Simulation of x-ray imaging devices for regulatory evaluation

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1. Introduction to the FDA/CDRH/OSEL/DIDSR

- The **Food and Drug Administration** (FDA) is responsible for protecting the public health, in the U.S.A., by ensuring the *safety*, *efficacy*, and *security* of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation.

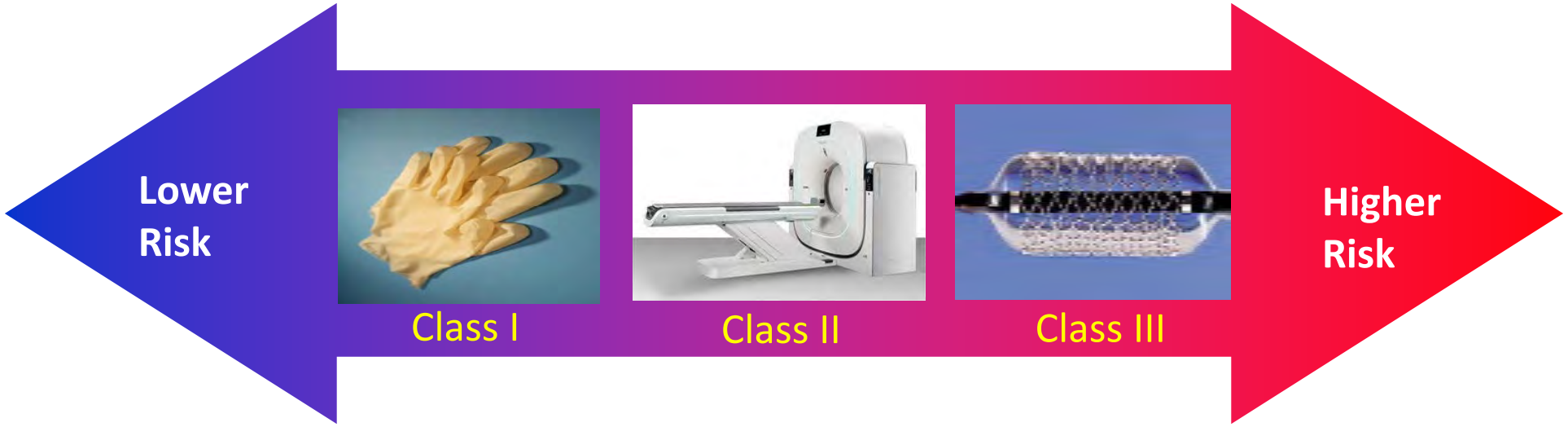
- FDA's White Oak campus in Silver Spring, Maryland

DISCLAIMER: The mention of commercial products herein is not to be construed as either an actual or implied endorsement of such products by the U.S. Department of Health and Human Services.

- The Center for Devices and Radiological Health (**CDRH**) is the part of the FDA dedicated to regulating medical and radiation emitting devices.
  - ~2'000 employees, ~25'000 device submissions/year, ~20'000 manufacturers
- The Office of Science and Engineering Laboratories (**OSEL**) is the part of CDRH dedicated to regulatory science research.
  - 3000+ pre-market regulatory consults for CDRH every year.
- The Division of Imaging, Diagnostics and Software Reliability (**DIDSR**) is the part of OSEL dedicated to imaging research. Research programs:
  - Medial Imaging and Diagnostics
  - Digital Pathology
  - Medical Extended Reality
  - Artificial Intelligence / Machine Learning

2. Medical device classification and regulatory evaluation

- FDA employs a risk-based classification paradigm for medical devices:
  - Medical devices are classified and regulated according to degree of risk to the public.
  - Both the technology and intended use and Indications for use inform the risk level.
    - **Intended Use**: general purpose of the device or its function.
    - **Indications for use**: disease or conditions the device will diagnose, treat, prevent, cure or mitigate, including a description of the intended patient population. [*21 CFR 814.20(b)(3)(i)*]



