

A Unified Multiscale Field/Network/Agent Based Modeling Framework for Human and Ecological Health Risk Analysis

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Abstract - A conceptual framework is presented for multi-scale field/network/agent-based modeling to support human and ecological health risk assessments. This framework is based on the representation of environmental dynamics in terms of interacting networks, agents that move across different networks, fields representing spatiotemporal distributions of physical properties, rules governing constraints and interactions, and actors that make decisions affecting the state of the system. Different deterministic and stochastic modeling case studies focusing on environmental exposures and associated risks are provided as examples, utilizing the bi-directional mapping between discrete, agent based approaches and continuous, equation based approaches. These examples include problems describing human health risk assessment, ecological risk assessment, and environmentally caused disease.

I. INTRODUCTION

Advances in computing processing power and in availability of environmental and biological data enable the use of large scale network/agent simulation techniques for studying the impact of environmental toxicants on human and ecological health. Furthermore, there is a need to assess human and ecological health risks in a preemptive manner in order to address and manage the impact of the introduction of new chemicals and manufacturing techniques, of a changing environment, and of rapidly changing landuse/landcover, evaluating alternative environmental regulatory options for mitigating the risks. Several human and ecological health risk problems have been studied in isolation, often focusing on a single chemical, single medium and pathway of exposure, and even a single toxic end-point. However, the state of the science is evolving towards assessing health risks to populations from exposures to multiple chemicals through various routes and pathways. In fact, various simulation platforms are becoming available for studying different aspects of human health risks. Examples of such platforms include the Modeling ENvironment for TOrtal Risk studies (MENTOR; [1, 2]), DOse Response Information ANalysis system (DORIAN;

[3]), Multimedia, Multipathway, and Multireceptor Risk Assessment system (3MRA; [4]), etc. Additionally, in the context of prognostic modeling of impacts of future environmental conditions (e.g., due to climate change, reductions of toxicant emissions, altered land use, etc.) the exposure-to-outcome system is sensitive to the decisions to be made at multiple scales: personal scale (e.g. developmental and aging factors, changes in human activities and consumption patterns); neighborhood scale (e.g. altered local patterns and roadway emissions, changes in zoning restrictions and landuse), regional scale (e.g. use of cleaner fuels), and global scale (e.g. reduction of greenhouse gas emissions). A conceptual framework is presented for supporting human and ecological health risk assessments; this framework is based on constructs of networks, fields, agents, and actors, and aims to provide a unified toolset for better prioritizing health risks and for improved targeting of mitigation efforts.

At any given time, human health state reflects the dynamics of coupled (signaling, regulatory, and metabolic) bionetworks that span multiple scales of time and "biological space." Understanding of human health risks can benefit from the study of hierarchical structures, interactions, and functional states of these networks, as they are perturbed by behavioral and environmental influences: the latter include the presence of various contaminants (xenobiotics). Developmental and aging processes, as well as the past history of the network state, play critical roles in overall system dynamics. Several efforts have been presented in the literature aiming to achieve network-based representations of human health systems [5] and hybrid/ecological systems [6, 7]; however, these have been primarily contaminant- or medium-specific. An integrative approach is presented here for studying human and ecological health risks, that employs a wide range of complementary modeling techniques.

The present approach considers inter- and intra-cellular networks (regulatory, signaling and metabolic networks), physiological networks, ecological (e.g. foodweb) networks, population networks, networks of microenvironments in which human activities take place, etc. These networks interact with each other and with spatiotemporal fields of multiple environmental and demographic attributes (e.g., concentrations of toxicants and population densities). In the context of both human and ecological health risk assessment, receptors of concern can be studied as agents that navigate through multiple networks, linked with various

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fields of contaminants. Additionally, in the context of prognostic modeling of impacts of future environmental conditions (e.g., due to climate change, reductions of toxicant emissions, altered land use, etc.) these networks and agents are affected by ensembles of alternative decisions made by actors within the system.

II. TERMINOLOGY

The major constructs in the unified framework for studying human and ecological health effects include (a) networks, (b) spatiotemporal fields (either random or deterministic), (c) agents that are affected by and affect other components of the system, and (d) actors that make decisions regarding the state and rules of the system. These constructs exist across multiple hierarchical levels and scales, and clearly they interact at various levels. For example, a coarser-level component can provide boundary conditions or forcing functions to a finer-scale component, while aggregates of finer-scale components can provide parameter values or distributions of parameter values to a coarser-scale component.

At each hierarchical level, each of the generalized networks under consideration is defined through network nodes, network edges or links (relationships, interactions), and network function (states, dynamics). The nodes can be defined as static (e.g. tissues within an organism, microenvironments, etc.) or dynamic (e.g. humans moving from one microenvironment to another, in which case they can also be represented as agents). Each node can itself be a network, an agent, or an actor, or a combination of them.

