CORNERSTONES TO SHAPE MODELING FOR THE 21ST CENTURY:
INTRODUCING THE AKA-GLUCOSE PROJECT

Ray Boston, Darko Stefanovski, Peter Moate, Oscar Linares, and Peter Greif*

INTRODUCTION

For some reason, the start of a new century, as though magically demarcating history, seems to confer the right to reflect on progress as we embrace a ‘new’ period or ‘new’ phase of endeavor. Accordingly, we begin this paper by reviewing what computer-based mathematical modeling in biology (CMMB) has brought us thus far, as we begin the 21st century (or could we say, ‘the third millennium’). We will decompose the stages of CMMB evolution in the last century into three generations, noting the hallmark accomplishments in each.

After considering historical developments in CMMB, we address two important questions which arise as we leave one epoch and begin another: what have we learned from our work effort in CMMB so far, and what are the areas which will have the highest returns per unit of effort in the new epoch? It is against this backdrop that we present the sections on ‘cornerstones’ that will shape modeling in the 21st century. We believe that the first cornerstone is the model development environment (which embraces modeling philosophy and software). This is exemplified by the modeling program ‘WinSAAM’ which has been significantly enhanced by the work of co-authors R.C. Boston and P. Greif. In the discussion of this cornerstone, we describe some of the features of WinSAAM and focus on a new tool called ‘the project manager’ which enables population analysis of kinetic models. As the second cornerstone, we chose the addition of database technology to modeling. This cornerstone is built on work by R.C. Boston, D. Stefanovski, E. Janczewski, M. Petrova and P.J. Moate (Biomathematics Unit, School of Veterinary Medicine, University of Pennsylvania). We focus on an entirely new approach to model dissemination, the AKA-Glucose project. We consider the third

* Ray Boston, Darko Stefanovski, and Peter Moate, Biomathematics Unit, School of Veterinary Medicine, University of Pennsylvania, Kennett Square, PA 19348. Oscar Linares, University of Michigan Geriatrics Clinic, Ann Arbor, MI 48105. Peter Greif, Laboratory of Computational and Experimental Biology, Division of Cancer Biology and Diagnosis, National Cancer Institute, Bethesda MD 20892.

cornerstone of modeling to be data exchange. Contributions by co-author R.C. Boston and A.E. Sumner (Diabetes Branch, NIDDK) are highlighted. We demonstrate how both project management and database technology in the CMMB setting can be conducive to data exchange. Finally, we believe that a fourth cornerstone of modeling for the 21st century is the establishment of a structured modeling community working together to promote and apply modeling methodology in the biomedical sciences. This effort has been spearheaded by co-author R.C. Boston and N. Canolty (Department of Foods and Nutrition, University of Georgia). We present the case for such a community and propose a plan for its implementation.

HISTORY OF CMMB: GENERATION 1

In its first generation, CMMB used scientific subroutines tightly linked into a batch-processing environment (program) to enable program users to perform a limited number of (pre-scheduled) processing steps to explore systems. The very limited power of computers available in this generation (conceivably spanning 1960 to 1975) meant that a rigid input, output, and processing structure was the best that could be provided. Indeed, when we recall that computers of this period were one thousandth the size, one thousandth the speed, and one thousand times the cost of today's computers (a $10^9$ deficiency), it is remarkable that anything was achieved at all. And yet remarkable were the feats of the CMMB pioneers of this generation. Necessity gave birth to modeling constructs and operational units, to accurate and extremely fast numerical integrators, and to robust and efficient data fitting procedures. Of course, the most important outgrowth of this era was the unequivocal emergence of a role for mathematical modeling in biology, specifically in nutrition, in clinical science, and in agriculture and the environment.

The tools and techniques developed and refined in this generation were of such high quality and so germane to the CMMB setting that, in many instances, they endure even today. Specifically, a recent re-assessment (Boston et al., 1996) of a specific numerical integrator of this generation has shown it to be both faster and more accurate than other more modern integrators when used in its preferred setting. Furthermore, an evaluation of optimizers (Boston and McNabb, 1990) has revealed that optimization performance of software of this generation [specifically the SAAM (Simulation, Analysis, and Modeling) optimizer] is approximately 10 times faster than other competing systems with no loss of precision.

The SAAM software was a prime example of CMMB software of this generation. Areas to which it was applied include iodine metabolism (Lewallen et al., 1959; Berman et al., 1968), glucose-insulin interaction (Insel et al., 1974; Sherwin et al., 1974), lithium (Temple et al., 1972), magnesium (Avioli and Berman, 1966, 1968), phosphorus (Brauer et al., 1960), calcium (Neer et al., 1967; Birge et al., 1969), and anticancer drug action (Leme et al., 1975).

HISTORY OF CMMB: GENERATION 2

A severe, though entirely unintentional, shortcoming of the first generation of CMMB was the virtual exclusion of all but the mathematically and computationally