FDA Total Product Lifecycle activities

- **Pre-market:**
  - **Class I** (lowest risk): most exempt of FDA notification; follow general controls (Good manufacturing practice, Registration, Adverse Event Reporting, etc.).
  - **Class II**: general and specific controls; Premarket notification [**510(k)**]
  - **Class III** (highest risk or no predicate): General Controls; Premarket Approval [**PMA**]
  - Pre-Submissions [**Qsub**] available to request feedback before submission
  - Investigational device exemption [IDE]
  - De Novo Petitions to classify devices as class I or II (class III is default for new devices)

- **Post-market:**
  - Compliance, Inspections, Recalls, Surveillance**:** adverse event reporting or medical device reports, trends, and signals from a variety of sources

510(k) Pre-market Notification

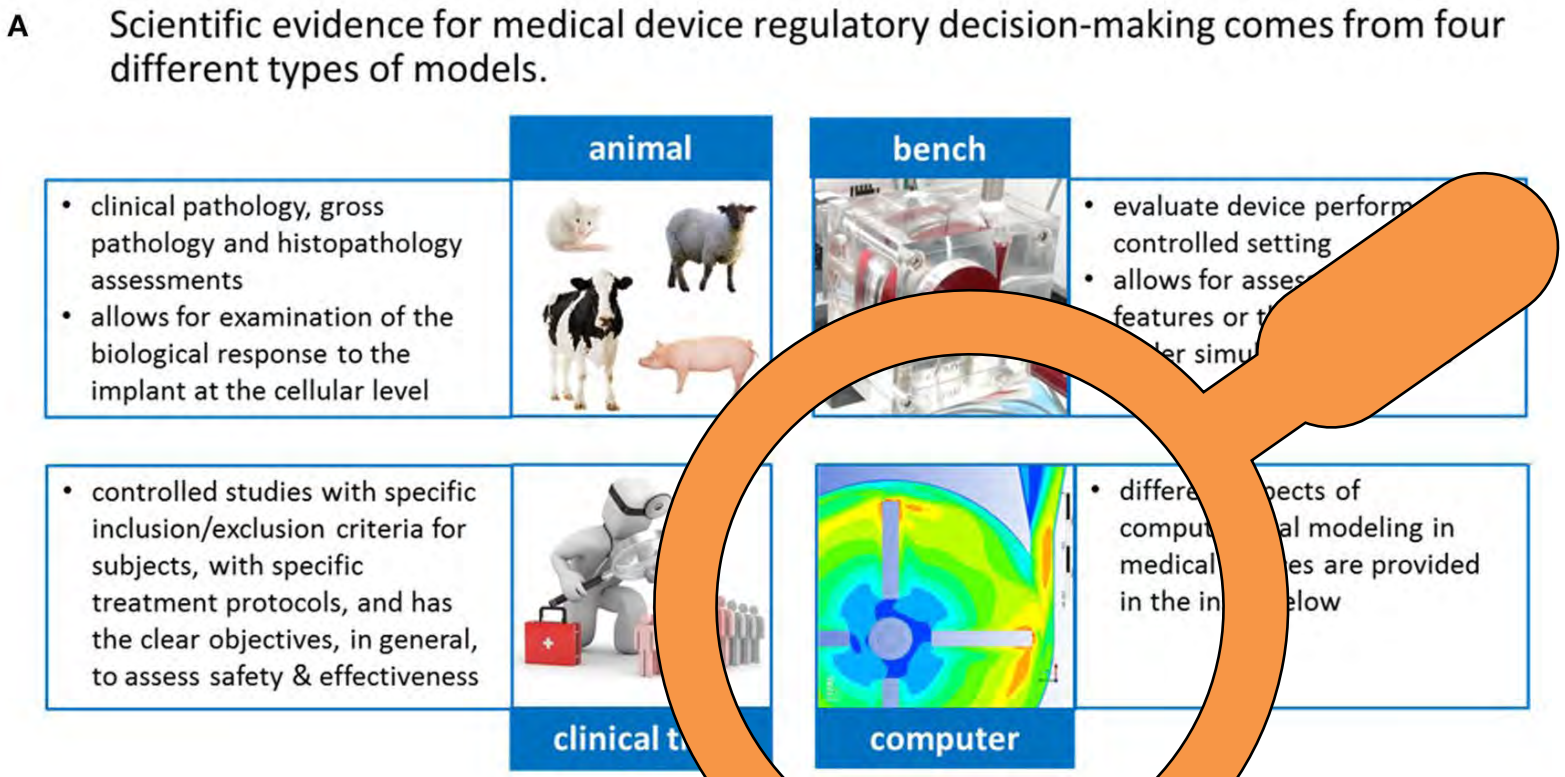
- Path to market for the majority of image acquisition (hardware) devices and image processing (software) devices (Class II)
  - Software *in* a Medical Device (SiMD)
  - Software *as* a Medical Device (SaMD)
  - AI/ML software is evaluated essentially in the same way as other software devices, with addition of information on network architecture and training/testing datasets.

