

Holistic Approach to Applying Systems Biology

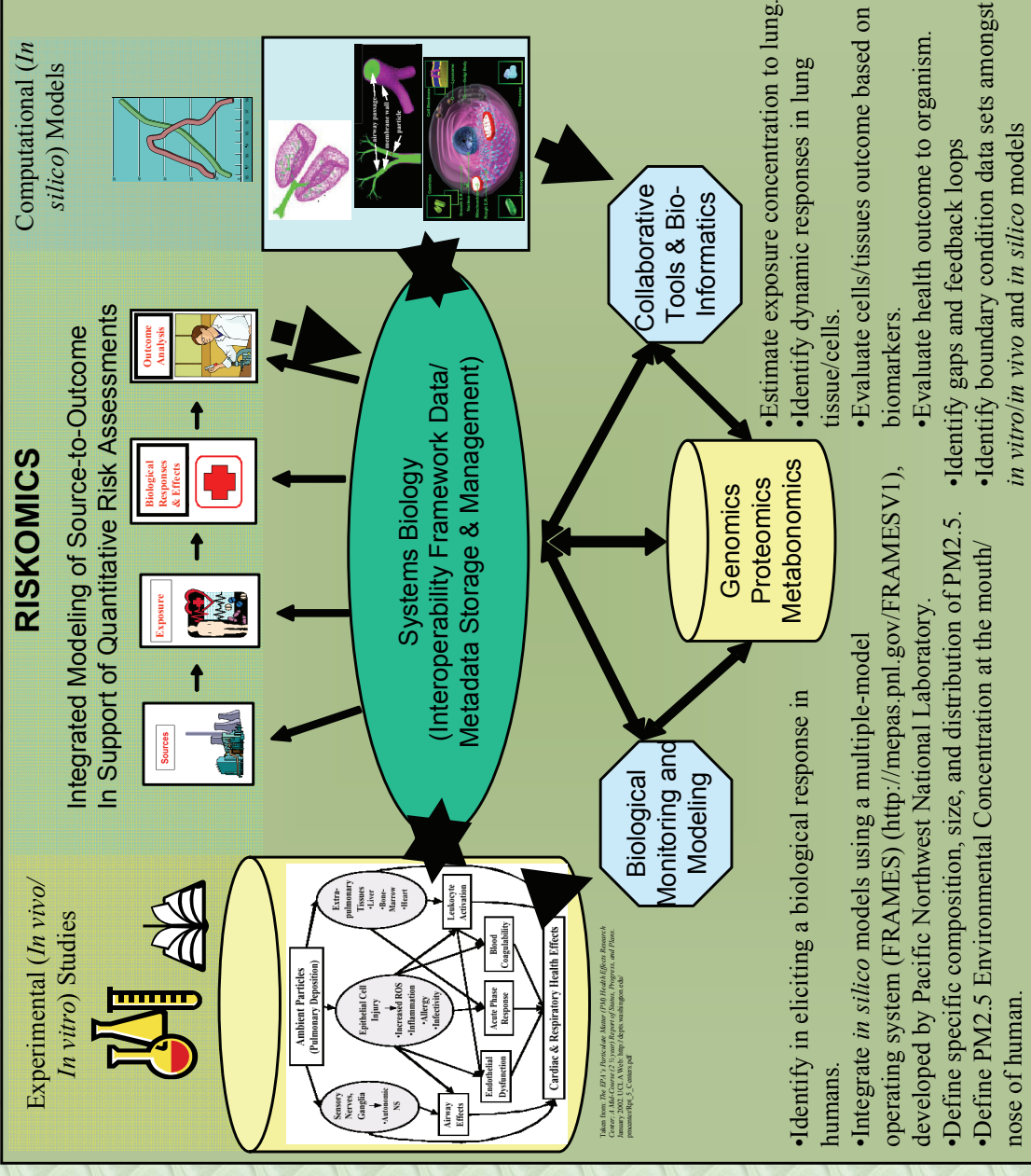
Integration of *In vivo*/*In vitro* and *In silico* Models/Studies for Quantitative Risk Assessment of Particulate

