Tissue, Organs and Physiology Modeling

Reverse Engineering the Brain

The brain is the most complex system we know…and the compelling biological challenge of the century. How do thought, action, emotion, arise from the building blocks of life?

Bottom up understanding of function, predicting consequences of activation, intervention

Synthetic cognition: information encoding and processing architectures, spatio-temporal dynamics; neuromimetic and neuromorphic systems

Multi-scale physiological models of organ systems

Systems of models, the *Physiome,* Individual organ systems

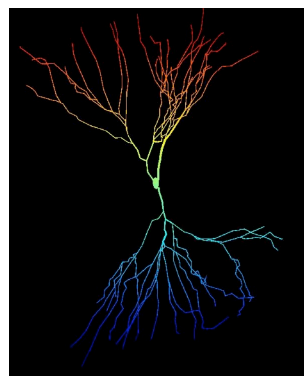
Capture function: mechanical, biochemical, electrophysiological,…

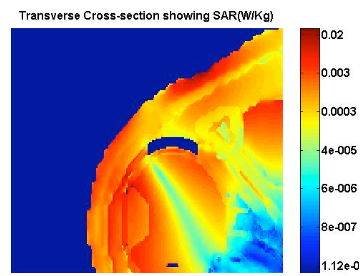
Model development, interpret diagnostics, tailor intervention

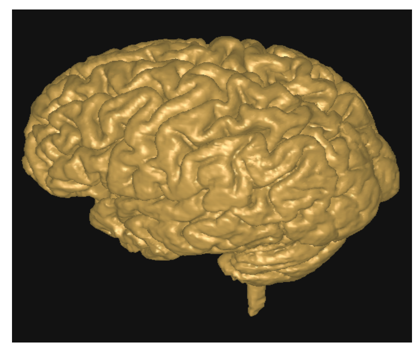
Health risks of environmental insults

Discriminate between effects and risk factors: Radiation, nanoparticles, byproducts of energy production…

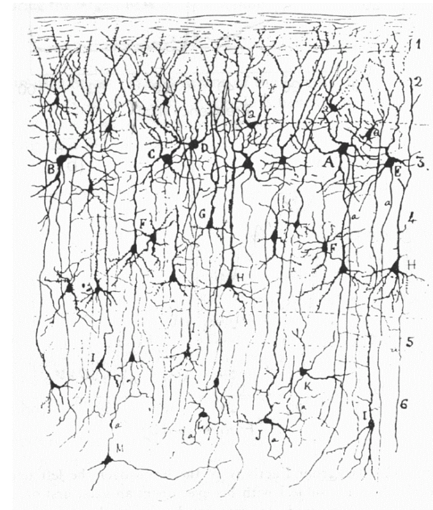
Address low probability events, high backgrounds, perturbation of homeostasis.







Common themes and challenges



- Detailed Cellular model

  => tissue (differentiation, self-assembly)

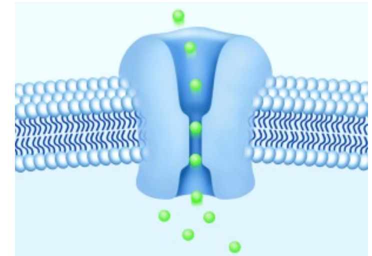
  => organ (function)
- Increasing spatial scale, complexity
  - 10^{8}-10^{11} cells, hundreds to thousands of cell types
- Wide range of temporal scales
  - 100 μsec=> decades

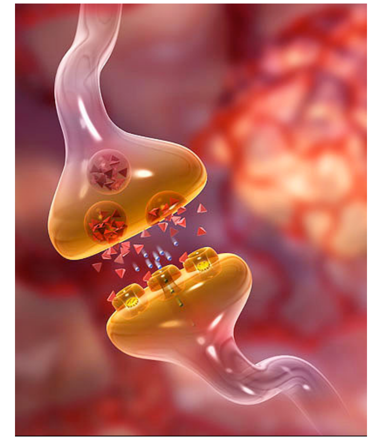
- Ground theories in knowledge of biological implementation
  - Granularity, resolution, a function of question..
- Inadequate knowledge of systems: equations, parameters… models drive new data collection (for model building and validation)…enable exploration of parameter space