Interactions among the networks and processes governing the states of the networks are defined in relation to spatiotemporal "fields" (random or deterministic) of environmental, biological, demographic, etc., properties. The constraints on the types of interactions (possible chemical reactions, transport of contaminants across different media, probabilities associated with migration of agents from one network node to another, etc.) constitute the rules governing the evolution of the networks. Major hierarchies relevant to human and ecological health risk assessment are described here:

- *Intra-cellular level networks* (network nodes are biomolecules, biocomplexes, organelles), that include intra-cellular signaling networks, genetic regulatory networks, and metabolic networks.
- *Intra-organism level networks* (network nodes are cells, cellular assemblies, tissues, organs, physiological systems), that include inter-cellular signaling networks and physiological networks.
- *Environmental networks* (network nodes are geographical regions, microenvironments, etc.), that include networks of different contaminant sources, of inter-connected media, and of person-specific or population-specific microenvironments where exposures occur.

- *Ecological level networks* (network nodes are interacting species and biomes) that include food webs.
- *Intra-population level networks* (network nodes are individuals within a human population, selected demographic groups, etc.), that include networks of social and economic interactions.

In the context of human health risk assessment, the agents involve humans that move from one microenvironment to another, coming into contact with different environmental exposures. Human activities continuously modify the environment, and the changed in the environment can affect human activities. For example, in the realm of personal exposures, human activities can increase the levels of a contaminant in a microenvironment (e.g. smoking, cooking, spray painting, etc.), while the increased concentrations can affect the activities of the humans (e.g. through movement to another microenvironment). At larger time scales, population activities can contribute to climate change, while climate change can in turn affect numerous attributes of these populations.

III. DESCRIPTIONS OF STATES AND INTERACTIONS OF NETWORKS

Network dynamics coupled with the properties/dynamics of environmental fields can be described by various combinations of descriptive (phenomenological) and predictive (mechanistic) models, depending on the available data and scientific knowledge. When the number of constituents in a network is quite large, it may be more appropriate to represent the states of the system in terms of probability distributions of key parameters.

A. Descriptions of agent-movement

Movement of agents within a system is typically modeled as a stochastic process, using constrained random walk models with associated probabilities of transition from one network node to another (e.g. movements of animal species in an ecological network) [8]. Even though longer-range travel of humans can be described by multi-parameter random walk models, these movements (e.g. across microenvironments) are more structured and show regularity [9]. In the case of human health risk modeling, these motions can be represented through a set of commuting probabilities or through random realizations from sets of discrete, scripted activity pattern records [2, 10].

B. Boundary conditions of fields and interactions across different networks

Critical variables in environmental health risk assessment include concentrations of contaminants in a specific region (e.g. in a microenvironment, in a tissue, etc.), which are scale dependent, and distributions of other factors affecting the system (e.g. geographic distributions of occurrences of specific genetic polymorphisms within a region of interest). However, networks of different scales, and nodes within a network, may experience vastly different fields. Simulation

of these fields requires process-based models with inter-network boundaries defined via differential gradients.

IV. MATHEMATICAL APPROACHES AND DATA NEEDS

The major mathematical complexity associated with multiscale system modeling is the consistent linking of different scales for simulating time-varying states of network components, agents, and actors [11]. Additionally, significant uncertainties and “noise” exist within these systems. However, the level of complexity required to adequately represent a system is primarily dependent on the problem being studied and on the decision metrics of importance. The following techniques allow the simplification of a complex system consisting of networks, agents, and fields.

A. Lumping of networks into a single node or module

This is a commonly used approach in exposure-dose modeling. At the intra-individual scale, sets of heterogeneous cells, tissues, and organs are represented in terms of “rapidly perfused” or “slowly perfused” compartments. At a microenvironmental scale, a well-mixed microenvironment may be assumed for assessing exposures. At the metabolic level, a large, dynamic system of metabolic reactions can be simplified through the use of pseudo steady-state assumptions [12], and can sometimes be expressed in terms of macroscopic reactions relating to extra-network parameters [13]. Techniques such as perturbation analysis allow the identification of slow and fast processes within the network [14]. *A priori* identification of these processes significantly reduces the data requirements associated with identification of parameters describing fast processes. The identification of functional modules facilitates lumping of different networks [15]. Modules essentially consist of nodes that are inter-linked but without significant links to external nodes, and affect a specific state variable of interest. The original system can then be described in terms of a network of modules.