- 510 (k) requires determination that the new device [subject device] is substantially equivalent to a legally marketed device [predicate device].

[*21 CFR 807.92(a)(3)*]

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/510k-program-evaluating-substantial-equivalence-premarket-notifications-510k

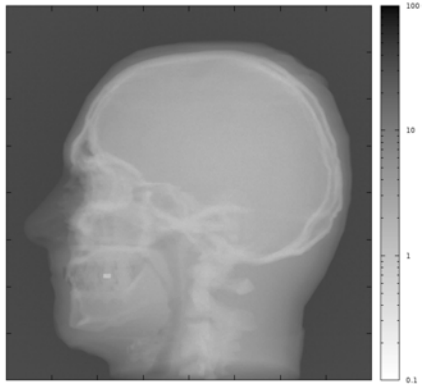
- Performance data needed to support a pre-market submission depends on submission type, device technology, and intended use of the device:
  - Computational methods have a great potential to accelerate the development and regulatory evaluation of new imaging devices



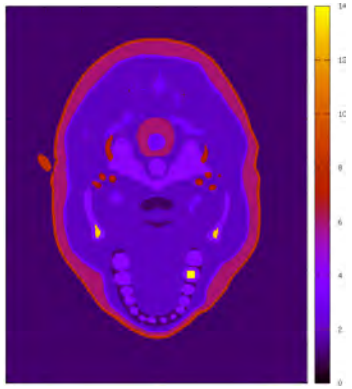
Morrison et al. "Advancing regulatory science with co tional modeling for m devices at the FDA's office of science and engineering laboratories." *Frontiers in Medic* .org/10.3389/fmed.2018.00241

3. MC-GPU: digital replica of x-ray imaging devices

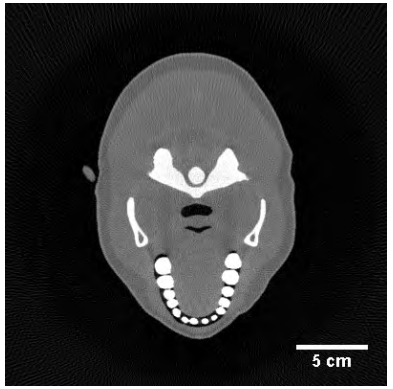
- To promote the use of in silico imaging in device evaluation, in 2009 we developed the first GPU-accelerated Monte Carlo x-ray tracking code:
  - **MC-GPU**: a version of the PENELOPE photon transport routines that can be efficiently executed in NVIDIA Graphics Processing Units (GPU) using CUDA.
    - X-ray transport through voxelized geometry with delta scattering; binary tree.
    - Open-source code available at: https://github.com/DIDSR/MCGPU
      - Badal and Badano, **Accelerating Monte Carlo simulations of photon transport in a voxelized geometry using a massively parallel GPU**, Medical Physics 36, p. 4878-4880 (2009)