Heterogeneous Data

- **Molecular Biology:** Genomics, proteomics, expression profiling
- **Physiology:** channel, unit, network, extended systems: by microelectrodes, arrays, optical, MEG/EEG, fMRI, PET, hybrid technologies, multi-modality techniques… *computational interpretation, integration*
- **Anatomy:** channels, spines/synapses, dendrites, cells, micro- and macroscopic system geometry…*synthetic cognition may automate data extraction*
- **Connectivity:** cellular, tissues, columns, cortical areas, tracts, systems: physiological correlation, EM data, labeling, DTI…*datasets on a range of scales, different computational requirements*
- **Function:** Endocrine/ exocrine. Perfusion. Neural computation(…sensory, motor; behavior, perception, psychophysics). Learning and memory, social evolution. End-state characterization
- **Supporting systems:** metabolism, efficient function, system protection, self repair… *models for engineered systems*

Whole Brain Modeling Levels of Detail





Structural

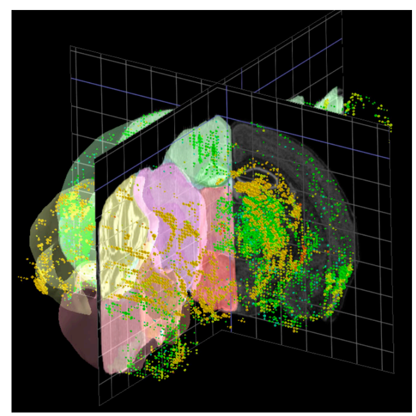
- Individual neuron morphologies, channels, synapses, spines
- Tissue, layers, columns, areas, nuclei, systems,
- Local circuits, long-range small-world connectivity

Functional

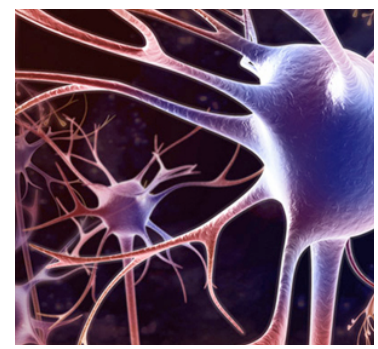
- Single ion channel
- Firing properties
- Synaptic responses
- Plasticity, neuromodulation
- Connectivity, micro- and macro-circuits
- Network dynamics
- Behavior, perception, psychophysics