B. Representing network heterogeneity via uncertainty distributions

This approach is based on representing heterogeneity in terms of variables that are “unknown” but random. The aggregate properties of random distributions present a global scale picture while providing finer-scale detail through tails of the distribution (e.g. identification of susceptible sub-populations, high-end exposures/doses, overall probability of disease occurrence, etc.). For example, the heterogeneity in housing structures, population employment characteristics, etc., in a geographic region of interest can be represented through probability distributions describing links to outdoor environment (air exchanges with outdoors, penetration factors for different environmental toxicants, etc.). The corresponding inter- and intra-individual variability in physiological parameters for populations is

described in terms of probability distributions of inhalation rates, metabolic rate constants, etc.

C. Collapsing a network by reducing the number of possible states and interactions

This approach allows for substantial simplification of interactions among different networks. The most common technique is to employ a one-way nesting of network interactions (i.e. the properties of a coarser-scale network are assumed to be unaffected by the properties of a finer-scale network). However, assumptions that lead to neglecting the influence of finer-scale components on coarser-scale properties need to be evaluated on a case-by-case basis. Examples include neglecting the impact of indoor sources on immediate outdoor concentrations, neglecting the impact of exhaled contaminants on personal air concentrations, and neglecting the impact of toxicant fraction bound to ligands in a tissue when calculating tissue-level concentrations of the chemical. A useful technique for further collapsing the network based on reduction in the number of possible states is via qualitative simulations [16], which can overcome the computational demands associated with combinatorial explosion in the number of possible states and the limitations that arise from sparse data.

A unified multiscale modeling platform requires tools for physics-based modeling (lumped- and distributed-parameter systems represented by ordinary and partial differential equations), for object-oriented modeling of agents and actors, and for event-driven simulations. Almost all modern programming environments provide such tools (e.g. Matlab, Java, R, etc.), with some environments providing a hierarchy of toolboxes that are specific to different scales (e.g. the Systems Biology and Bioinformatics toolboxes in Matlab). These tools must be also complemented by modules for diagnostic analysis, such as (a) model-data fusion through Bayesian parameter estimation and numerical inversion [17], and (b) systematic simplification of models through perturbation-analysis [14] or model-structure independent methods such as the High Dimensional Model Representation [18].

V. EXAMPLE APPLICATIONS

A. Modeling Human Health Risks from Exposures to Chemical and Biological Contaminants

This application area involves the modeling of health risks from exposures to chemical, physical, and biological environmental stressors in a network-field-agent-actor framework. In this case, the network nodes are geographical entities with properties such as population density, housing characteristics, etc. The environmental fields include contaminants (e.g. number concentrations of a biological stressor, of fine particulates, or molar concentrations of a chemical contaminant). The next coarser-level network consists of various, individual-specific microenvironments, with properties such as air exchanges with other

microenvironments. Further, finer scale networks include the intra-body physiological network. For the purposes of the risk assessment, the sub-organ level networks are represented in terms of lumped systems with uniform concentrations.

The agents in this system include humans (“virtual individuals”) that stay in, and move through different micro-environments [3]. Inter-individual and intra-individual variability associated with physiological factors is lumped into a set of variables that are assumed to be fixed for a given virtual individual, but is assumed to vary across the population. Simulations are conducted using a large set of virtual individuals and realistic environmental fields estimated via transport-transformation models.

B. Ecological Risks from Chemical Contaminants

The study of ecological health involves modeling the movement of contaminants through environmental media and the biological organisms that constitute the ecosystem, coupled with the dynamics of food webs. These networks may then link with modules for assessing human health via different human exposure pathways. Examples include the accumulation of pesticides within the components of food webs ecosystems.

C. Modeling Environmentally Caused Disease

Approximately one quarter of global disease burden and more than one-third of the burden among children has been attributed to modifiable environmental factors, such as outdoor air pollution, unsanitary water, etc. [19]. A unified analysis framework can provide insight into specific aspects of this problem through effective identification of disease mechanisms [20]. An example is the initiation of disease through the formation of reactive oxygen species (ROS) as by-products of the metabolism of environmental toxicants; modeling this process helps linking outcomes to exposures. Simplifications that may be employed to accomplish this task at the individual and population level include the use of Michaelis Menten kinetics to “lump” multiscale biochemical processes, the use of lumped representations of organs and tissues, and the use of statistical distributions to characterize inter-individual variability within populations.

VI. DISCUSSION

A unified representation of multiple factors affecting human and ecological health can facilitate informed risk assessments with focus either on individuals, the general population, or susceptible sub-populations, etc. Diagnostic tools for rational simplification of complex networks allow systematic comparison of different modeling representations and identification of the most appropriate level of detail for a specific health risk assessment problem. The examples presented here demonstrate the feasibility of addressing multiscale and multi-objective health risk assessments in a unified manner, while staying within the bounds imposed by available computational and data resources.

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