On top of the ciliated epithelial cells that line the airway, there's a layer of liquid that must be maintained to a very specific depth in order to achieve mucus clearance. **Nicolas Warren, PhD**, a graduate student in Tawhai's group in the ABI and co-supervised with **Edmund Crampin, DPhil**, from the ABI , developed and validated a model of such cells joined together with liquid moving through multiple cells. Tawhai's team then put the cell model into the whole organ model, distributing cells along airways and through the airway tree, and then directing the lung to breathe with different temperatures and humidity. They found that the epithelial cells alone couldn't transport enough moisture to maintain the depth of the surface liquid during normal breathing. "So there has to be some other significant source of moisture," Tawhai says. "And it's something we couldn't have seen without putting it into the real anatomical framework." Possibly submucosal glands or transport of fluid from the lung periphery provide the additional fluid needed, Tawhai says, but it's really not known. Still, now there's a model on which experimentalists can test various hypotheses. Tawhai's team is currently working on adapting the epithelial cell model to make it more specific to disorders such as cystic fibrosis.

The epithelial cell model is also the starting point for a new NIH grant led by Lin. It will integrate *in vitro* cell data and *in vivo* image data together with Lin's in-house computational fluid-structure-interaction technologies and the cell model to understand the interplay between organ, tissue, and cells. A predictive computational lung model across these scales will allow researchers to assess individuals' response to therapy over time. Ultimately, Lin says, "We will be able to use this information to better tailor a treatment plan for the individual at the most basic level."

THE MUSCULOSKELETAL PHYSIOME

Physiome efforts for neuromuscular modeling are ramping up. A relatively new and major effort is Europe's VPH Osteoporosis project (VPHOP), a collaboration among 19 European academic and industrial partners, led by **Marco Viceconti, PhD**, technical director of the Medical Technology Laboratory at the Istituto Ortopedico Rizzoli di Bologna in Italy. The project seeks to predict the risk of fracture in people with osteoporosis. As people age, their bones weaken and lose calcium, causing a condition known as osteoporosis. Meanwhile, they lose neuromuscular control, which can lead to falls. These changes happen at the cellular level in the bones and muscles and manifest as changes in morphology at the tissue level. "So in order to predict risk of fracture over time, you have to account for whole body, organ and tissue scales," Viceconti says. "That's what we're doing in VPHOP."

By September of this year, two years into the VPHOP project, Viceconti expects to run a very large probabilistic model that accounts directly or indirectly for all factors that act or contribute to the risk of fracture in one patient at any possible scale. The simulation should answer the question: "Of the dozens of possible parameters that can define the multi-scale phenomenon, which ones really are important and make a difference?" he says. "That answer will drive the most critical part of the project—not the modeling itself, but the ability to measure in patients the information we need with the accuracy we need."

The VPHOP is partnering closely with industry to develop the technologies for measuring this key patient information in a cost-

Standardizing the Physiome

Multi-scale quantitative models need to be validated and reproducible if they are to be useful for clinical workflows, says Hunter. The Physiome infrastructure developed by Hunter, Dr Poul Nielsen and their colleagues (and provided at www.cellml.org) makes that process more robust and transparent, he says. Researchers can confidently download an annotated model from www.cellml.org knowing that it's reproducible. The model can then be incorporated into larger scale workflows for use in a clinical setting.

"Having the means to incorporate the outputs of different groups through standards and interoperability is quite a worthwhile goal," Hunter says. "And an essential one if we're to get the modeling of biology into clinical processes."

Models held by the models.cellml.org model repository use CellML, a markup language for biophysical models of cells. A repository at the European Bioinformatics Institute (EBI) contains models marked up with SBML, a language for systems biology models. Hunter's group is also creating a new standard called FieldML for integrating spatial information. In recent years, Hunter says, the CellML and SBML communities have become more integrated. "SBML and CellML are now working together jointly to curate models and develop standards around metadata."

From funding agencies' point of view, "We don't want people to have to reinvent models," Peng says. But at this point, "The different formats are all co-existing. No one wants to stand up and say one is better than another."

It's also true that some multi-scale models require information that goes beyond what CellML or SBML can provide, McCulloch says. "It's not possible to describe everything in our cardiovascular model using that system." So McCulloch is building a database that includes metadata about his models that will be consistent with CellML and other model description formats but goes beyond them to include additional information.

Nic Smith agrees that standards are useful for sharing between different academic centers, but he says, an important step to embedding multi-scale models in clinical workflows is a demonstration that they add extra information that can be made available to physicians in a familiar format. "We are working on developing interfaces and putting them in a context where physicians are used to seeing them—in connection with imaging and clinical data accessed directly from the hospital's computer system."