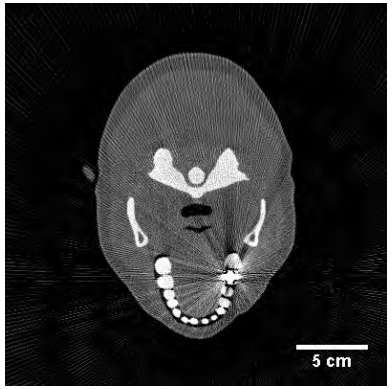
- Simulated radiograph



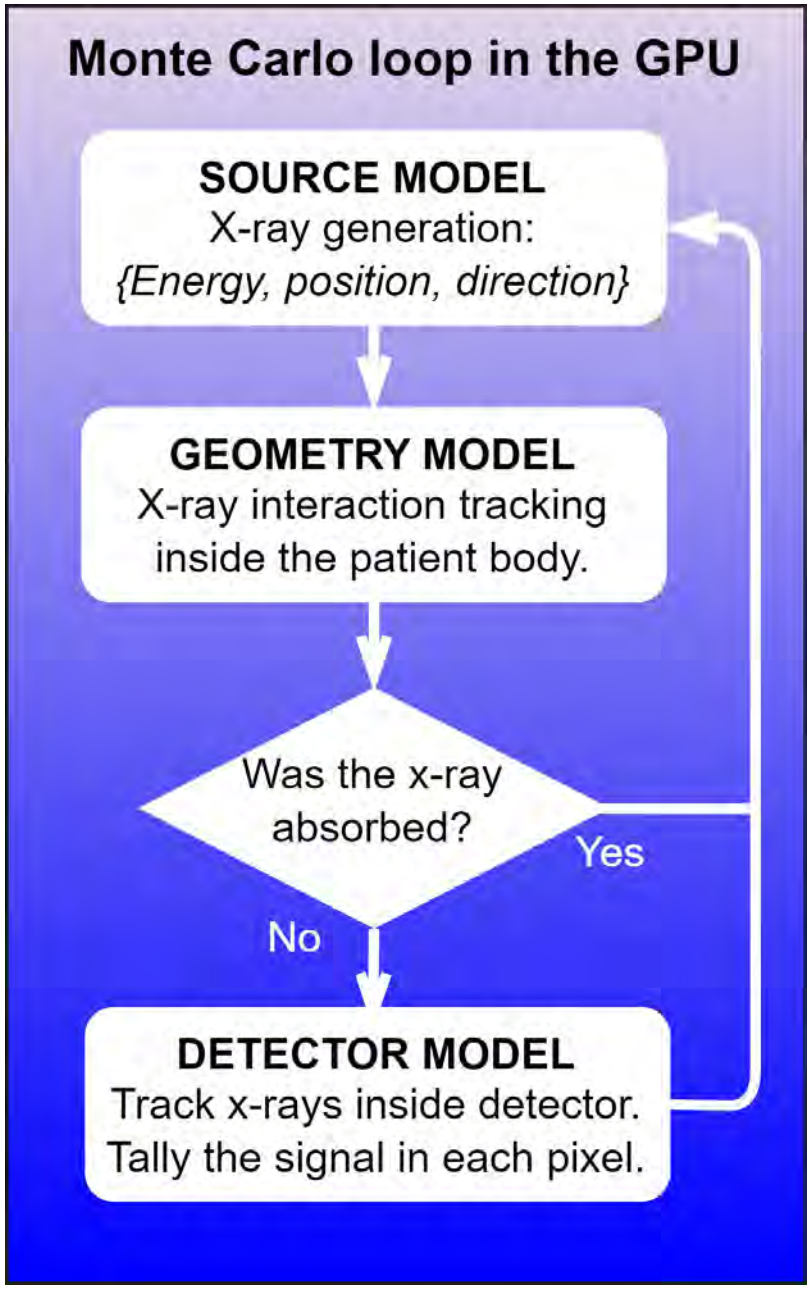
- Original anatomy



- CT recon. no metal



- CT recon. with metal



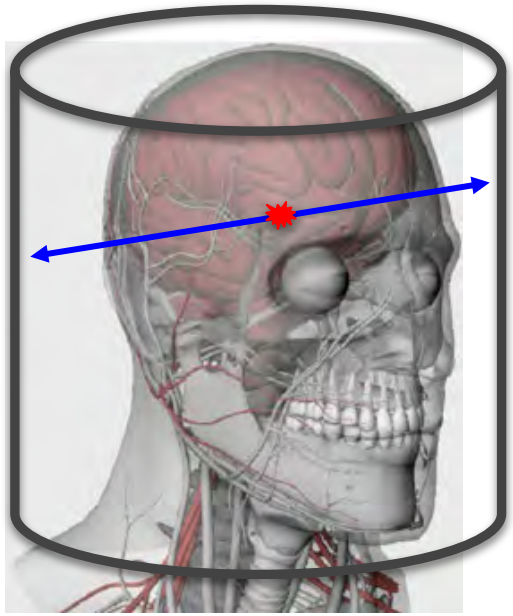
- Simple flow chart repeated for each x-ray track:
  - **~10^{11} x-ray tracks** per simulation, as in real acquisition
  - **>400 million x-rays/sec** in a NVIDIA GeForce RTX 4090

- The quality of the simulation results has to be evaluated with solid *Verification, Validation and Uncertainty quantification* studies:
