be saturated, which will likely result in an increased need for point-of-care (POC) diagnostics.
- In addition, a multiplex analysis system will require some integrated data processing capability able to perform sophisticated algorithms.
- Semiconductor companies could contribute their expertise in automation and miniaturisation gained in the traditional semiconductor manufacturing. However, their access to biological expertise is currently a bottleneck, which considerably limits them in producing relevant POC devices.

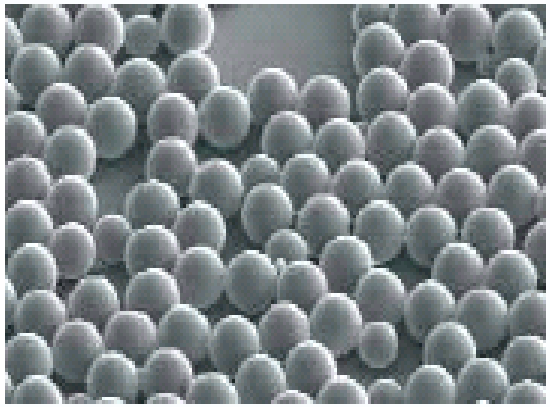
R&D Priorities - Diagnostics



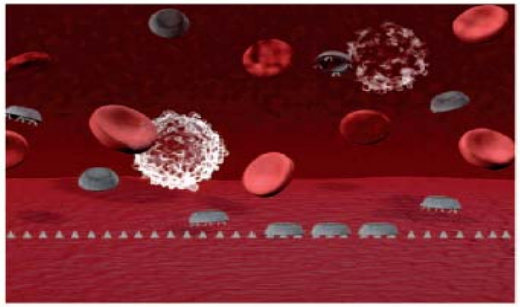
- In vivo Imaging
  - Magnetic particle imaging (MPI)
  - MRI, MPI contrast agents
  - Hyperthermia applications
  - Computed Tomography with small equipment footprint and (mobile equipment)
  - Luminescence based optical contrast agents
  - Image guided therapy and remote triggering of genetic therapy or local drug release
  - Microfluidics for PET (personalized doses in PET imaging)
  - Molecular optical imaging (e.g., molecular fluorescence imaging)
- In vitro Diagnostics
  - In vitro diagnostic decentralized testing applications (POC)
  - Multi-parameter testing (multiplex detection)
  - Therapeutic monitoring (continuous monitoring of drug delivery and its therapeutic effect)
  - (glyco) Proteom / RNA/ Epigenom Map (development of molecular X ray)
  - (Quantitative) Biopsies (potentially on the cellular level)
  - Genomic based diagnostics (cancer, infectious diseases)
  - Proteomic based diagnostics

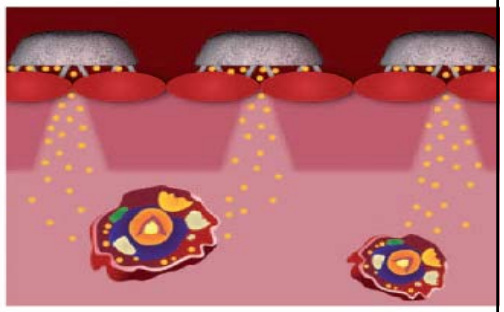
R&D Priorities – Drug Delivery

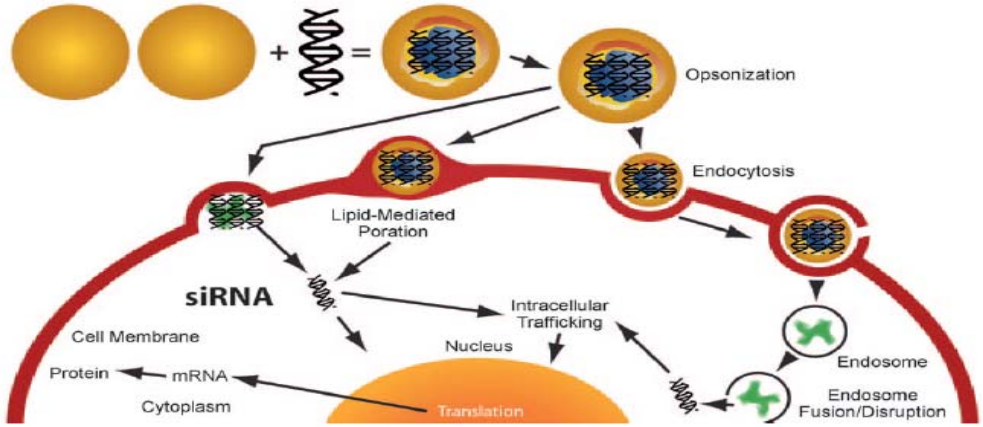
- Nanopharmaceuticals



- Therapeutic nanoparticles and polymers
- Nanocarriers and transporter molecules / particles
- Computational tools (self-assembly prediction)
- Activatable therapeutic nanoparticlesLuminescence based optical contrast agents
- Activatable nanoparticle devices
- Targeting drugs to facilitate cell differentiation
- Understanding of nanoparticle trafficking and disposal







