Artificial Intelligence, Digital Twins and Pre-Clinical Imaging.

Geoff Currie

Geoff Currie[1,2]

[1]Charles Sturt University, Wagga Wagga

[2]Baylor College of Medicine, Houston

Introduction

Pre-clinical molecular imaging is an essential part of drug and radiopharmaceutical development. While a variety of biological models are used in pre-clinical imaging (eg. rats, fish, birds), mice represent the vast majority. This relates to a number of factors including cost and convenience associated with a short life span, short gestation, and housing. More importantly, mice share some genetic similarity to humans and can be readily modified genetically to produce various pathological models. There remain ethical, political and social challenges that require consideration. At the core of most ethical guidelines for animal research are three long standing principles (reduce, refine and replace):

- Justify the number of animals used without compromising the value of insights gained.
- Optimise methods to maximise the benefit while minimising risk and invasiveness.
- Limit use of animals when alternative options are available.

A number of approaches have been adopted to reduce the use of mice including using algorithmic approaches to animal modelling, ethic-exempt insects for foundation processes (fig 1), 2-D and 3-D tissue cultures, organoids and “organs on a chip”. Digital twins have been used to create a virtual model of mice and require exploration in the research space (fig 2).

Digital Twins

Digital twins are a virtual version or digital replica created of an actual object (fig 3). In drug and probe development, digital twins of genetic strains of mice could be used for pharmacokinetic and compartment modelling with vary parameters (eg. tumour or control) and / or doses (drug or radiopharmaceutical) to predict outcomes (eg. metabolism, elimination, radiation dose, renal toxicity etc.). This could be used to optimise experimental methods while minimising the number of both mice and experimental arms required (fig 3). In this case, multiple copies (instances) of a control and experimental mouse would be made of the digital twin. A large number of instances could replicate on a larger scale some aspects of mouse based pre-clinical investigations.

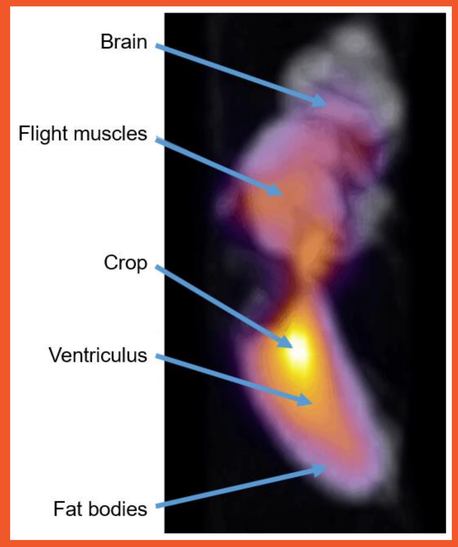


Figure 1 (left): PET/CT image of a bee demonstrating movement of orally administered 18F FDG into the hemolymph and distribution to flight muscles and brain .

