

1. Project title: An integrative statistics-guided image-based multi-scale lung model  
PI Ching-Long Lin, The University of Iowa
2. The ultimate goal of the research is to achieve precision medicine via tailored treatments for asthma and COPD sub-populations (clusters). I have been developing a multi-scale (CT) imaging based cluster analysis (MICA) method based on asthma (Ref. #1) and COPD (Ref. #2) populations to bridge individual and population scales and explore the notion of cluster-guided computational fluid dynamics (CFD) analysis (Ref. #3) that generates model-derived variables to better understand structure-function relationships in the human lungs by diseased sub-populations. I further explore the effect of genetically-determined airway variants on COPD symptoms (Ref. #4).

References:

- 1) Choi S, Hoffman EA, Wenzel SE, Castro M, Fain SB, Jarjour NN, Schiebler ML, Chen K, **Lin CL**, for the National Heart, Lung and Blood Institute's Severe Asthma Research Program. Quantitative computed tomography imaging-based clustering differentiates asthmatic subgroups with distinctive clinical phenotypes. *J Allergy Clin Immunol*, 2017, 140(3):690-700. PMID:28143694 <https://www.ncbi.nlm.nih.gov/pubmed/28143694>
  - 2) Haghighi B, Choi S, Choi J, Hoffman EA, Comellas AP, Newell Jr. JD, Barr RG, Bleecker E, Cooper CB, Couper D, Han M, Hansel NN, Kanner RE, Kazerooni EA, Kleerup EAC, Martinez FJ, O'Neal W, Rennard RI, Woodruff PG, and **Lin CL**. Imaging-based clusters in current smokers of the COPD cohort associate with clinical characteristics: the SubPopulations and intermediate outcome measures in COPD study (SPIROMICS). *Respiratory Research*, in press, 2018
  - 3) **Lin C-L**, Choi S, Haghighi B, Choi J, Hoffman EA. Cluster-Guided Multiscale Lung Modeling via Machine Learning. In: Andreoni W, Yip S, editors. *Handbook of Materials Modeling: Applications: Current and Emerging Materials*. Cham: Springer International Publishing; 2018. p. 1-20. [https://link.springer.com/referenceworkentry/10.1007%2F978-3-319-50257-1\\_98-1](https://link.springer.com/referenceworkentry/10.1007%2F978-3-319-50257-1_98-1)
  - 4) Smith BM, Traboulsi H, Austin, JHM, Manichaikul A, Hoffman EA, Bleecker ER, Cardoso WV, Cooper C, Couper, D, Dashnaw SM, Guo J, Han MK, Hansel NN, Hughes EW, Jacobs DR Jr, Kanner R, Kaufman JD, Kleerup E, **Lin CL**, Liu K, Lo Cascio CM, Martinez FJ, Prince MR, Rennard S, Rich SS, Simon L, Sun Y, Watson KE, Woodruff PG, Baglolle CJ, Barr RG. Human airway branch variation and chronic obstructive pulmonary disease. *Proc Nat Acad Sci (USA)* 2018; epub Jan 16. pii: 201715564. DOI: 10.1073/pnas.1715564115 <https://www.ncbi.nlm.nih.gov/pubmed/29339516>
3. By following the CPMS Ten Simple Rules (TSR) format, we have:
    - Rule 1 – Define context clearly. Plan and develop the M&S activity with clear definition of the intended purpose or context accommodating end-users needs.  
  
Response 1 – We develop multi-scale imaging-based cluster analysis (MICA) to identify sub-populations with unique structural and functional characteristics in healthy, asthmatic and COPD populations to bridge individual and population scales, enabling improved tailored treatments of diseased lungs guided by cluster membership.
    - Rule 2 – Use appropriate data. Use data relevant to the M&S activity, which can ideally be traced back to the source.

Response 2 – We use computed tomography (CT) volumetric lung CT images and biomarkers acquired by NIH-funded multi-center trials, such as the Severe Asthma Research Program (SARP) and the SubPopulations and intermediate outcome measures in COPD study (SPIROMICS) funded by NHLBI.

Rule 3 – Evaluate within context. Evaluate the M&S activity through verification & validation, uncertainty quantification, and sensitivity analysis faithful to the context/purpose/scope of the M&S efforts, with clear and a-priori definition of evaluation metrics and including test cases.

