ABSTRACT
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COMPUTATIONAL TOOLS FOR THE SOURCE-TO-OUTCOME PARADIGM

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Advances in affordable computing processing power; in software for the management and analysis of massive, distributed, multiscale and multidimensional datasets; in fast algorithms for numerical simulation and uncertainty analysis; etc., combined with the development and availability of new databases of environmental, demographic, physicochemical, biological, and other data, are forcing a major "paradigm shift" on the approaches for analyzing and quantifying the complex interactions of humans and their environment. Assessing the health risks associated with environmental factors requires to understand and quantify, in a mechanistic way, the complete sequence of events and processes involved in the "environmental health sequence" from "source" (e.g. release or the formation of a stressor, such as a chemical contaminant, in an environmental medium) to "dose" and then "outcome" (e.g. environmentally caused disease).

In the past, assessing the human impact on the environment, and the subsequent impact of environmental change on human well-being, was typically performed on a "stressor by stressor" basis, separately for each exposure route. In recent years a major change has been taking place, through the development of "person-oriented" (i.e. anthropocentric) approaches and models, that aim to account for total ("cumulative" and "aggregate") exposures of individuals and populations to co-occurring stressors (i.e. mixtures of chemical, biological and radiological agents, present in environment and "microenvironmental" media, i.e. in indoor and outdoor air, drinking and bath/shower water, food and beverages, dust, cosmetics, etc.). These new approaches focus on individuals, real or "virtual", with well defined physiological, socioeconomic, behavioral, etc. attributes, and take into account how the detailed activities of these individuals in space and time affect (a) their "personal microenvironments," and their corresponding exposures to stressors, and (b) the physiological and biochemical processes determining biologically relevant dose and eventually biological effect (e.g. uptake rates; metabolic rates and pathways; toxicodynamics).

This presentation overviews ongoing research efforts on the development, evaluation and application of an integrated modeling and database framework for probabilistic analyses of the complete source-to-outcome sequence. This framework consists of two complementary software "sets of model and data components," operating on Linux clusters: the Modeling ENvironment for TOtal Risk studies (MENTOR), that addresses the "source-to-dose" steps, and the DOse-Response Information ANalysis system (DORIAN), for the biological "dose-to-effect" steps.

Various problem-specific implementations of this framework, primarily with the MENTOR set, have been developed and applied to a wide range of environmental issues in the USA, including: regional/ urban/local scale inhalation exposures to complex mixtures of co-occurring ozone, particulate matter, and air toxics; contaminant releases from forest and urban fires; groundwater contamination; multimedia and multipathway exposures to mixtures of metals/metalloids and their compounds, to pesticides, to organic solvents, to water chlorination by-products, etc. Special focus has been on novel methods for systematic simplification of complex models and for uncertainty analysis and reduction. These applications demonstrate the feasibility and the potential of using holistic, "person-oriented," approaches to improve the quantitative understanding of complex environmental health issues, that typically involve genetically heterogeneous populations experiencing simultaneous exposures to multiple, often interacting, environmental stressors.