  - FDA guidance**: Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions**: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-credibility-computational-modeling-and-simulation-medical-device-submissions

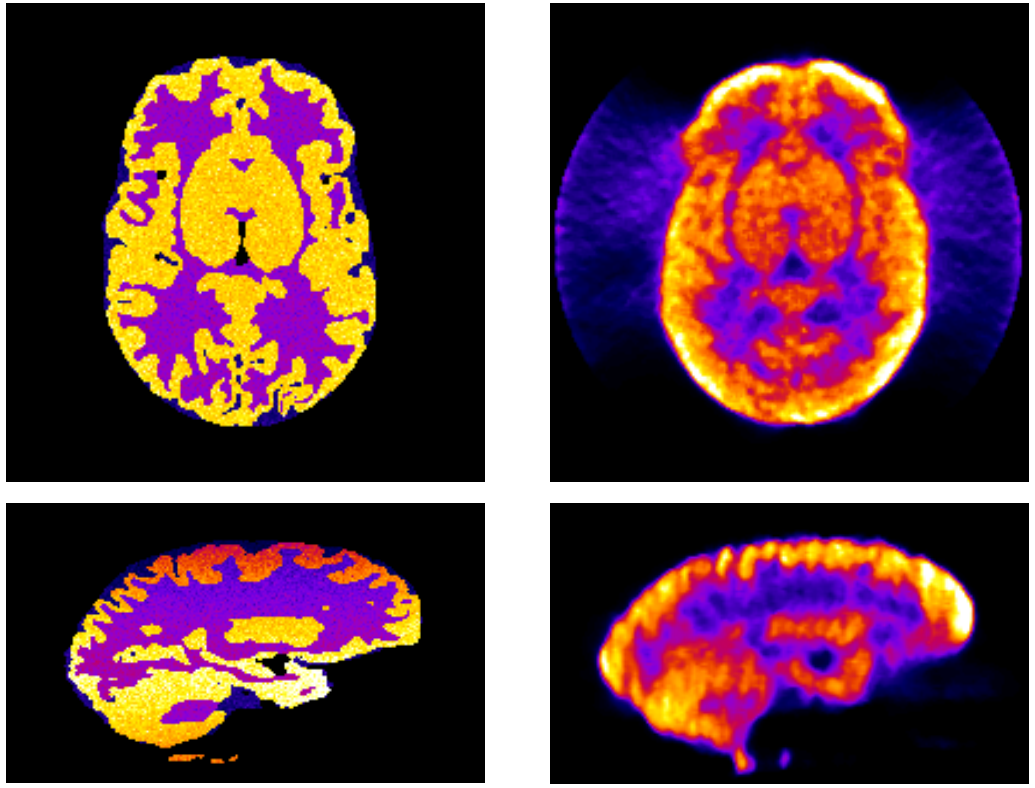
- **MC-GPU-PET**: extension of the GPU-accelerated Monte Carlo code to simulate PET imaging: https://github.com/DIDSR/MCGPU-PET
  - Example: ^{18}F-FDG PET head scan simulated in 43.7 s in 1 GPU.

