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Preclinical irradiations at conventional and very high dose rates (FLASH-RT) on small animals at the ARRONAX research cyclotron: repositioning, margins and field sizes

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Context

In the framework of **translational research**, it is envisioned to irradiate mice on **radiobiology platforms**, as the one of the **ARRONAX cyclotron**. In general, these facilities do not feature an **integrated imaging system**, which makes irradiation of organs without external anatomical landmarks challenging. Moreover, the **field size** cannot be tailored to each animal but must be set for a cohort.

This study aims to address the parameters required to determine the optimal field size for a selected cohort, which can be expressed as:

$$\text{Optimal Field size (cohort)} = \text{Field size (cohort)} + \text{Margins}_{\text{Targeting}} + \text{Margins}_{\text{Respiratory}}$$

①

②

③

① Targets dimensions and inter-animal variability

The volumes of the boxes containing the **brain**, the **lungs** and the **intestines** were measured on 3x3 distinct tomographic images (XRAD225Cx, μ CBCT, 40kVp, 0.2mm isotropic voxel size) for **11 mice** (C57BL/6 - 5 females, 6 males) and compared to the animal's weight, as shown in **Fig. 1**. The relative uncertainty on the volume is the quadratic sum of the uncertainty of each length, corresponding to the size of two pixels.

- Brain volume was found to be **independent** of the weight
 → **Unique** field size
- Lungs and intestinal volumes are **correlated** with the mouse weight
 → Selection of a cohort on the weight criterion enables a **unique** field size

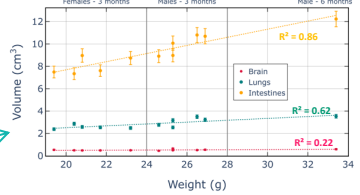
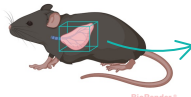


Figure 1. For the three locations, volume containing the organ with respect to the animal weight.

② Immobilization and targeting system

The system, shown in **Fig. 2**, consists of a patient-like **3D-printed bed** and harmless contentions, together with **graduations** as external markers for the lasers.

The targeting accuracy was assessed by resetting 10 times an anaesthetized C57BL/6 mouse for the **brain, lungs and intestines**. Each time, a μ CBCT (40kVp, 0.2mm isotropic voxel size) was acquired using the XRAD225Cx. The TPS μ Raystation® was used for **organ contouring** on the images and to perform rigid registrations, without rotation, with respect to the reference image.

The **maximum offsets** in the three directions were recorded in the **Table 1**. To ensure the target coverage, equivalent margins should be applied for each organ. An example of the histogram of deviations obtained for a site is also shown in **Fig. 3**.

| | Right/Left | Longitudinal | Antero-Posterior |
|------------|------------|--------------|------------------|
| Brain | 1,4 | 0,6 | 0,9 |
| Lungs | 2,0 | 3,4 | 0,4 |
| Intestines | 2,3 | 3,0 | 0,7 |

TABLE 1 – Maximum offsets with respect to the reference image (mm)

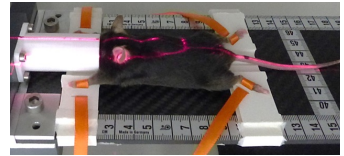


Figure 2. Photograph of the mouse holding and targeting system.

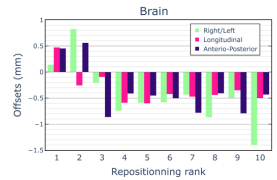


Figure 3. Histogram of brain offsets measured on the 10 images.

③ Respiratory motion

In addition to the accuracy of the targeting, margins should also take into account potential **organ motions** such as respiratory motion. The **fluoroscopic** mode of the XRAD225Cx (40kVp, 0.1 mm voxel size) was used to acquire 10 respiratory cycles for a mouse. The wider cycle is displayed in **Fig. 4**.

Measured maximum amplitudes (full inspiration) relatives to full expiration position (**Fig. 5**) are:

- 1.7 mm** in the longitudinal direction (diaphragm)
- 0.6 mm** in the antero-posterior direction.

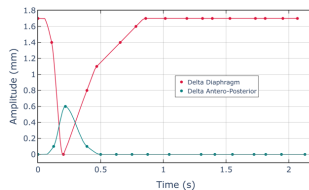


Figure 4. Maximal amplitude cycle found with respect to time. Interpolation with Akima method.

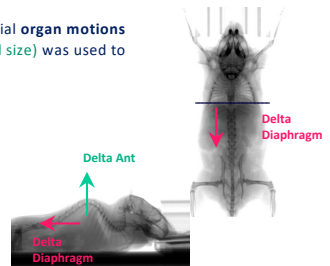


Figure 5. Fluoroscopic mouse views.

Moreover, the respiration duration, which lasts 2.3 s in total, is long in comparison with **FLASH-RT irradiation time** (few hundred milliseconds) [1]. Then, the above amplitudes must be added to the **margins** to ensure the lungs coverage, where a loss could occur for 30% of the irradiation time in conventional dose rate and up to 100% of the time in FLASH-RT.

Conclusion and perspectives

- The margins obtained and the study of inter-animal variability guarantee **optimal field sizes** for irradiation of the brain, lungs and intestine.
- The methodology developed ensures accurate and reproducible positioning for **targeted preclinical irradiations** at ARRONAX.

Following steps will involve **Monte Carlo GATE simulations** to:

- Evaluate of the dosimetric impact of the respiratory cycle using the **4D digital mouse phantom (MOBY)** [2],
- Verify the **organ coverage**, as well as **distal and lateral dose homogeneity**, on the cohort with adapted field size and margins found in this study.