Progress within the group can be measured in part by the publications produced. The citations of those publications are provided below along with brief descriptions of the work.

Professor Hunt has been invited to organize a short symposium at the 2009 meeting of the American Association of Pharmaceutical scientists, November 8–12, in Los Angeles, titled “The Modeling and Simulation Frontier: Multi-level, Multi-scale, Multi-attribute, Adaptable, and Extensible, Discrete Event Models.” Levent Yilmaz, MMSN member, is one of the four invited speakers.

Applications for two grants were submitted in April 2009, one proposing leveraging the ISL work described in Park et al. (below), and the other leveraging the epithelial morphogenesis work described below. Levent Yilmaz is a coinvestigator on the latter.

**Publications: Journals 2008–June 2009**


We developed and used an agent-based model of cultured Madin-Darby canine kidney (MDCK) epithelial cells specified the analogue's operating principles so that simulated and observed behaviors matched. A new experimentation framework enabled tracking relative axiom use and roles during simulated cystogenesis along with establishment of the consequences of their disruption. We documented the causal chains of events, and their relative roles, responsible for simulated cystogenesis. The results stand as an early hypothesis-a theory-of how individual MDCK cell actions give rise to consistently roundish, cystic organoids.


Using game theory and reinforcement learning, we created and analyzed generalized agent-based models of hepatic toxin elimination processes to explore plausible causes of hepatic functional zonation.


We developed and used an agent-based model of cultured alveolar type II (AT II) cells and early simulation results that provide better mechanistic insight into generative principles that underpin alveolar morphogenesis in 3D cell culture. The findings enforce the idea that complex alveolar morphogenetic phenomena are a consequence of adherence to a small set of epigenetic principles.


We developed and used an agent-based model of cultured alveolar type II (AT II) cells to answer the following questions. When and how does an AT cell choose to switch from one activity to another? Why does it choose one action rather than another? We obtained plausible answers using a rigorous, multi-attribute modeling and simulation approach. We discovered a set of cell-level operating principles that enabled in silico cells to self-organize and generate systemic cystogenesis phenomena.
that are quantitatively indistinguishable from those observed in vitro. We suggest that the in silico operating principles presented may have a biological counterpart and that a semiquantitative mapping exists between in silico causal events and in vitro causal events.


We discovered in silico axioms that are plausible representations of the operating principles realized during characteristic growth of EMT6/Ro mouse mammary tumor spheroids in culture. We created an analogue made up of quasi-autonomous software agents and an abstract environment in which they could operate. In sequence, we used a list of targeted attributes to falsify and revise these axioms, until the analogue achieved prespecified similarities to referent data. We posit that the validated analogue's operating principles are reasonable representations of those utilized by EMT6/Ro cells during tumor spheroid development.


We sought and discovered a single set of mechanisms that could provide a quantitative explanation of three pairs of published time series data: perfusate concentration of digoxin and its metabolite in perfusates of isolated perfused rat livers 1) in the absence of any predose and with a predose of either 2) an uptake inhibitor or 3) an efflux inhibitor. Validated, quasi-autonomous components formed mechanistically realistic analogues of livers undergoing perfusion (Recirculating In Silico Livers: RISLs). Each RISL was a hypothesis about plausible mechanisms responsible for the referent time series data. Simulations tested each hypothesis. The mechanisms simulated unanticipated loss of hepatic viability during the original wet-lab experiments: erosion of hepatic accessibility and of enzyme and transporter activities.


We present normal and “diseased” versions of an agent-oriented In Silico Liver, and validate their mechanisms against disposition data from perfused normal and diseased rat livers. Dynamic tracing features enabled spatiotemporal tracing of differences in dispositional events for diltiazem and sucrose across five levels, including interactions with representations of lobular microarchitectural features, cells, and intracellular factors that sequester and metabolize. Differences in attributes map to measures of histopathology. The approach and technology represent an important step toward unraveling the complex changes from normal to disease states and their influences on drug disposition.


Simulation experiments falsified the hypothesis that a uniform distribution of a hypothetical drug through an In Silico Liver will produce a uniform level of enzyme induction. Comparable wet-lab enzyme induction experiments are infeasible. Simulated induction is intended to have a hepatic counterpart. We discuss methodological considerations regarding this type of model and its referents.


The differences between traditional, inductive biomedical models and what we refer to as synthetic analogues (agent-based, agent oriented, and agent-directed) are discussed in the context of future directions for mechanism focused biomedical M&S.


