Applicability Analysis of Validation Evidence for Biomedical Computational Models

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BACKGROUND

- Computational modelling has the potential to revolutionise 21st Century healthcare
- However, despite decades of research, progress in translating computational models to clinical care has been limited.
- One major challenge is **demonstrating the reliability of predictions from *in silico* approaches**

CURRENT VVUQ METHODS

- Current practice for demonstrating credibility relies on verification, validation, and uncertainty quantification (VVUQ) and sensitivity analysis (see Table)
- The overall goal is to evaluate the **credibility** of the computational model, the belief in its predictive capability, for a **specific context of use (COU),** which is the specific role and scope of the computational model and simulation results used to inform a decision

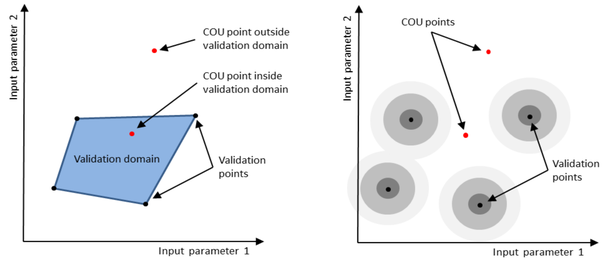
Terminology	Question addressed
Verification	Does the computational model accurately solve the underlying mathematical model?
Validation	How well does the computational model reproduce reality?
Sensitivity Analysis	How much do changes in inputs of the model (e.g. parameters, initial conditions) affect model outputs that are of interest for the context of use?
Uncertainty Quantification	What is the uncertainty in inputs of the model (e.g. parameters, initial conditions), and what is the resultant uncertainty in the model outputs that are of interest for the context of use?
Applicability	How relevant is the validation evidence to the context of use?

VALIDATION LIMITATIONS

- One contributor to the success of computational modelling in engineering applications is the ability to perform a validation study using a carefully designed comparator (e.g., an experimental setup) that **closely matches the setting of the COU**
- For biomedical models, close matching between the validation and the COU settings is **often not possible**
  - Ethical concerns
  - Technological difficulties
  - Financial limitations
- For models with clinical COUs, the **validation setting often has significant differences compared to COU**
  - Human COU vs animal/bench/phantom/cadaver validation
  - Diseased state vs healthy state
  - Pediatric vs adult
- Therefore, when evaluating biomedical models it is critical to rigorously assess ***applicability* – the relevance of the computational model and its validation evidence to a proposed context of use.**
- *If there is agreement between the outputs from the model and experiment in the validation setting(s), can we (or: why can we) be confident in the model predictions for the context of use?*
  - requires consideration of the computational model, the COU, and the available evidence
  - subjective decision typically must be made based on evidence and subject matter expertise.
- Currently, there is no well-established method for assessing applicability.

APPLICABILITY ANALYSIS

- Current methods based around the concepts illustrated in the following figure are useful only if the validation and COU settings are sufficiently similar



- We believe that **current approaches are not sufficiently well developed** to be relevant to the broad range of models, applications, and feasible validation settings that occur with biomedical models

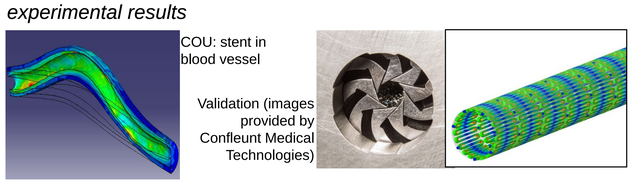
How applicable are the below models and validation evidence to the proposed contexts of use?

Model 1: *electromagnetic simulations with human body models are used in safety assessment of new implantable devices which could heat during magnetic resonance (MR) imaging. Validation of the model involves simulation and experiments using a saline-filled phantom containing the new device.*

COU (image courtesy Maria Iacono)

Validation (images courtesy Elena Lucano)

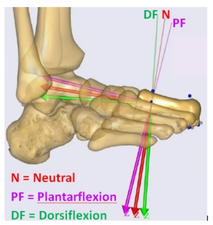
Model 2*: finite element analysis is used to provide supporting evidence to initiate a clinical trial for a new intravascular stent. Validation of the model might involve comparison to bench-top experimental results*



COU: stent in blood vessel

Validation (images provided by Confleunt Medical Technologies)

Model 3: *a musculoskeletal foot model was previously validated by comparing muscle recruitment experimental data with model predictions during normal gait. The model is to be used to study loading following hallux valgus osteotomy (bunnion surgery)*



Courtesy Mehul Dharia, Zimmer Inc

APPLICABILITY FRAMEWORK

- We have developed a **systematic step-by-step method for assessing applicability of a model for a specific COU**
- Enables the practitioner to break down the broad question of applicability into **a series of specific tractable questions**
- Questions can be addressed using supporting evidence and/or subject matter expertise

SET-UP

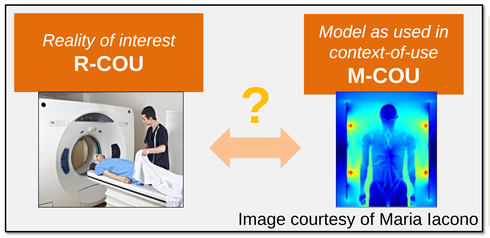
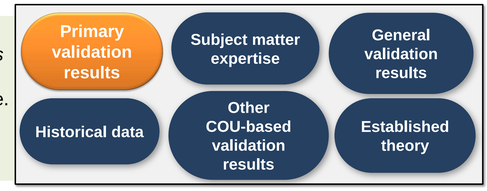
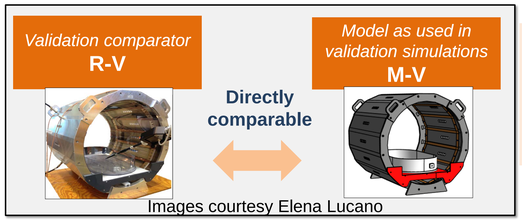


