18th DIA Japan Annual Meeting 2021

Application of Computational Modeling and Simulation for Medical Devices; Topics from the PMDA report
数値シミュレーションの医療機器開発への応用；
PMDA科学委員会報告書から

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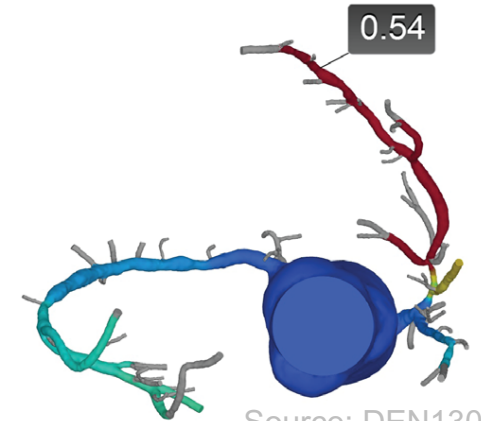
PMDA Science Board Report on CM&S

▶ Published March 2021

▶ Not intended to be a mandatory document

▶ Scope

- How **emerging CM&S** applied to medical devices?
  - CM&S as a medical device
  - CM&S for a part of device evaluation
- What **CM&S factors** impact in regulatory science?
- How far **CM&S will change medical devices**?

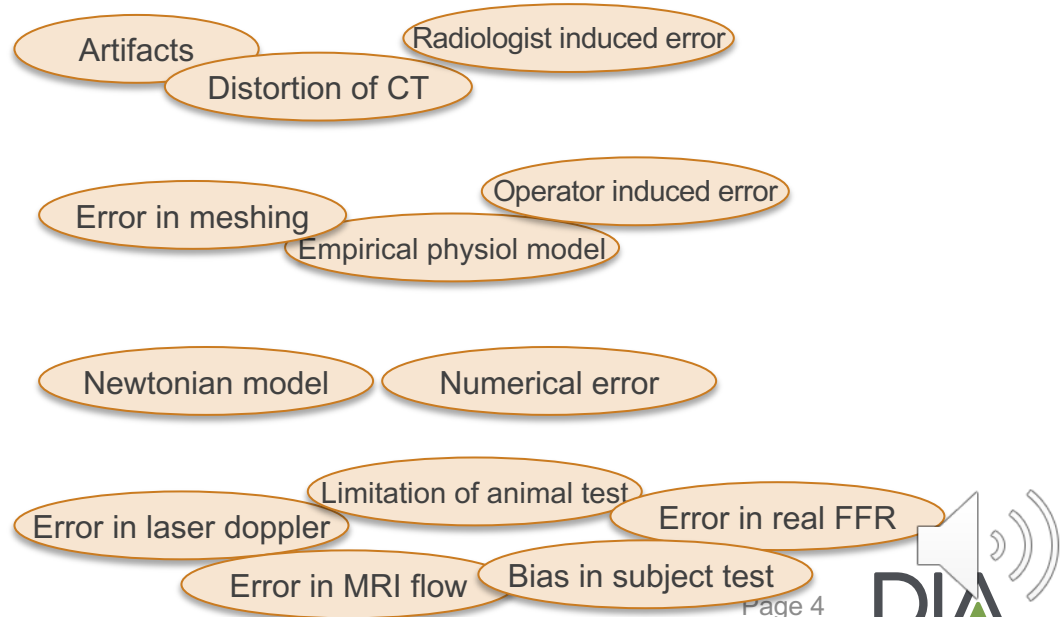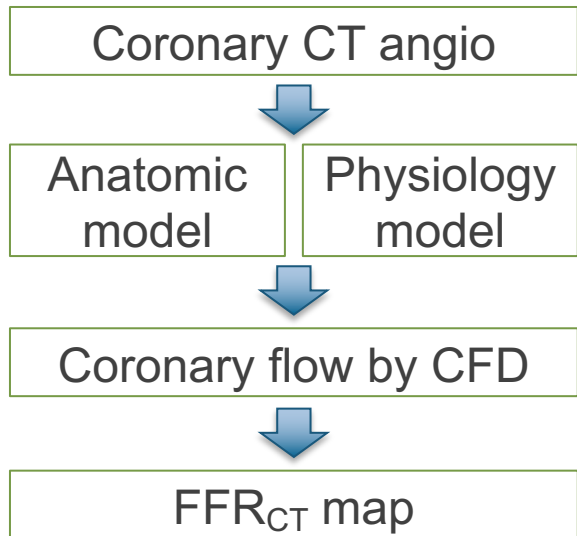https://www.pmda.go.jp/files/000240657.pdf
(in Japanese)

CM&S as a Medical Device

Source: DEN130045

- Examples
  - FFR$_{CT}$ (Fractional Flow Reserve)
  - Radiation dose simulator

- Errors directly impact patient effica̶c̶y̶/safety

FFR$_{CT}$ is	Color	Average Error to FFR$_{CATH}$* +/- 1SD
	Red	-0.05 +/- 0.1
0.70 - 0.75	Red to Orange	-0.04 +/- 0.1
0.76 - 0.80	Orange to Yellow	-0.03 +/- 0.0
	Yellow to Green	-0.04 +/- 0.0
0.90	Green to Cyan	-0.03 +/- 0.0
0.91 - 1.0	Cyan to Blue	-0.01 +/- 0.0
All		-0.03 +/- 0.0

