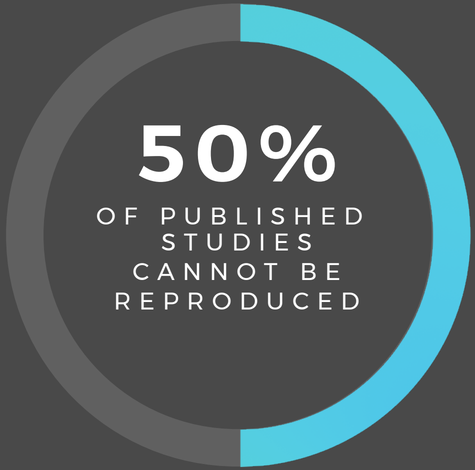
BIOVOLUME®

A GLOBALLY CONNECTED AI IMAGING AND ANALYSIS PLATFORM REVOLUTIONISING THE COLLECTION OF SUBCUTANEOUS TUMOUR DATA IN PRE-CLINICAL ONCOLOGY.

MORE THAN 50% OF PRE-CLINICAL STUDIES CANNOT BE REPRODUCED



50%

OF PUBLISHED STUDIES CANNOT BE REPRODUCED

COSTING THE PRE-CLINICAL INDUSTRY

$28.8BN

ANNUALLY.

PLOS Biology, The Economics of Reproducibility in Preclinical Research

EFFECTS OF ANTI-CANCER DRUGS CAN BE EASILY MISSED

[WITH CALIPERS] AS TUMORS WILL TEND TOWARDS BEING DETERMINED WITH A GREATER BIAS AS THEY GROW LARGER.

Ishimori et al. Acad Radiol2005; 12:776–781

CREATING A COMMERCIAL CHALLENGE

JOURNEY FROM

LAB TO PATIENT = 12 YEARS

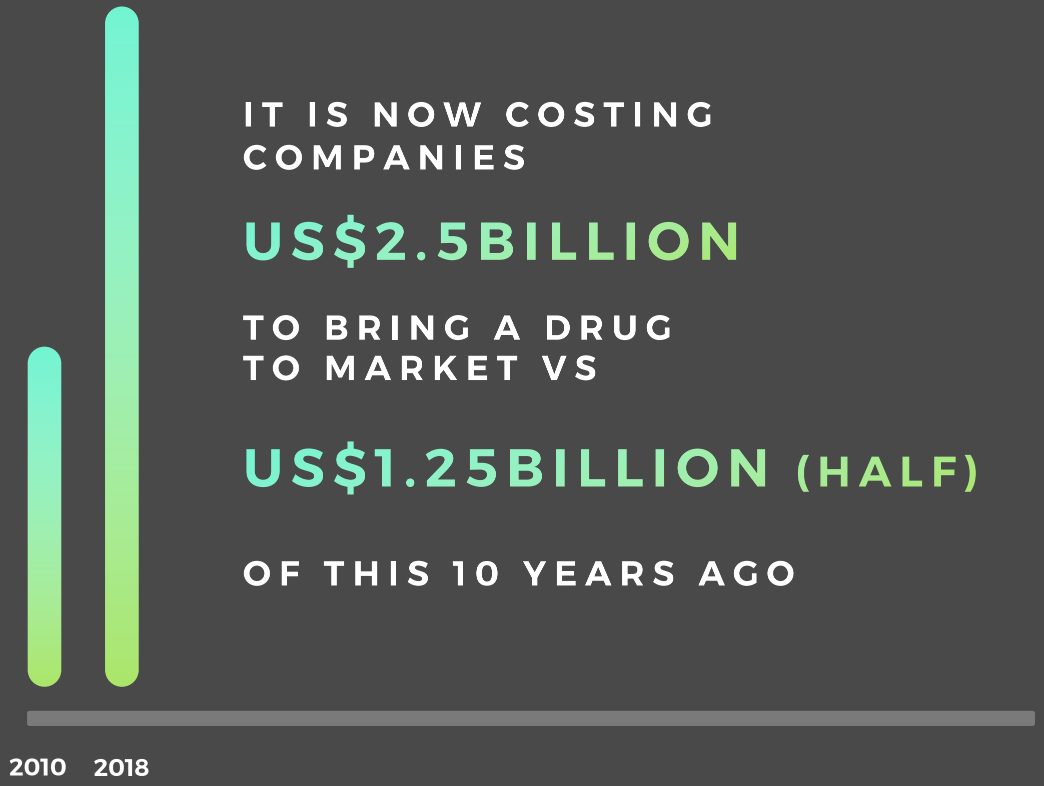
5 IN 5,000

DRUGS THAT BEGIN PRE-CLINICAL TESTING MAKE IT TO HUMAN TESTING

1 IN 5

WILL NEVER BE APPROVED FOR HUMAN USE

Hollingshead. JNCI. Vol. 100, Issue 21, November 5, 2008



IT IS NOW COSTING COMPANIES

US$2.5BILLION

TO BRING A DRUG TO MARKET VS

US$1.25BILLION (HALF)