INPUT

- Voxelized positron source
- Voxelized anatomy (Zubal phantom)
- Setup: Scanner, Acq. & Sinogram



PET RECONSTRUCTION



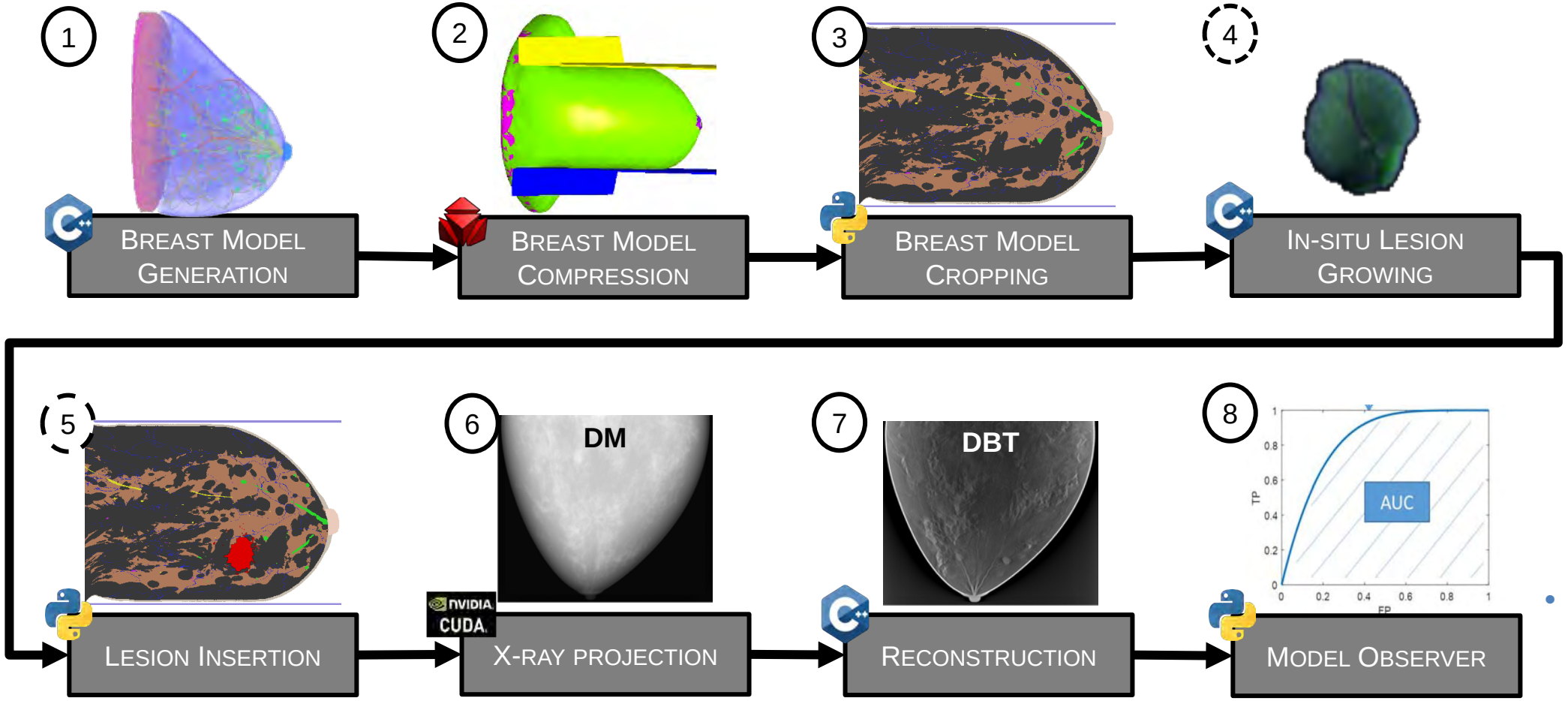
- Ideal and reconstructed emission maps

Example application:
Virtual Imaging Clinical Trials for Regulatory Evaluation (VICTRE)

- The VICTRE project demonstrated that it is feasible to use computational modeling to reproduce an existing clinical trial.
  - Context of use: comparing the detectability of a solid mass and a calcification cluster in full-field digital mammography (FFDM) and digital breast tomosynthesis (DBT).
  - Images of 3000 breast phantoms were simulated with a model of a Siemens Mammomat Inspiration system using MC-GPU.
  - Detectability was estimated as area under the ROC curve with a channelized Hotelling observer with Laguerre-Gauss channels.

