A “Threshold-based” Approach to Determining an Acceptance Criterion for Model Validation

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Introduction

A "credible" computational model has the potential to provide a meaningful evaluation of safety in medical-device submissions. One major challenge in establishing model credibility is determining the extent to which the model yields useful results from a safety perspective. This study proposes a "threshold-based" validation approach. It provides a well-defined acceptance criterion, which is a function of how close the simulation and experimental results are to the safety threshold. The method is applicable for scenarios in which a safety threshold can be clearly defined, such as the viscous shear-stress threshold for hemolysis in blood contacting devices or thermal-damage threshold for ablation devices.

The validation criterion developed following the threshold approach is a function of Comparison Error, E, which is the difference between experiments and simulations. The approach but also takes in to account the risk to patient safety represented by a given value of E.

Threshold based approach

In threshold approach, the comparison error, E, and "proximity" Ω for the quantity of interest U (ex. viscous shear stress to evaluate red-blood cell damage caused by a device) are expressed as follows

$$\text{Comparison Error, } E = |U_{Comp} - U_{Experiment}| \quad (1)$$

$$\text{Proximity, } \Omega = |U_{Threshold} - U_{Comp}|. \quad (2)$$

where the subscript "comp" denotes the computed value. Comparison error is the difference between experiments and simulations while proximity measures the difference between safety threshold and simulations for the quantity of interest.

If the uncertainties in the experiments, computational model, and threshold are properly quantified, then both E and Ω can be expressed in terms of confidence intervals as CI_E and CI_Ω. Figure 1 illustrates the threshold-based validation approach qualitatively for two different scenarios. In the first scenario (Fig 1a), the uncertainties for computations and experiments (represented by green and blue square brackets, respectively) are non-overlapping. However, E is less than Ω and the CI_E and CI_Ω are non-overlapping suggesting that the computations still provide valid data for the quantity of interest. In the second scenario (Fig 1b), the computed and the experimental results are closer to each other with overlapping uncertainties. However, the computed result is closer to the threshold than to the experiments. In addition, CI_E is overlapping with CI_Ω suggesting that the simulations do not provide sufficient validation at the prescribed level of significance (e.g. α=0.05).

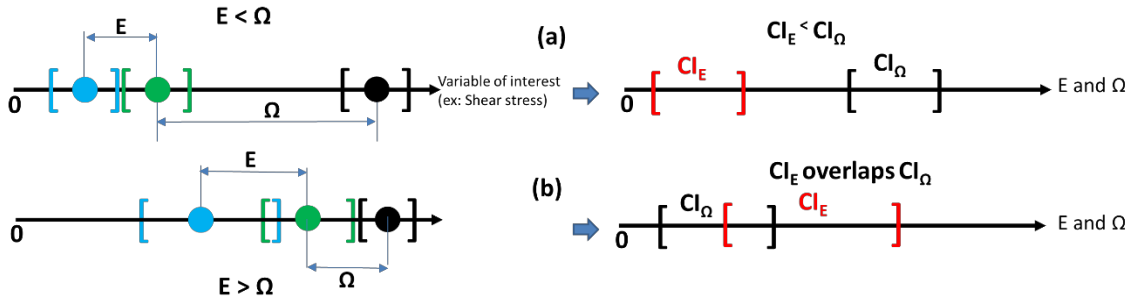

Fig 1. Qualitative explanation of the threshold approach for two different scenarios Black – Threshold; Green – simulation and Blue –experiment. [ ] represent mean±uncertainty. a) Model is valid and b) Model not necessarily valid. In scenario (a), both the experiments and simulations are far away from the threshold and CI_E smaller than CI_Ω. In scenario (b), the simulations are closer to the threshold than to the experiments and CI_E is larger than CI_Ω.

The confidence interval CI_Ω for Ω is given by :

$$CI_\Omega = [\Omega - t_{d_1^{"},1-\alpha/2}\sqrt{B_1^2/n_1 + B_2^2/n_2}\,,\ \Omega + t_{d_1^{"},1-\alpha/2}\sqrt{B_1^2/n_1 + B_2^2/n_2}\,] \quad (3)$$

Here the subscripted t values represent critical values of the Student's t-distribution, the degrees of freedom $d_1^{"} = \frac{\left(B_1^2/n_1+B_2^2/n_2\right)^2}{\left(B_1^2/n_1\right)^2/(n_1-1)+\left(B_2^2/n_2\right)^2/(n_2-1)}$, n_1 and n_2 are the number of samples associated with each variable, α=0.05 (for 95% CI limit), B_1 is the variance in the computational results, B_2 is the variance in the threshold. An analogous expression holds for CI_E and can be written as

$$CI_E = [\,\mathrm{E} - t_{d_2^{"},1-\frac{\alpha}{2}}\sqrt{B_1^2/n_1 + B_3^2/n_2}\,,\mathrm{E} + t_{d_2^{"},1-\alpha/2}\sqrt{B_1^2/n_1 + B_3^2/n_2}\,] \quad (4)$$

where the degrees of freedom, $d_2^{"} = \frac{\left(S_1^2/n_1+S_3^2/n_3\right)^2}{\left(S_1^2/n_1\right)^2/(n_1-1)+\left(S_3^2/n_3\right)^2/(n_3-1)}$, and

B_3 is the variance in the experimental results.

A model can be considered sufficiently validated if *E* is less than *Ω* and CI_E and CI_Ω are non-overlapping (max(CI_E) <min(CI_Ω)).

A case study describing this validation approach is presented in

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0178749