Key Lessons from Multi-scale Modeling of Body, Tissue, Cell, and Sub-cellular Structures

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INTRODUCTION: Modeling the effects of electromagnetic fields on biological structures on the order of the body and tissues to the micro (10^{-6}) and nano (10^{-9}) level of cells and sub-cellular structures presents formidable challenges. Here are some major lessons learned using COMSOL Multiphysics™ AC-DC module in biological models.

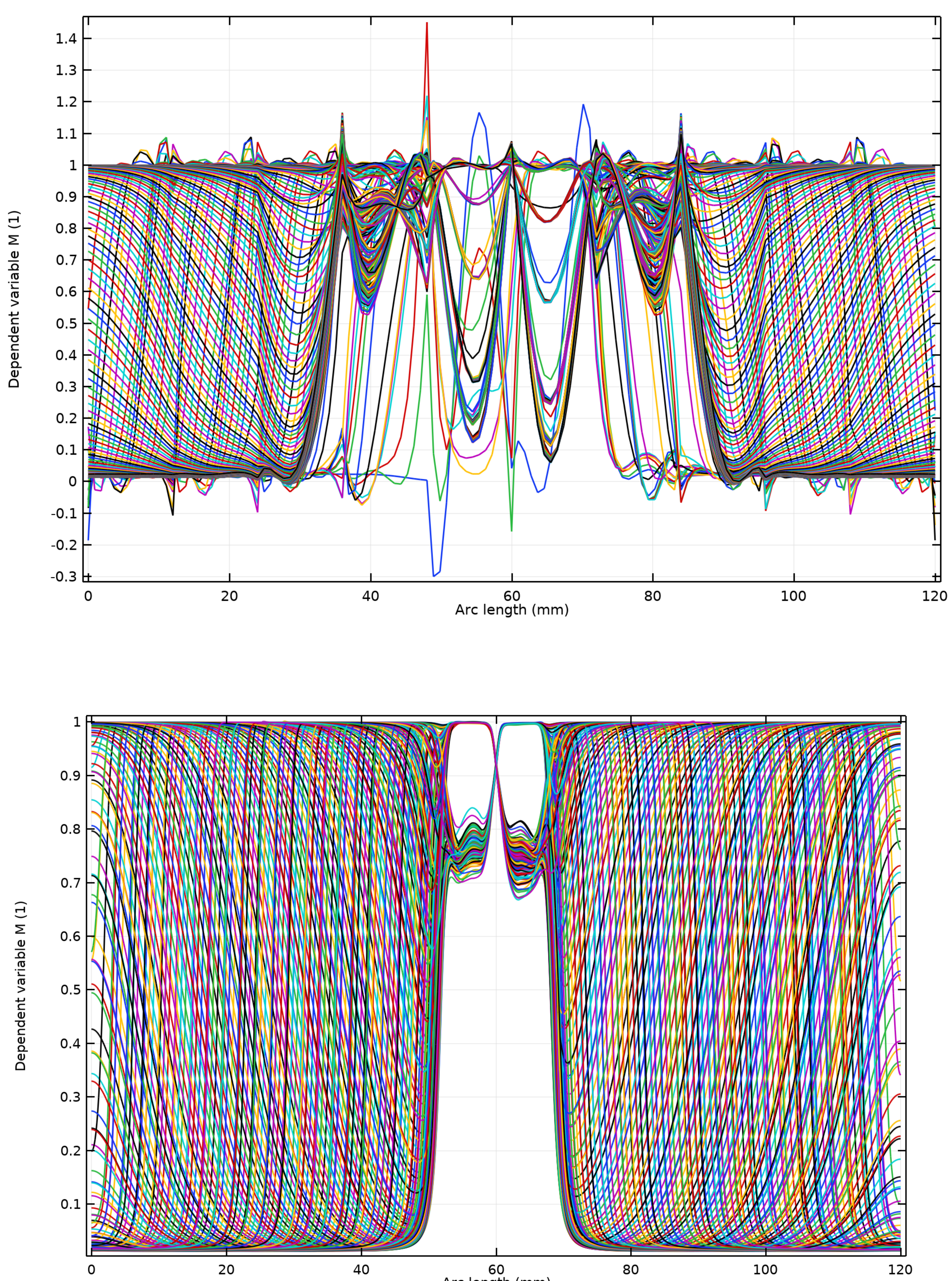

Figure 1. Top Numerical overshoot. Y-coordinate is a probability, which must be between 0 and 1. Bottom: Finer spatial mesh solution.

•LESSON ONE: Finite element physical and time scales must approximate the smallest physical component, the shortest time constant, or the physical or time component that is most sensitive to scaling.[1] Example: the opening or closing of an ion channel gate (10^{-6} s, 10^{-3} m). Using too long a time step or a mesh much coarser than nerve fiber node spacing results in numerical over- and undershoot (Fig. 1, probability of ion channel gates being open along a nerve fiber).

•LESSON TWO: Interweave analytic and empirical approaches with finite element modeling.[2] Biological models tend to be under-calibrated and therefore under-constrained. Calibrate to one or more analytic results, and to multiple empirical datasets that are orthogonal in some sense.[3]

LESSON THREE: Use small, simple, specialized models — built and validated in hours or days — to answer carefully-defined specific questions.[3] Large, complicated models take months or years to build, can be difficult to validate and understand, and should be built when the coupled interaction of their parts must be studied. Restrict models to one biological systems level. Use results of a lower systems models as assumptions in higher-level models.[4] Use higher-level systems model results as constraints, calibrations, and validations of lower-systems level models.

•LESSON FOUR: Dimensionless modeling is a powerful tool to circumvent vexing problems when modeling the microcosm or several systems levels. Write your differential equations using as many simplifying assumptions as possible. Then re-scale your constants (length, electric field, charge, etc.) imagining a simpler problem on the same order of magnitude as the one you want to solve (Fig. 2).[5] Dimensionless variables are obtained by dividing each model dimension by its corresponding re-scaled constant. Solve your equations with these variables and convert back to a scaled model by inverting the re-scaling procedure.[6]

$$\text{Length scale: } L_0 = L = 1.8\times 10^{-8} \text{ m}$$

$$\text{Time scale: } t_0 = \frac{1}{\omega} = 5\times 10^{-6} \text{ s}$$

$$\text{Electric field scale: } E_0 = E_i = 200 \text{ Volts/m}$$

$$\text{Potential scale: } V_0 = E_0 L_0 = E_i L = 4\times 10^{-6} \text{ Volts}$$

$$\text{Current density scale: } J_0 = \sigma_c E_0 = \sigma_c E_i = 20 \text{ A/m}^2$$

$$\text{Charge density scale: } \rho_0 = \frac{\varepsilon_0 V_0}{L_0^2} = \frac{\varepsilon_0 E_i}{L} = 0.0854 \text{ C/m}^3$$

$$\text{Electrical conductivity scale: } \sigma_0 = \sigma_c = 0.1\ 1/(\Omega\text{m})$$

Figure 2. Re-scaling dimensions in dimensionless modeling.

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