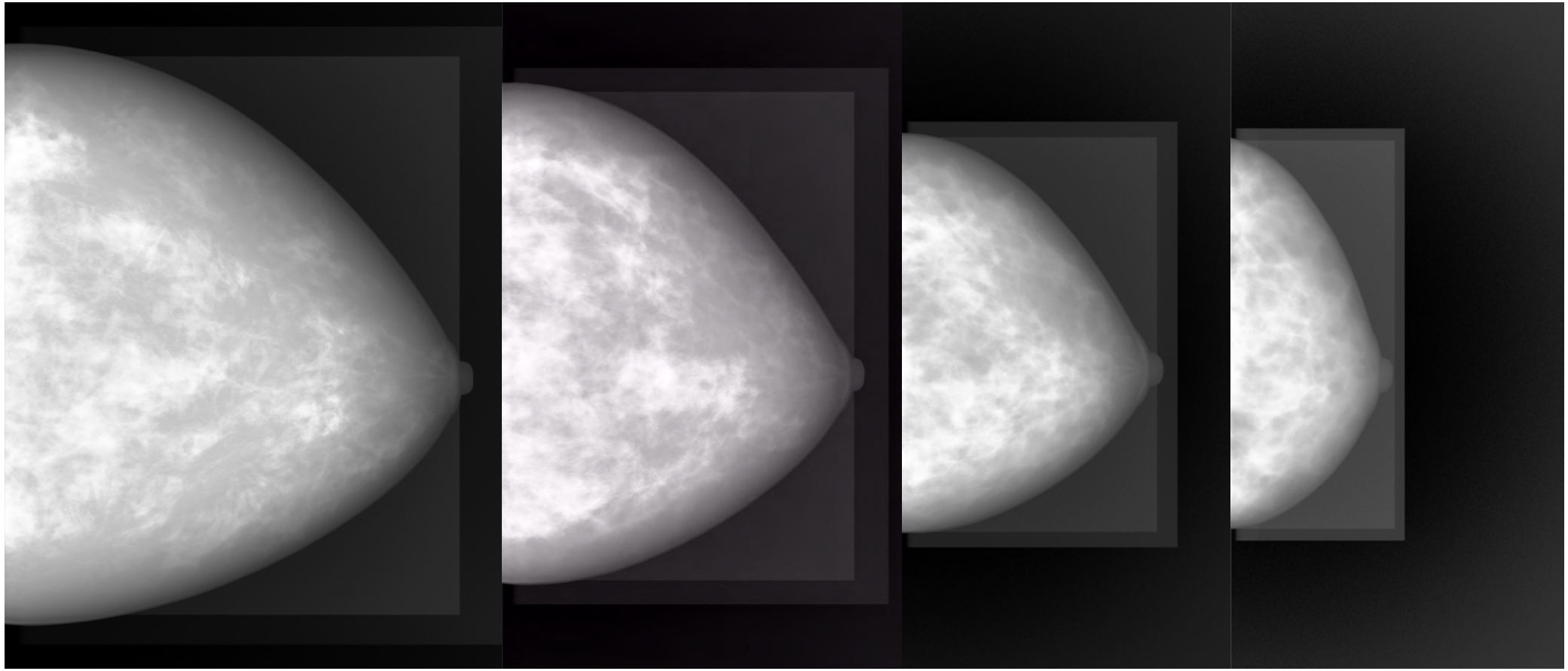
- Badano et al., Evaluation of Digital Breast Tomosynthesis as Replacement of Full-Field Digital Mammography: An In-Silico Imaging Trial, JAMA Network Open 1, 185474–185474 (2018)
- Badal et al., Mammography and breast tomosynthesis simulator for virtual clinical trials, Computer Physics Communications 264, 107779 (2021)