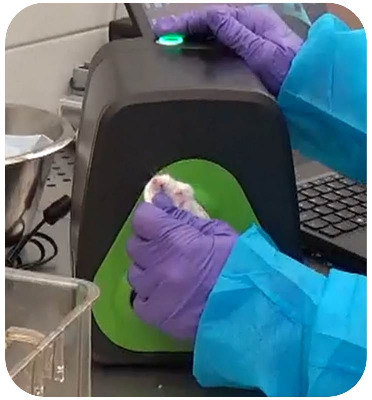
OF THIS 10 YEARS AGO

Scientific American – Cost to Develop New Pharmaceutical Drug Now Exceeds $2.5B. – Rick Mullin.

FUEL3D
SHAPING FUTURES

BIOVOLUME PROCESS

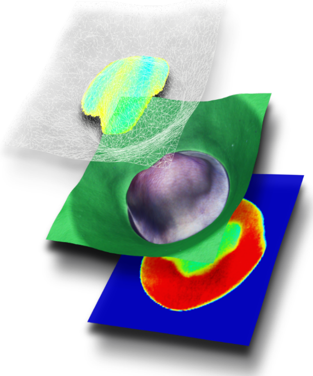
SCANNER, LAPTOP

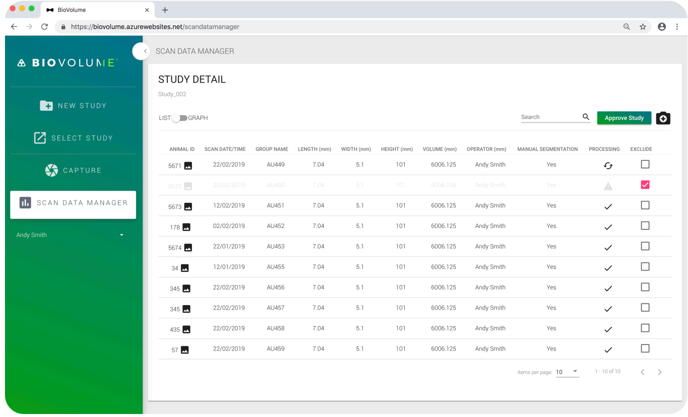


3D & THERMAL CAPTURE

AZURE CLOUD PLATFORM

3D STEREO





SCAN DATA MANAGER

STUDY DETAIL

Study_002

LIST GRAPH

Search

Approve Study

ANIMAL ID	SCAN DATE/TIME	GROUP NAME	LENGTH (mm)	WIDTH (mm)	HEIGHT (mm)	VOLUME (mm)	OPERATOR (mm)	MANUAL SEGMENTATION	PROCESSING	EXCLUDE
5671	22/02/2019	AU449	7.04	5.1	101	6006.125	Andy Smith	Yes	↻	☐
5672	22/02/2019	AU450	7.04	5.1	101	6006.125	Andy Smith	Yes	⚠	☑
5673	12/02/2019	AU451	7.04	5.1	101	6006.125	Andy Smith	Yes	✓	☐
178	02/02/2019	AU452	7.04	5.1	101	6006.125	Andy Smith	Yes	✓	☐
5674	22/01/2019	AU453	7.04	5.1	101	6006.125	Andy Smith	Yes	✓	☐
34	12/01/2019	AU455	7.04	5.1	101	6006.125	Andy Smith	Yes	✓	☐
345	22/02/2019	AU456	7.04	5.1	101	6006.125	Andy Smith	Yes	✓	☐
345	22/02/2019	AU457	7.04	5.1	101	6006.125	Andy Smith	Yes	✓	☐
435	22/02/2019	AU458	7.04	5.1	101	6006.125	Andy Smith	Yes	✓	☐
57	22/02/2019	AU459	7.04	5.1	101	6006.125	Andy Smith	Yes	✓	☐

Items per page: 10

1 - 10 of 10

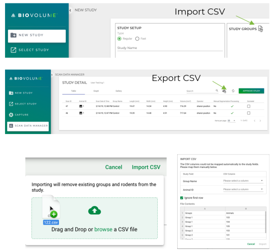
THERMOGRAPHY

RECONSTRUCT

SEGMENT

ANALYISE

INTEGRATE



Importing will remove existing groups and rodents from the study.