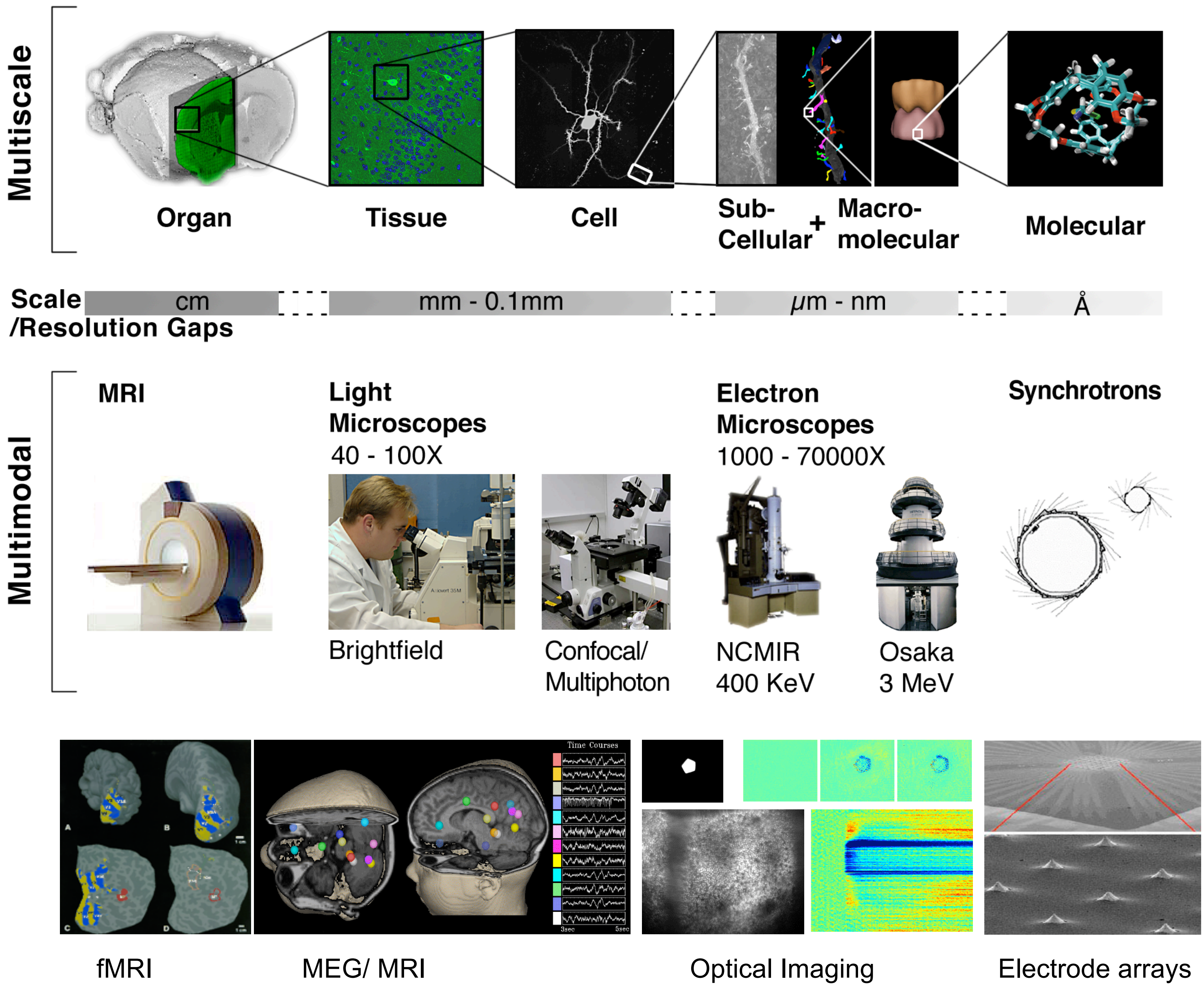
Stimulation

- Physiological, e.g. sensory organs
- Electrical, magnetic stimulation
- Pharmacological



Imaging data for mouse brain at EM resolution: 30 PetaVoxels




Multiscale
Organ
Tissue
Cell
Sub-Cellular + Macro-molecular
Molecular
Scale /Resolution Gaps
cm
mm - 0.1mm
μm - nm
Å
Multimodal
MRI
Light Microscopes
40 - 100X
Brightfield
Confocal/ Multiphoton
Electron Microscopes
1000 - 70000X
NCMIR 400 KeV
Osaka 3 MeV
Synchrotrons
Time Courses
fMRI
MEG/ MRI
Optical Imaging
Electrode arrays

Example: Cellular Level Brain Model – A Grand Challenge

Human Brain

1,000X

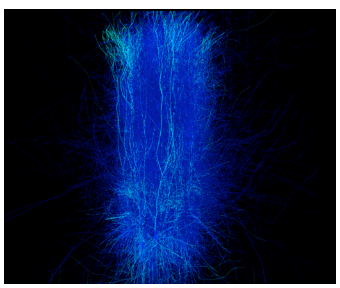
10^11 neurons
10^14-10^15 synapses
500 neurons/core

Rat Brain

20,000X

200,000,000 (10^8) neurons
10^11 synapses
500 neurons/core

Rat Neocortical Column

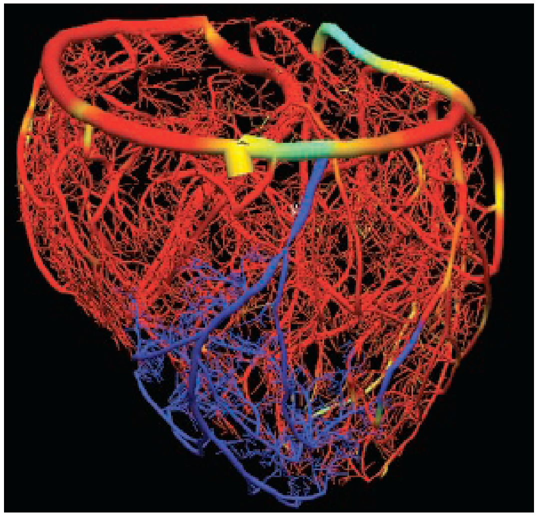


10,000 (10^4) neurons
30,000,000 (10^7) synapses

1 neuron/core

4 rack BG/L	PetaScale HPC	ExaScale HPC
~10TeraFlops ~TeraBytes	~PetaFlops ~100TeraBytes	~ExaFlops ~100PetaBytes

