Introductory Remarks on Modeling in Biomedical Research
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Professor Jusko and I would like to start by thanking Stacey Tannenbaum and Dick Brundage for their vision for this meeting, which showcases the broad spectrum of applications of modeling and simulation in drug development. This meeting provides us with the opportunity to codify our knowledge, clarify our thinking and define new directions for modeling and simulation in drug development. These are, of course, also some of the same oft cited benefits for the application of modeling itself as we try to better understand the world around us.

The field of PK/PD has recognized these and other benefits of mathematical modeling almost from its formal inception over 50 years ago. This early adoption and use of modeling, which was on full display in the 1960' 70's and 80's, was certainly not embraced in other areas of biomedical research during that same time period. For example, modeling and the systems framework that underpins all good modeling was largely absent during that time period in immunology, virology, cancer biology, molecular biology and other areas of biomedical research (although there were some notable expectations in the neurosciences and endocrinology).

Over the last 20 years, with dramatic advances in analytical and other measurement techniques, PK/PD modeling has continued to develop with great advantage to the process of drug development.

Also during this more recent time period, the application of mathematical and computational modeling to some of the previously mentioned areas of biomedical research has flourished (in its scope and novelty, perhaps surpassing its use in PK/PD); and now modeling provides an important framework for understanding basic mechanism of action in many areas of biology.

Yet their remains a significant gap between modeling in service to the drug development enterprise and the cell and molecular level modeling that is now the hallmark of systems biology. The intent of this session is to focus our attention on how we may continue to bridge this divide.

While modeling and simulation can help link our understanding of drug action at the cellular and molecular level in a way that might actually help

the busy (stressed) drug development scientist, we must always remain vigilant in recognition of the well-known limitations of modeling including: the subjective nature of the modeling process; models represent isolated systems, whereas the systems being modeled operate as part of a whole; models as hypotheses are logical strongest when they fail, but psychologically most appealing when they succeed.

These and other cautions have been enumerated on numerous occasions – include 30 years ago by Gene Yates, a colleague at USC, upon the inauguration of a new journal in the AJP series. Gene also reminded us at the time about the "middle course" of the modeler in reference to one of Francis Bacons' aphorisms to the scientist in 1620 in his Novum Organum, which states:

> *-The men of experiment are like the ant; they collect and store*
> *-The reasoners resemble spiders, who make cobwebs out of their own substance*
> *-But the bee takes a middle course; it gathers its material from the flowers of the garden and of the field, but transforms and digests it by a power of its own.*

This wisdom continues to serve us well and provides the touch stone for the work to be presented in this session of the ACoP meeting on Mechanistic Modeling and Systems Biology.