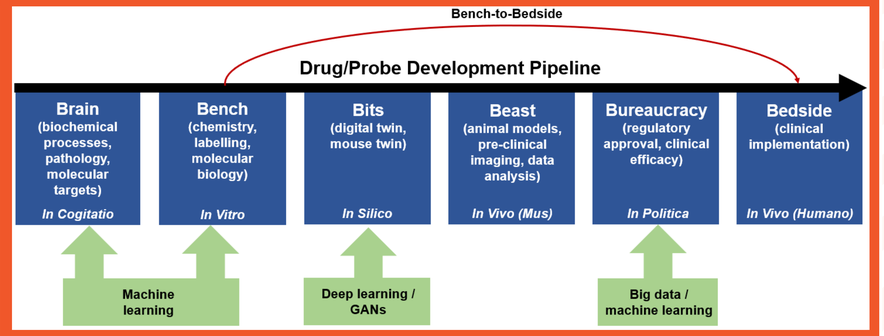
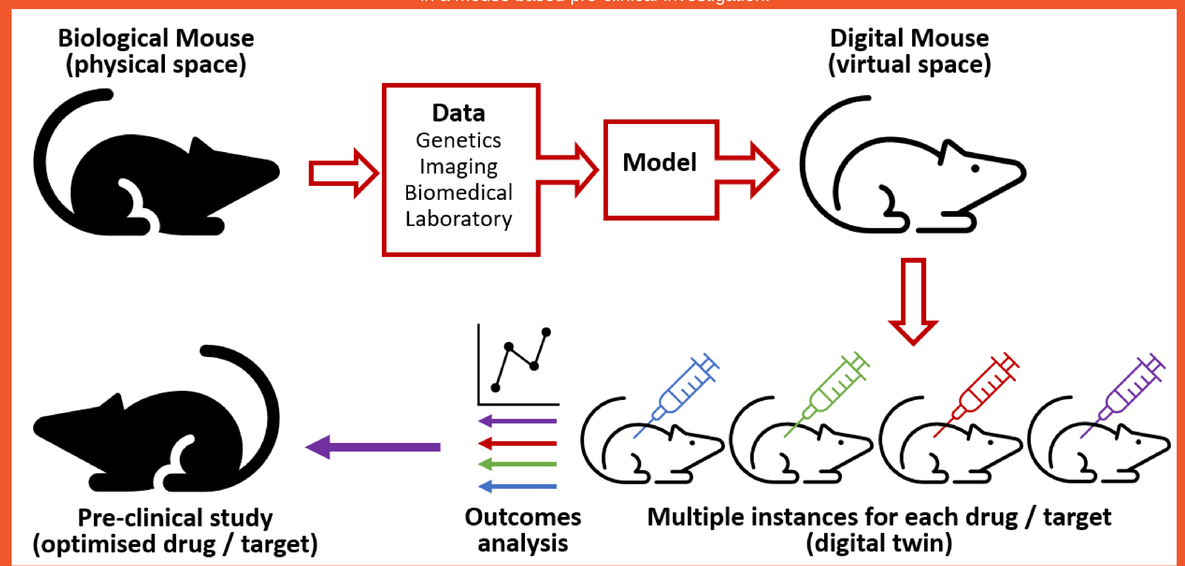


Figure 2 (above): Drug or probe development pipeline extending the bench-to-bedside maxim to include conceptual development (brain), digital twin in silico studies (bits), pre-clinical studies (beast) and the regulatory processes; the 6B pipeline.

Figure 3 (below): Schematic representation of the development phase of a digital twin from mouse data and then of the implementation of a digital twin where variations to inputs (drugs or targets) are evaluated in multiple instances of the digital twin to predict optimal drug / target for further evaluation in a mouse based pre-clinical investigation.