Coronary CT angio → Anatomic model / Physiology model → Coronary flow by CFD → FFR$_{CT}$ map

- Artifacts
- Distortion of CT
- Radiologist induced error
- Error in meshing
- Operator induced error
- Empirical physiol model
- Newtonian model
- Numerical error
- Error in laser doppler
- Limitation of animal test
- Error in real FFR
- Error in MRI flow
- Bias in subject test

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CM&S impacts for Regulatory Science

- What extent **interpolation** & **extrapolation** of CM&S applicable?

- What extent **uncertainties in CM&S** impact?

- CM&S to validate experiment?

- How can we use **digital evidence** in medical device evaluation?
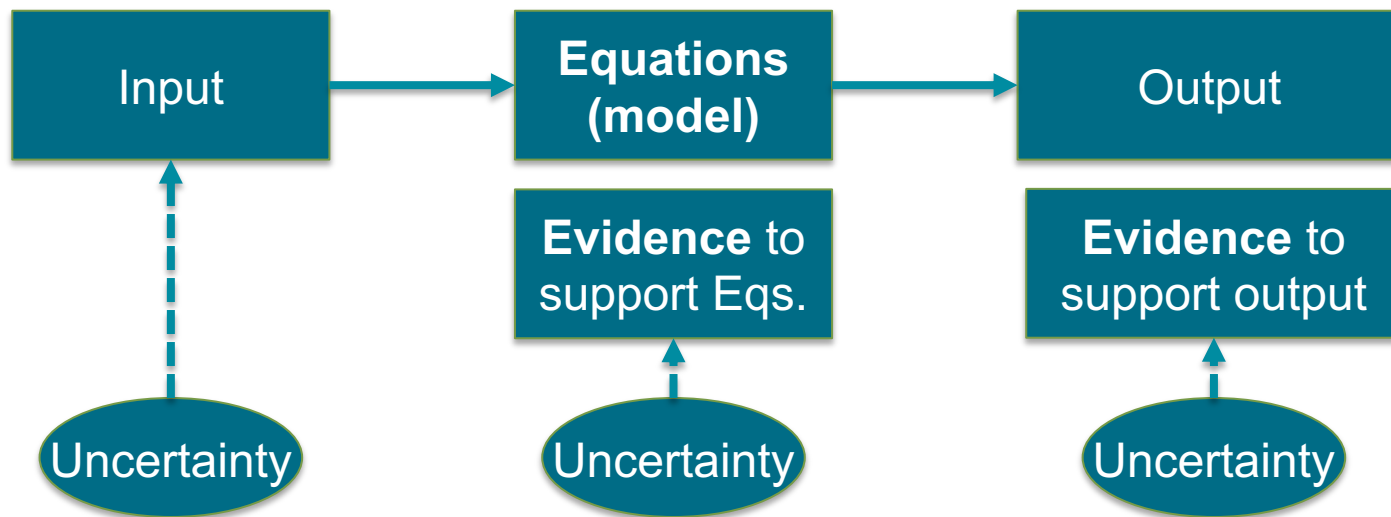
- CM&S in machine learning: **Surrogate model?**

How we assess the _credibility_ of CM&S?

Uncertainty Quantification (UQ)

Credibility of CM&S

- Equations (model) credibility
  - Theoretically deduced?
  - Experimentally fitted?
- Input/evidence credibility
  - Directly obtained from subject in focus?
  - Indirectly obtained from surrogate subject?

Uncertainty of model & evidence

Input	Equations (model)	Output

	Evidence to support Eqs.	Evidence to support output

Uncertainty   Uncertainty   Uncertainty

Model / Evidence Matrix

	Examples	Deductive model	Experimental model
		Diffusion equation	Least square fitting
Direct evidence	- Bone shape of the patient by CT	A	B
Indirect evidence	- Mechanical property of aneurism from cadaver - Electrophysiological behavior of heart cell in vitro	C	D

Interpolation & extrapolation

A) Extrapolation may be discussed quantitatively.
- Reduced N of evidence?

B) Extrapolation can be discussed if stability of simulation demonstrated and agrees evidence.

C) Extrapolation might be discussed.

D) Extrapolation might be discussed but limited to subjectively.
- Clinical validity may be discussed.

Provided affecting factors are also known & predictable.

	Deductive model	Experimental model
Direct evidence	A	B
Indirect evidence	C	D

Digital evidence, surrogate model

▶ As a tool to discuss credibility of experiment

- Sensitivity against disturbance.

▶ CM&S with machine learning

- CM&S → ML: reinforcement learning to add learning
- ML → CM&S: surrogate model to reduce computation

▶ Regulatory science should prepare for such uses of CM&S