- We implemented a complete computational pipeline for virtual breast phantom creation, image generation and interpretation.
  - All tools are open-source and available at: https://github.com/DIDSR/VICTRE



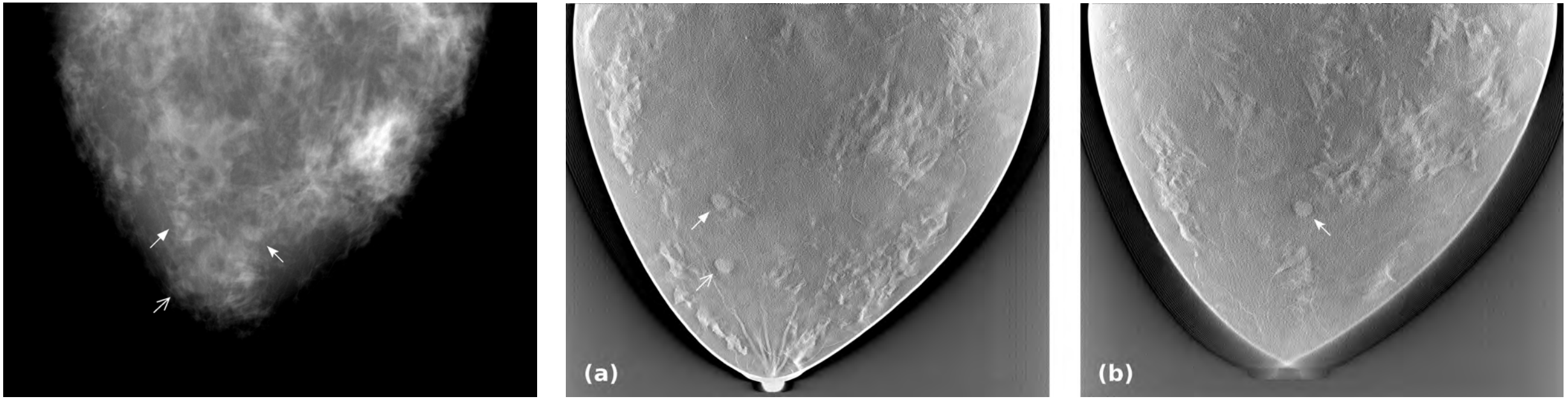
- Badano et al., JAMA Network Open 1, 185474 (2018)

- Example mammography simulations in the virtual trial:
  - 50 μm voxels; 85 μm pixels (a-Selenium direct detector model)
  - 4 breast glandularity classes and sizes



(a) Fatty (b) Scattered (c) Heterogeneous (d) Dense

- Example **mammography** and **tomosynthesis** simulation with MC-GPU:
  - 25 projections (Siemens protocol); 10^{11} x-rays/projection (~ 1 mGy)
  - <10 min/mammogram (~4×10^{8} x-ray/sec in an NVIDIA Tesla V100 GPU)



- Mammogram (left) and two DBT slices (right) of a fatty breast with 3 masses inserted at two depths (arrows)

- The results of the VICTRE in silico trial supported the real clinical trial results of slightly superior performance of DBT compared to mammo.

Summary

- The FDA is working towards increasing the use of modeling and simulation in regulatory submissions and evaluation of medical devices.
- Computational imaging methods that simulate medical imaging devices with high realism can be a source of valuable evidence for research and development, and regulatory evaluation, of imaging devices.
  - Solid methods to establish the credibility of computational modeling results needed.
- The CDRH/OSEL develops open-source regulatory science tools that can support regulatory submissions of medical devices.
  - **Regulatory Science Tools Catalog**: https://cdrh-rst.fda.gov/

Thank you!

- More information on FDA/CDRH **medical device regulations**:
  https://www.fda.gov/training-and-continuing-education/cdrh-learn
- CDRH/OSEL **Regulatory Science Tools Catalog**:
  https://cdrh-rst.fda.gov/