Multi-scale physiological models of organ systems



Objectives:

- Understand the functional *interactions* between (key components) of cells, organs and systems
- Quantify how these interactions change in disease states

Physiome Project:

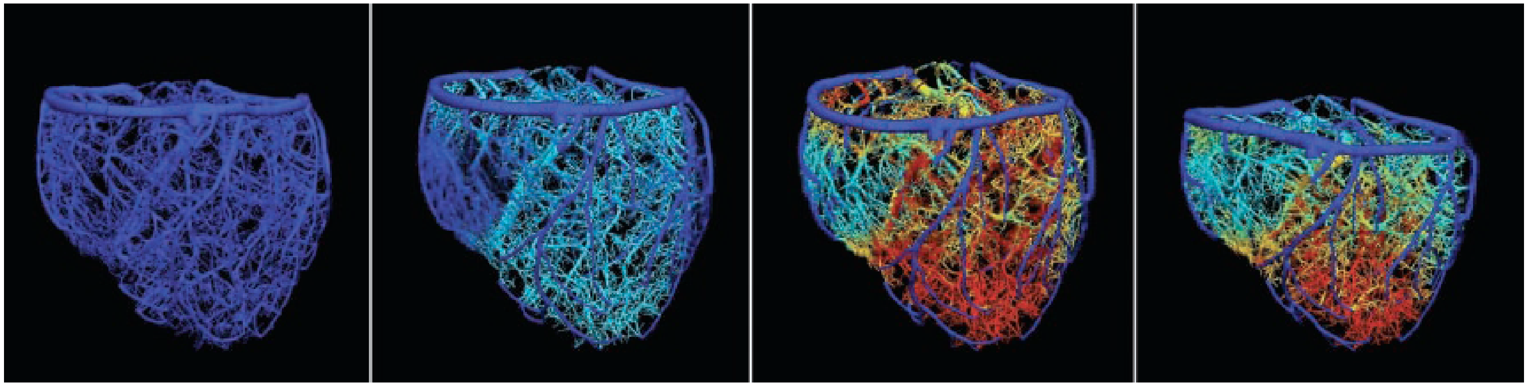
- Multi-scale models of 12 main organ systems: heart, lungs, liver, kidney, reproductive system…)
- Capture function: mechanical, biochemical, electrophysiological,…

Impact:

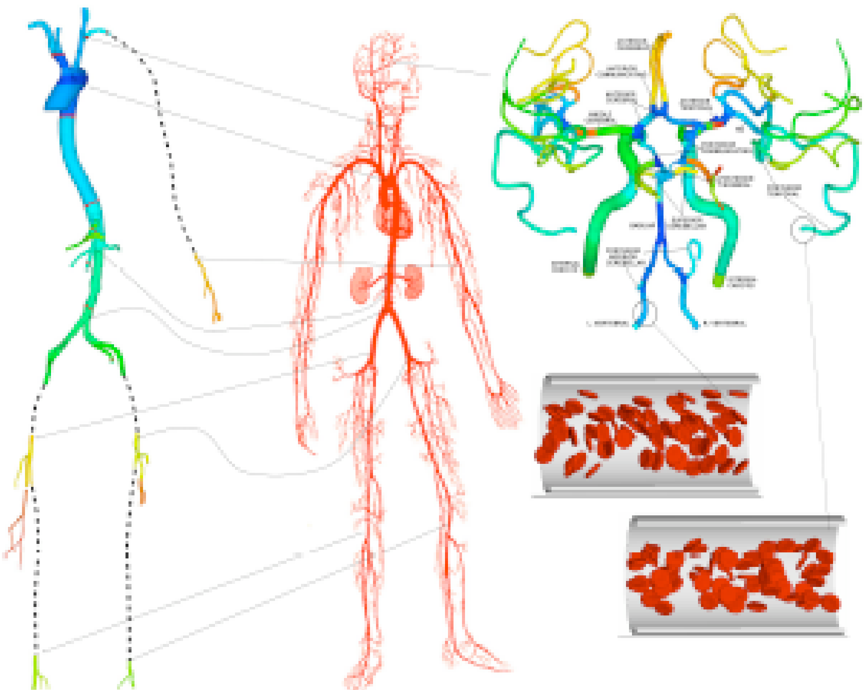
- Implications for Personalized Medicine: Improved intervention