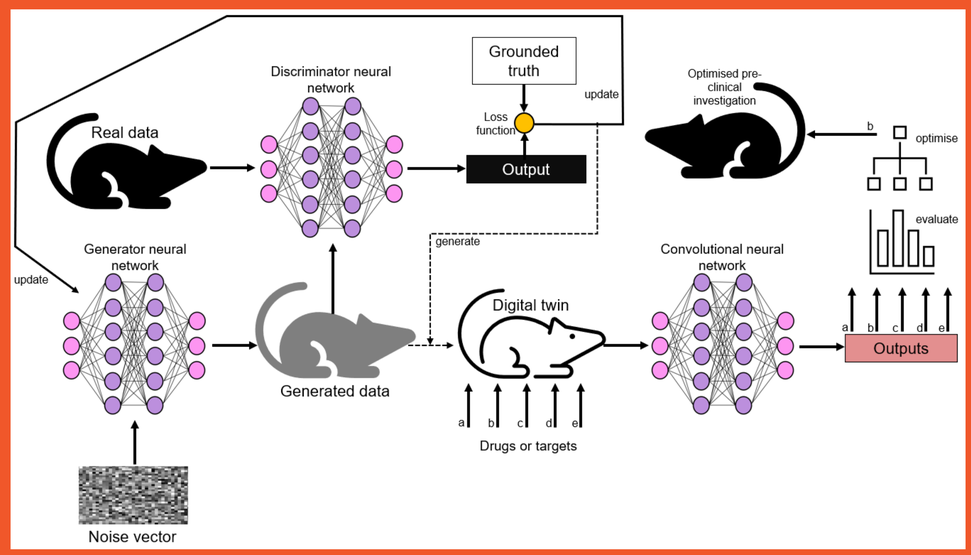


Figure 4 (above): Schematic representation of the GAN with generator and discriminator neural networks producing a digital twin. The digital twin can be replicated (instances) with multiple drugs or targets investigated to determine the optimal approach for further pre-clinical imaging.

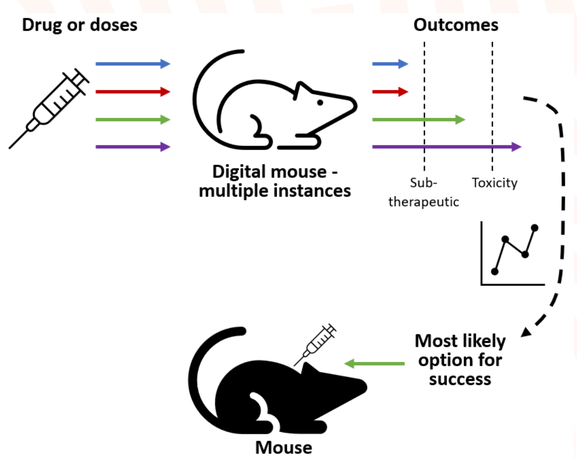
Conclusion

Pre-clinical imaging is a key part of the drug / probe development pipeline and for driving precision theranostics. The emergence of CNNs, GANs and DL have enhanced the capabilities in complex modelling that could allow digital twins (digital mouse) to substitute for some aspects of pre-clinical investigation to narrow the scope of investigations, shorten the timeline, reduce the costs and reduce the volume of mice required. This approach provides rich insights while being consistent with the foundations of animal ethics; justify (reduce), optimise (refine) and limit (replace). There remains significant work to be undertaken in this space, however, digital twin developments are likely to emerge as an important feature in the pre-clinical imaging landscape.

AI and Digital Twins

- Generative adversarial networks (GANs) have their foundations in social media and production of fake images.
- Conventional neural networks confront challenges in identifying organic images outside the training set.
- GANs have been used to generate fake images to boost the training sets and improve performance outside the training set.
- A GAN uses a discriminator neural network in tandem with a generator neural network (fig 4).
- The discriminator neural network functions the same as a CNN to predict an image classification while the generator neural network produces fake images that are fed into the discriminator neural network.
- The GAN could be adapted to create digital twins.
- GAN based digital twins have been reported in the broader medical literature, including in radiation oncology, but there is a paucity associated with molecular imaging and pre-clinical imaging.
- Rich mouse data and specific mouse-model conditions can be used in a generative model to create a probabilistic digital twin.
- The point of digital twins is to model the heterogeneity of data among complex individuals but difficulties with that kind of data generally results in more homogenous representation of key model functions.
- Specific genetic mouse models or strains have greater homogeneity making them more receptive to modelling and suitable specifically for digital twin simulation.

Summary



References:

1. Currie G. Biodistribution of 18F FDG post oral administration to a honeybee (apis mellifera); PET/CT proof of concept. *Journal of Nuclear Medicine*. 2019;60:1493.
2. van Riel N, Müller R, Dall’Ara E. The Digital Mouse: why computational modelling of mouse models of disease can improve translation. bioRxiv preprint. 2020.05.04.075812; doi: https://doi.org/10.1101/2020.05.04.075812
3. Currie, G & Rohren E 2022, Radiation dosimetry, artificial intelligence and digital twins: old dog, new tricks, *Seminars in Nuclear Medicine*, vol. 52; pp. 498-503.

Scan the QR code for more advanced practice info.