We present an In Silico Intestinal Device (ISID) for exploration of the mechanistic details of absorption for compounds that are passively absorbed but are also dual substrates of metabolic and
transport enzymes (represented by different, separately validated autonomous objects) that have

different location and relative values within the analogue. The Devise represented intestinal features

at different scales and levels of detail. Different proximal-to-distal mixes of mechanisms had

substantial effects on measures of simulated absorption and metabolism. The approach represents an

important advance in experimental methods for unraveling the mechanistic details of intestinal drug

absorption and in anticipating the absorption consequences of drug interactions.

New Simulation Methods to Facilitate Achieving a Mechanistic Understanding of Basic


An agent-based simulation tool to aid the study of basic pharmacology principles was presented. We

suggest that simulations and their representation of laboratory experiments in the classroom can

become a key component in student achievement and learning scientific inquiry. We present

validation results and a classroom example demonstrating how this tool can be seamlessly integrated

within the traditional pharmacology learning experience.

Predictions of Hepatic Disposition Properties Using a Mechanistically Realistic, Physiologically

Based Model. L. Yan, S. Sheihk-Bahaei, S. Park, G.E. Ropella, and C.A. Hunt. Drug Metab


Quantitative mappings were established between drug physicochemical properties and parameter

values of an In Silico Liver. Quantitative relationships were established between sets of drug

properties and corresponding In Silico Liver parameter values; those relationships were used to

predict actual hepatic disposition properties. All predicted disposition profiles were judged

reasonable (within a factor of two of referent profile data).

Modeling and Simulation of Hepatic Drug Disposition Using a Physiologically Based, Multi-


We validate a physiologically based, mechanicistic, In Silico Liver for studying the hepatic disposition

and metabolism of antipyrine, atenolol, labetalol, diltiazem, and sucrose administered alone or in

combination. The synthetic analogue enabled us to posit that static and dynamic ISL mechanistic
details, although abstract, map realistically to hepatic mechanistic details in physiologically based
pharmacokinetic simulations.


Agent-Based Modeling of Alveolar Type II Cyst Formation In Vitro. S.H.J. Kim, S. Sheikh-


Symposium (ADS'09), The Society for Modeling and Simulation International, San Diago, CA.

We developed and used an agent-based model of cultured alveolar type II (AT II) cells and early

simulation results that provide better mechanistic insight into generative principles that underpin

alveolar morphogenesis in 3D cell culture. The findings enforce the idea that complex alveolar

morphogenetic phenomena are a consequence of adherence to a small set of epigenetic principles.

Multi-Agent Based Modeling of Liver Detoxification. S. Sheikh-Bahaei, S.H.J. Kim, and C.A.

Hunt. Spring Simulation Multiconference 2009, Agent-Directed Simulation Symposium

(ADS'09), The Society for Modeling and Simulation International, San Diago, CA.

Using game theory and reinforcement learning, we created and analyzed generalized agent-based

models of hepatic toxin elimination processes to explore plausible causes of hepatic functional

zonation.

Focus on Discovering Mechanisms: A Relativistic, Agent-directed, Perfused Liver. T.N. Lam,


Simulation Symposium (ADS'09), The Society for Modeling and Simulation International, San

Diago, CA.

We designed, constructed and validated an analogue of a recirculating, isolated perfused liver used in

a study of drug interactions between digoxin, rifampicin and quinidine. We showed can evolve into
executable biological knowledge embodiments that provide concrete instances of knowledge and means to falsify mechanistic hypotheses.


We developed and experimented on an in silico analogue that mimics the fundamental cell-level operating principles and system-level phenotypes of in vitro MDCK tubulogenesis. The analogue was used to test hypotheses about mechanisms and in silico operating principles that may have in vitro counterparts.


In Silico Liver experiments were designed and conducted to answer this question. Will enzyme induction (EI) within different hepatic lobular zones, following initial exposure to a single xenobiotic, be homogeneous or heterogeneous? The results may have a hepatic counterpart.


We built, studied, and explored mechanistic explanations for complex, unexpected wet-lab phenomena. The methods provided improved insight into the referent system, while providing a straightforward, scientific means of testing the plausibility of mechanistic hypotheses.


Experiments were conducted using a multilevel, agent oriented, in silico analogue of an in vitro experimental system for studying leukocyte rolling, activation, and adhesion during inflammatory conditions. Results provided insights into the diffusion and clustering events of the LFA-1 integrin receptor on the leukocyte membrane during rolling and adhesion.


Use of an (agent-based and agent-directed) In Silico Liver is described in which drug-specific physicochemical properties are used to predict an In Silico Liver parameterization, which is then used to generate expected liver perfusion outflow profiles for those compounds.


A model morphing method is described in which models can be improved iteratively as part of a rational approach to translational research.