Dear Sir or Madam,

We enclose a manuscript titled “Toward standards for tomorrow’s whole-cell models” for consideration for publication in your special issue on Reproducibility in Biomedical Modeling in *IEEE Transactions on Biomedical Engineering*. Whole-cell modeling is a promising tool for learning new biology, engineering microorganisms, and tailoring medical therapy to individual patients. The manuscript describes the standard representation formats and software tools needed to reproduce whole-cell models and advance the field of whole-cell modeling. The manuscript is based on our experience encoding a recent whole-cell model of *Mycoplasma genitalium* into SBML at the 2015 Whole-Cell Modeling Summer School. summer school’s

We believe your special issue on Reproducibility in Biomedical Modeling would be an excellent forum for our manuscript because our manuscript describes the tools needed to reproducibly build whole-cell models. Furthermore, we believe that the reproducibility of whole-cell models is an important topic in computational systems biology which would be of great interest to your readers.

First, the manuscript describes the format and educational outcomes of the 2015 Whole-Cell Modeling Summer School. Second, the manuscript describes our efforts to encode a recent whole-cell model of *Mycoplasma genitalium* into SBML, to encode computational experiments into SED-ML, and to visualize the model using SBGN. The manuscript summarizes our progress, as well as the challenges we faced encoding the model into SBML and simulating the model using existing open-source simulators. Third, the manuscript describes the standards and software expansions which are needed to enable researchers to reproducibly build and quickly simulate whole-cell models.

In summary, we believe that whole-cell modeling is a promising methodology that could be accelerated by open standards and software tools. Furthermore, we believed that improved standards would enable researchers to build whole-cells more reproducibly which will help other scientists reuse and expand upon them. In our manuscript, we summarize the shortcomings of our existing standards and software tools, and describe how they must be expanded to support whole-cell modeling. Thank you for your time and consideration.

Sincerely,

Dagmar Waltemath, Junior Research Group Leader, University of Rostock, Germany



Jonathan Karr, Assistant Professor, Icahn School of Medicine at Mount Sinai, USA

Falk Schreiber, Professor, Monash University, Australia

on behalf of the participants of the 2015 Whole-Cell Modeling Summer School.