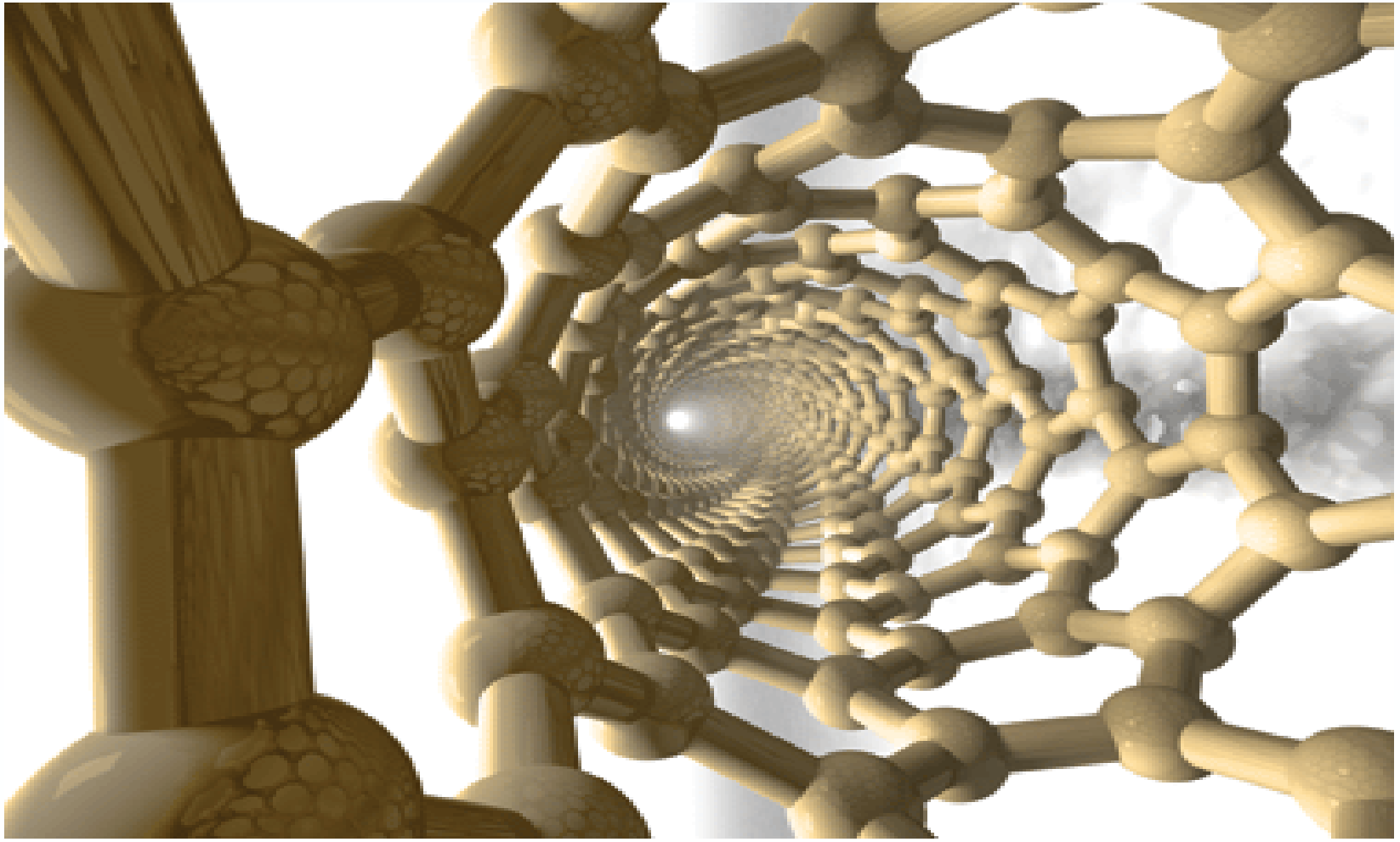
R&D Priorities – Drug Delivery

Nanodevices

- Devices for drug delivery (miniaturized systems for long term delivery of accurate drug doses)
- Minimally invasive, microneedle based transdermal drug delivery systems
- Localised therapy (MRI-guided non-invasive localized delivery).

Drug Delivery

- Development of reliable metering systems to verify the delivery of the correct amount of drugs/agents.
- Integrated monitoring of therapy either by external or internal devices (development of micro/nano electronic systems for disease control).



Thank you for your attention !