Drag and Drop or browse a CSV file

The CSV columns could not be mapped automatically to the study fields. Please map them manually below.

studylog

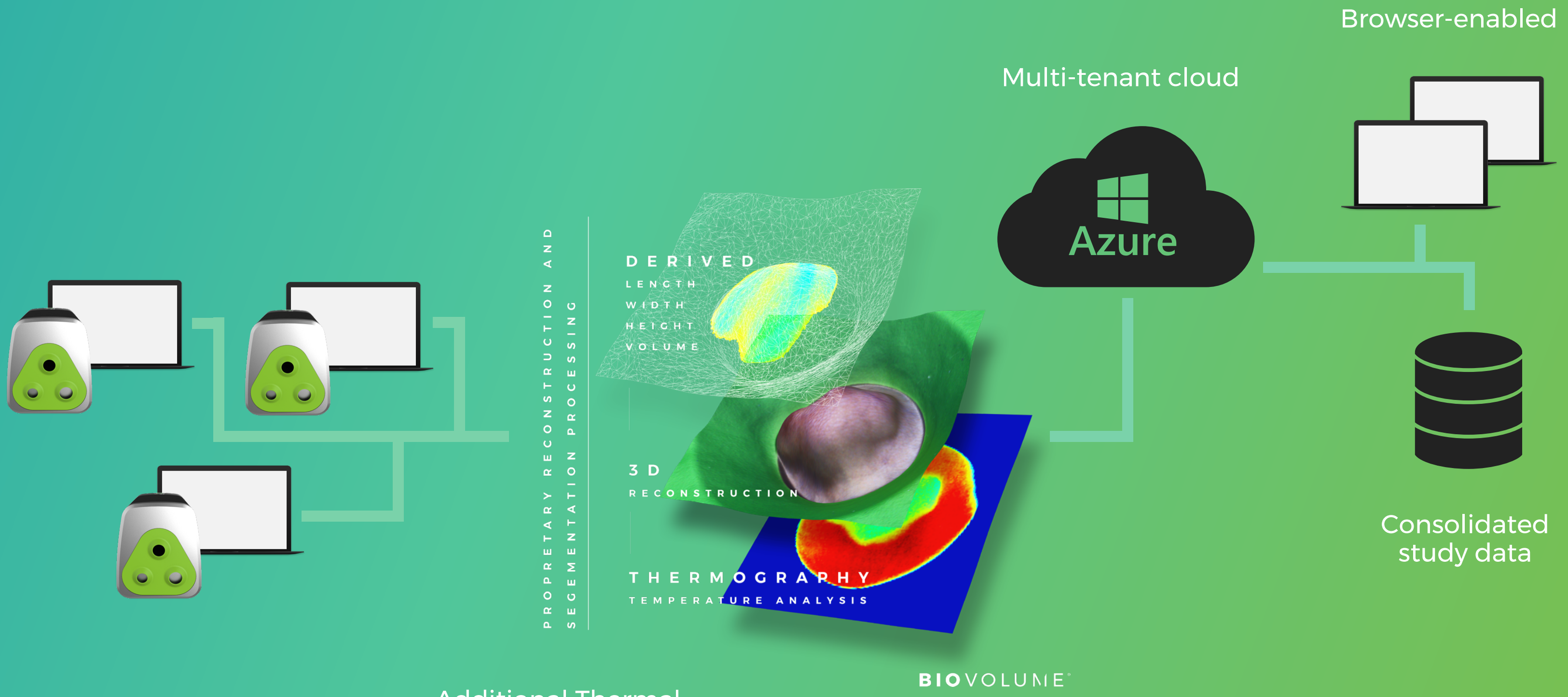
SOMARK

IMPORT EXPORT API

STATISTICS & MACHINE LEARNING ON AZURE

GREATER TRACEABILITY - THROUGH A CLOUD PLATFORM

- + THERMAL CAPTURE
- + MULTI-TENANTED CLOUD PROCESSING
- + BIG DATA SET
- + BROWSER ENABLED
- + CONSOLIDATED STUDY DATA & ANALYTICS DASHBOARD



