**MODEL CREDIBILITY PLAN**

The models proposed herein include both explanatory and predictive types, each being both qualitative and quantitative in nature. The explanatory models will often be used to falsify hypotheses, reduce the number of possibilities for experimental testing, and categorize the parameter/mechanism spaces. The predictive models, which are attained through extensive computational analysis and detailed experimental tests of explanatory models, may be further evaluated along with the explanatory models through five metrics: 1) sensitivity analysis and uncertainty quantification; 2) comparison with existing and published experimental data for qualitative behavior by testing hypotheses and the overall qualitative spatial and temporal dynamics of wound healing; 3) direct comparison with the data from new experiments that are specifically designed to test particular aspects of the proposed model at an individual scale or emerging from the multiscale interactions; 4) external evaluations by experts in software engineering, multiscale modeling, and wound healing; and 5) working with IMAG project scientists in the appropriate groups of the MSM Consortium.

**Qualitative assessment**: We will first assess our models at each scale using a range of techniques based on characteristics of each subset of models. For the proposed computational methods on single cell RNA-seq data on cell plasticity and lineage evolution, we will first develop forward cell lineage models to generate simulated data to mimic the real RNA-seq data, and then use them to analyze accuracy of the proposed reverse-engineering methods. For the proposed cell lineage models, we will compare the new models by choosing parameters for a model reduction to existing models for which we have published work on. For spatial models, we will use “smaller” or simpler models to analyze their qualitative behavior, and compare them with the existing/published experimental data. We will also use the coarse grain models for comparison to examine the qualitative behavior of wound healing. Our past experience in dealing with models at individual scales will help us in this assessment. Overall model validation will be accomplished by comparing the model-predicted output based on optimized parameter sets to the experimental data obtained in the proposed study.

**Quantitative assessment**: We will perform *sensitivity analysis* and *uncertain quantification* to study the robustness and reliability of the models. First, for models that will be solved using numerical algorithms with known order of accuracy, we will systematically check them (e.g. those based on continuum PDE models). We will systematically vary the parameters, in a biologically reasonable range for the processes under study, to investigate the parameter sensitivity. The performance of new numerical algorithms will be subjected to benchmarking and validation against standard functions available, for which we have extensive experience (<http://cmcb.math.uci.edu/software.html>). We also have established record and experience in stochastic simulations. We will add stochastic fluctuations in our models at different scales, a topic of our focused modeling effort, to quantify variation of the outputs from the models. Most importantly, as discussed in each Aim, the proposed models will be tested directly or indirectly through our experiments.

**Third party test**:We will potentially work with three groups of external evaluators within different areas of expertise. First we will closely work with identified MSM Consortium members who are willing to perform simulations using our multiscale models for our proposed systems, such as the members from the groups in Model and Data Sharing and Multiscale Systems Biology. This will enable us to better fulfill model rules for the ABM and equations in SMBL required on IMAG. In addition, we will work with people from other working groups in Consortium to address various challenging elements of the models (e.g. mechanics, cell-macroscale). Second, we will work with independent evaluators who are experts in computer science or system engineering issues related to input/output structures, open source libraries, visualization, and interfaces with other codes or using different computer languages. Third, we will identify systems biologists, who are familiar with the general modeling technique (e.g. Dr. Philips Maini - a leading expert on multiscale modeling and mathematical biology), and experts in wound healing or skin biology (e.g Cheng-Ming Chuong from U. of Southern California – a leading expert on hair and skin biology) to evaluate the biological outcomes of the codes. In addition to running our codes on the proposed systems, we will run the codes under conditions not specified in the proposal to identify new areas of improvement in models, computational methods, and implementations.

**Timeline**: The model evaluation process will directly follow major milestones of the specific aims starting from Year 1. Quantitative assessment will be carried out immediately following development of model and algorithms starting Year 2. The interaction with the MSM Consortium on model credibility will start in Year 2 while the other external evaluations will start in Year 3. The overall evaluation of the models and their comparison with experiments will take place in Year 4 or 5.