Response 3 – We verify and validate our MICA via establishing the associations of imaging-based clusters with clinical biomarkers and dividing the existing data set into training and validation (testing) sets. We have been conducting CT/SPECT human subject studies for further validation.

Rule 4 – List limitations explicitly. Provide an explicit disclaimer on the limitations of the M&S to indicate under what conditions or applications the M&S may or may not be relied on.

Response 4 – For clinical application, longitudinal data are needed to examine cluster stability and transition for disease progression. The current model and analysis are based on cross-sectional data.

Rule 5 – Use version control. Implement a version control system to trace the time history of the M&S activities, including delineation of contributors' efforts.

Response 5 – We do it via peer-reviewed journal publications.

Rule 6 – Document adequately. Document all M&S activities, including simulation code, model markup, scope and intended use of M&S activities, users' and developers' guides.

Response 6 – Documentation is provided in supplementary materials in peer-reviewed journals.

Rule 7 – Disseminate broadly. Disseminate appropriate components of M&S activities, including simulation software, models, simulation scenarios and results.

Response 7 – Done.

Rule 8 – Get independent reviews. Have the M&S activity reviewed by independent third-party users and developers, essentially by any interested member of the community.

Response 8 – It is done via broad collaborations and journal publications.

Rule 9 – Test competing implementations. Use competition of multiple implementations to check the conclusions of different implementations of the M&S processes against each other.

Response 9 – This would depend on complexity of the codes. Some have been developed over a decade.

Rule 10 – Conform to standards. Adopt and promote generally applicable and discipline specific operating procedures, guidelines, and standards accepted as best practices.

Response 10 – This depends on the complexity of the code.

Additional details:

A. List of planned actions outlined in Model Credibility plan

Answer: We have been conducting longitudinal CT/SPECT human subject studies to validate the MICA and cluster-guided approach.

B. Brief description of information gained by each credibility action

Answer: See the above responses.

C. Actions and activities classified within the CPMS TSR framework (item-by-item summary table).

If any of the TSR items are not being implemented/considered or additional items are being implemented, this information should also be explicitly stated

Answer: See the above responses.

D. Description of how the planned activities will lead to a credible model

Answer: See the above responses.

E. Progress to-date and plans for the next reporting cycle (6 months). What has been achieved since last reporting?

Answer: We have been analyzing more cross-sectional and longitudinal data, and continue to conduct CT/SPECT imaging human subject follow-up studies.

Data Management:

The imaging and clinical data used by this project are acquired by NIH-funded multi-center trials (MCT), including SARP and SPIROMICS. These MCTs have committees to oversee data request and journal publications, respectively. Thus, the management of raw data is standardized for all potential users.

Milestones:

Specific Aims 1-2: the statistical analysis and the image registration analysis. Milestones: perform cluster analysis on normal, asthma, and COPD using airway measurements, registration-derived and CFD-predicted data in Y1-5; develop GPU-based registration in Y1-2; perform registration analysis in Y1-5. (Done)

Specific Aims 3-4: the airway modeling, mesh generation, and CFD analysis. Milestones: improve airway tree modeling and meshing algorithms for diseased lungs; perform CFD analysis on selected subjects in sub-populations in Y1-2; perform CFD analysis on selected COPD subjects in Y3-5; continue to perform CFD analysis on subjects in sub-populations in Y1-5. (Done)

Specific Aim 5: DECT/SPECT human subject studies. Milestones: identify COPD subjects for longitudinal studies in Y2, submit an IRB application for human subject studies in Y2; conduct human studies in Y3-5; the team will interrogate experimental data along with image and CFD analyses in Y3-5. (Most done, imaging human subject studies are on-going).

4. Issues/concerns identified as critical or problematic to achieve the standard of credibility set by MSM Consortium.

Answer: There seems to have gaps between the standard developed and that of medical doctors for clinical applications.

5. What other factors, if any, contribute to credibility but cannot be reported within the TSR structure? In requesting this information, we seek to identify credibility activities/issues and appropriate ways to report them at upcoming IMAG/MSM meetings.

Answer: Involve MDs to bridge the gaps between modelers and MDs.