Image courtesy of Maria Iacono

1. Describe COU
Provide details on both the 'reality' to be modelled and the model that will simulate 'reality'. For example:
R-COU: Estimate the worst-case temperature change in the tissue around the implant that might occur during MRI across a wide-array of parameters…
M-COU: Solve an electromagnetic model and a thermal model using a human body anatomical model containing the device, to determine the maximum temperature change under simulated MRI conditions for a range of parameters that closely represent the clinical setting…

2. Sources of validation evidence
Describe the different types of validation results and sources of evidence. Denote one as the primary validation evidence
1. **Primary validation evidence:** Phantom validation experiments using the new device.
2. Animal validation experiments using a previous version of the device.
3. All historical validation evidence regarding similar models with different devices.
4. Literature regarding electromagnetic simulations using human anatomical models



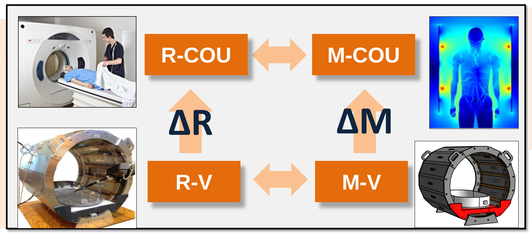


Images courtesy Elena Lucano

3. Describe primary validation evidence
Provide details on both the validation setting and the model for the validation setting.
R-V: A saline-filled phantom implanted with the new device was placed inside a radiofrequency (RF) coil; temperature changes were measured…
M-V: A geometrical model of the phantom was used with the embedded device with one RF coil. The EM/thermal model was used to compute temperature change…

4. Describe model aspects that are identical in M-V and M-COU
While the model that was 'validated' using the primary validation evidence will likely be different to the model that is used for the context of use, there will be many aspects of the model that remain the same. Therefore, describe the aspects of the model that are identical in M-V and M-COU:
- Maxwell's equations are solved
- Equations of thermal model
- Parameters for EM properties of the device
- ….

6. Describe ΔR
Describe the relevant differences between R-V and R-COU
- Phantom → human (both sexes, range of ages and BMIs)
- Path of device lead
- MR system present in R-COU, only RF coil in R-V
- …



5. Describe ΔM
Describe the aspects of the model that are different between M-V and M-COU
- Phantom → virtual human
- Path of device lead
- …

ASSESSMENT

7. Is it appropriate to use the model aspects listed in Step 4 to make predictions about R-COU? Provide rationale, evidence, or discussion. Assume that these model aspects are appropriate for R-V (or refer to the validation results) and then consider each of the differences in ΔR (listed in Step 6). *If the validation comparison is deemed adequate, can we be confident that the aspects that are the same in M-V and M-COU, as listed in Step 4, are appropriate for the COU? Differences between R-V and R-COU, listed in Step 6, might mean that this is not so. For **each** aspect listed in Step 4, provide rationale, evidence or discussion on whether the model aspect is appropriate for the COU, Use the Table on right, and for each entry, ask: "is it acceptable to use this model aspect (associated column) for making predictions about R-COU, given this difference (row)?"*

ΔR: R-V	ΔR: R-COU	Model aspects common to M-V and M-COU		
		Maxwell's equations (excluding parameters)	Equations of thermal model	…
Phantom	Human (both sexes, range of ages and BMIs)	Influence of body currents?	Perfusion? Metabolism?	
Specific lead path	Many lead paths			
RF coil only	Full MRI system		Cooling due to A/C?	
…	…			

8. Do the modifications to the computational model result in credible predictions for the COU? Provide rationale, evidence or discussion. *For each modification in ΔM, explain why the COU predictions can be trusted given each modification, keeping in mind the COU*
Q) Why can predictions be trusted given the virtual human body model in the COU?
Q) Why can predictions be trusted when the path of the conductor lead is altered?
Q) ..
Careful arguments are required, referring to all supporting evidence

ΔR: R-V	ΔR: R-COU	Raises any additional questions regarding M-COU?
Phantom	Human (both sexes, range of ages and BMIs)	
Specific lead path	Many lead paths	
RF coil only	Full MRI system	Impact of static or gradient magnetic fields?
…	…	

9. Provide rationale for credibility if the COU QOIs differ from validation QOIs
Justification needed if COU outputs analysed differ from the outputs that were 'validated'

10. M-COU in light of ΔR (Table on the left)
Consider M-COU in the context of differences between R-V and R-COU.

11. Assess the overall applicability of the computational model for the COU
By considering the responses to questions raised, assess the overall applicability of the computational model for the COU using sound scientific (albeit subjective) judgement.

Key takeaways
- ❖ Assessing the applicability of a computational model and validation evidence is **essential for rigorous assessment** and for avoiding 'leaps of faith' – especially for biomedical models
- ❖ Our proposed framework uses a novel structure and involves systematic analysis of differences in both model and reality
- ❖ It could help overcome some of the barriers inherent to validation of, and aid clinical implementation of, biomedical models.

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Instructions above are an **overview only**, for full details, see: *Applicability Analysis of Validation Evidence for Biomedical Computational Models, P. Pathmanathan, R. Gray, V. Romero, T. Morrison, in submission.*