Challenges

- Time scales from *msec* to *years*
- Spatial scales from *100 nm* to *10 cm*
- Multiphysics: mechanical/ biochemical/ electrical
- Geometric complexity/ 3D reconstruction
- Unknown/ uncertain properties
- Noisy/ gappy data/ multi-scale correlations
- Coupled atomistic/ continuum descriptions
- Heterogeneous data – Large, time-dependent outputs
  - (arterial tree: 1 Petabyte per cardiac cycle)
  - (brain: 100 Petabytes per cardiac cycle)



Computational Complexity



Human Body:

- 5 liters of blood travel 60,000 miles in one minute

Brain:

- 100s of large arteries &10 M arterioles on 1-10 Petaflops in 24 hours
- Capillary Bed: 1 B capillaries require > 10^{13} macro-particles at 10-100 Petaflops

Neurovascular Coupling:

- Possible at 100-1000 Petaflops

Directions

- Multi-rate time-stepping algorithms, Mesoscopic/ macroscopic discretization
- Coupled vs parameter-passing models, Rigorous low-dimensional models
- Stochastic sensitivity analysis, Multiscale property estimation (Monte Carlo)
- Integrated computational framework

Health risks of occupational/environmental exposure

e.g. low dose radiation

Challenges

Cancer frequency

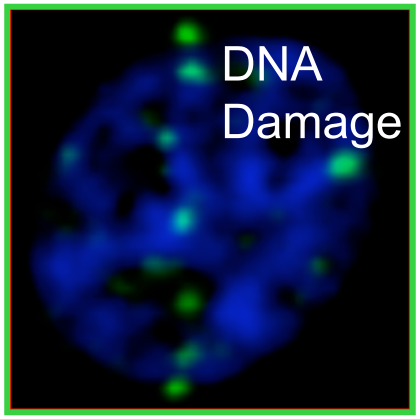
- in different populations (environment),
- in different people (genetics),
- in different tissues (physiology)

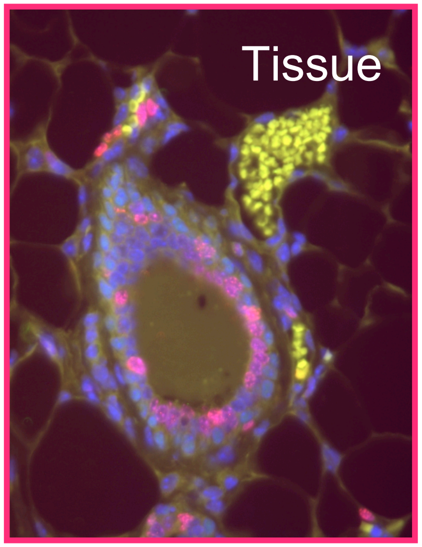
Complex exposure scenarios from discrete damage by byproducts of energy production (e.g. radiation, chemicals, nanoparticles)

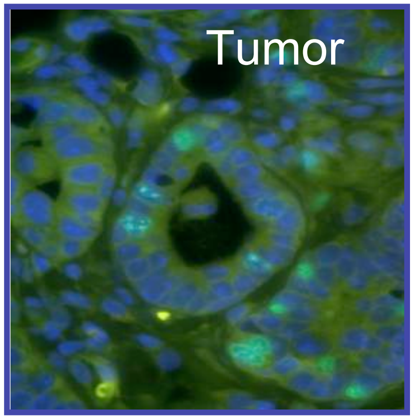
Complexity introduced by stochastic/rare events evolving and affecting cell interactions in tissue

Implications

Predicting risk, guiding protection and prevention, in different populations after different exposures







Directions

- Detection of rare events using various imaging modalities
- Discriminate between effects vs events that alter risk
- Definition of the response to discrete damage in terms of cell fate, phenotype, genomic stability over a time scale from minutes to decades
- Development of databases as a function of dose, dose rate, time and genetic background
- Linking data types from images to profiles to identify critical events/networks/hubs, e.g. systems genetics of susceptibility

Computational Challenges

- Models of normal tissue/organ function, (i.e. homeostasis) to study perturbation by exposure
- Long range modeling of stochastic, discrete, events evolving in complex heterogeneous microenvironments under different selective conditions
- Extrapolation from model organisms to humans