ABSTRACT

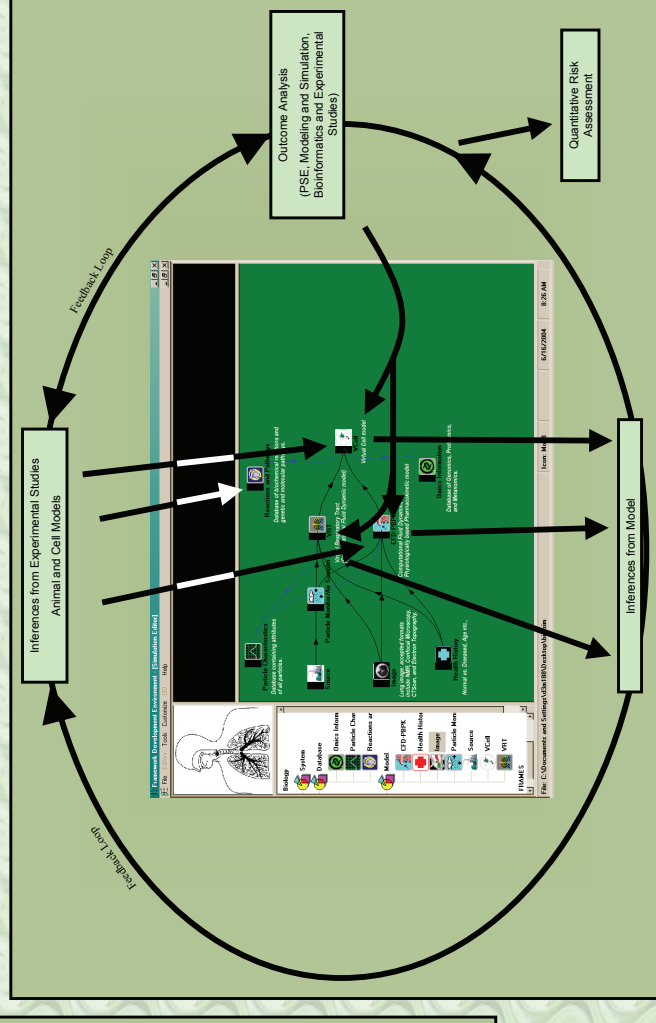
In vivo and *in vitro* studies have been used in combination to help solve many of the pieces of the puzzle related to an overall understanding of biological systems and processes. The advancement of computers and simulation techniques in recent years has led to useful *in silico* information that is becoming increasingly important to biological research. However, while research advances using *in silico* approaches that complement established experimental methods are a recent and fast-growing phenomenon, they are not always being implemented in a systematic fashion. At the same time, advances in experimental and computational approaches to biological research are extremely competitive, both vying to deliver targeted results without seeing the advantage of an integrated approach. Systems biology, as a new discipline, provides the appropriate framework for a holistic, integrated, and systematic approach to understanding biological systems and processes.

This presentation provides an example of the powerful, integrative approach by addressing the impact of 2.5 micron particulate matter (PM2.5) on the human respiratory track. PM is not a single compound, but rather a complex mixture that penetrates more readily into cells through tissue barriers, causes airway inflammation, and dissolves more rapidly in the lungs than larger particles, thus enhancing the bioavailability of solubilized agents. The integrated framework incorporates a detailed process-led path of research with feedbacks and flexible corrective strands to probe the *in vivo* functions of molecules identified by *in vitro* or *in silico* analyses. The process of designing and developing process and modeling flow diagrams and implementing them to integrate disparate biologically-based models provides modelers and experimentalists a common view of a biological issue. It also enables new discoveries through unique linkages between *in vivo*, *in vitro*, and *in silico* analysis techniques.

METHODOLOGY



APPROACH



RESULTS

The deposition and clearance of inhaled particles in different regions of respiratory tract depend on particle characteristics and respiration (e.g. mouth breathing versus nose breathing). It is important to relate specific particle size fractions to health effects. Thus, by linking the particle monitoring system with the VRT model, we can create a database of particle-specific information, consisting of its characteristics, patterns of its flow, deposition, and clearance in various regions of the respiratory tract for various species and eventually the biological response elicited.

The VRT model helps in understanding the impact of pollutants on the respiratory systems from structural alterations of airways, if any, morphology and physiology state of lung, particle-specific airflow and deposition pattern, information on the location of the lesion in a specific part of the respiratory tract, species differences in structure and cellular organization of respiratory tract, particle specific airflow, and deposition patterns.

Animal models play a major role in the elucidation of mechanisms and the development of therapeutic interventions for a variety of respiratory diseases. However, certain parameters like measurement of airflow and uptake are experimentally difficult (due to the small size and complex shapes of nasal airways); *in silico* Computation Fluid Dynamic (CFD) models play a key role in predicting uptake patterns quantitatively in three-dimensional reconstructions of the rat, rhesus monkey, and human nasal passages.

The geometry-based modeling capability enables us to capture the time-dependent, multi-scale, and multi-physics nature inherent in complex biological systems. Taking advantage of simulation capabilities provided by these hardware and software tools will aid biologists in understanding what might be occurring in experiments or better yet help expose new fundamental knowledge about the biology. This calls for co-existence of *in silico* and *in vivo*/*in vitro* models/studies in an integrated framework for deriving maximum benefit in terms of predictability, reliability, and managing resources efficiently for early detections.

There are several challenges when tackling the integration of biological systems and when providing them as a complement to experimental processes. The complex nature of biological systems requires complex computational models to simulate them. Integration of the various biological models is a challenge when crossing organizations and domains. In addition, the detailed process descriptions and verifiability of modeling results are critical for experimental processes to use them for the basis for insights and guidance for additional experiments.

This integrated approach helps lead to new insights, creates opportunities for innovative therapeutic interventions, and significantly improves human health risk assessments.