Additional Thermal Capture to aid accuracy and precision

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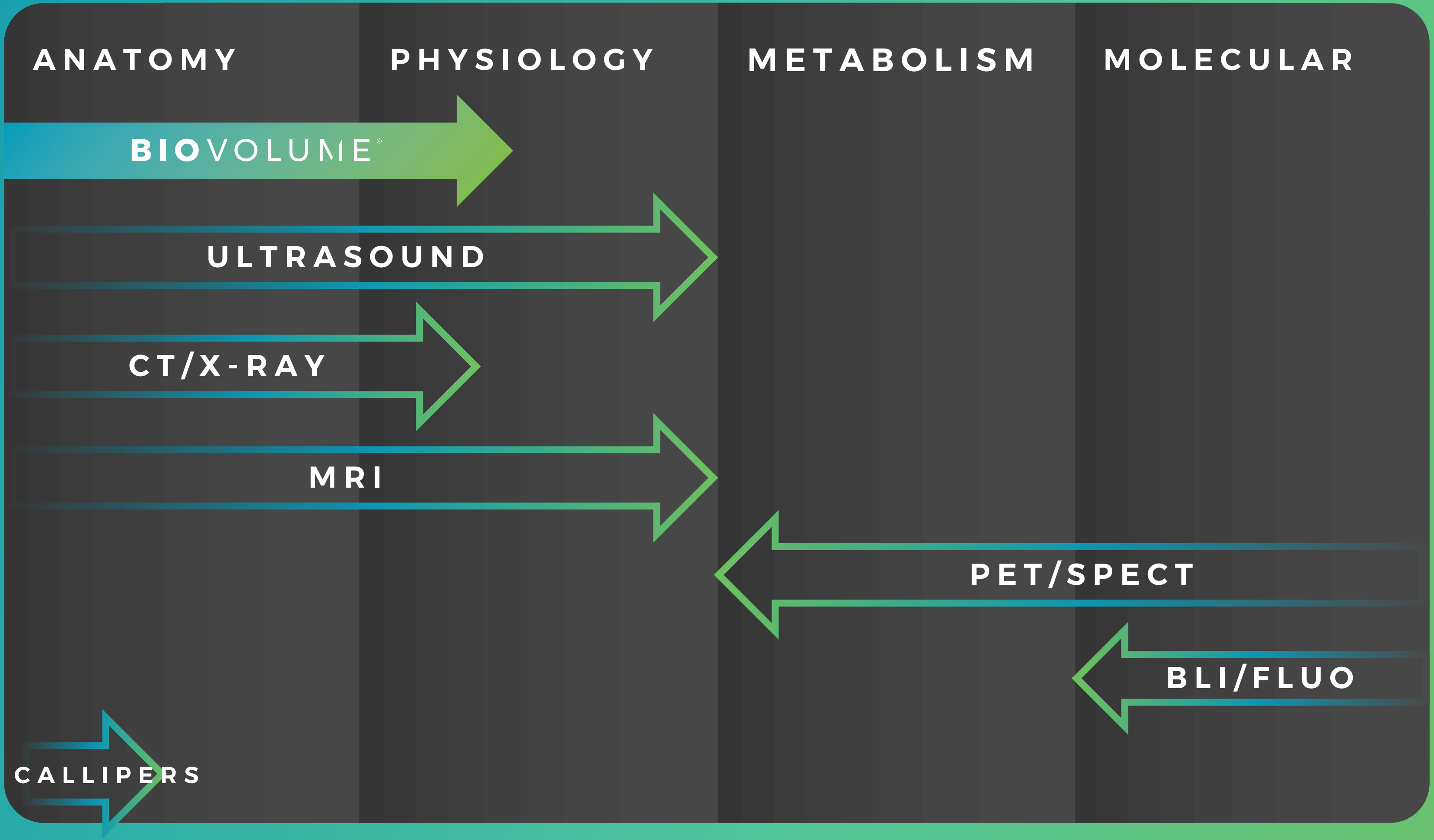
MUCH MORE THAN CALLIPERS



ANATOMY

PHYSIOLOGY

METABOLISM

MOLECULAR

BIOVOLUME®

ULTRASOUND

CT/X-RAY

MRI

PET/SPECT

BLI/FLUO

CALLIPERS

FUEL3D
SHAPING FUTURES

GLOBAL DATASET NOW IN EXCESS OF 10,000 SCANS

31^{ST} May

Total scans: 6,532

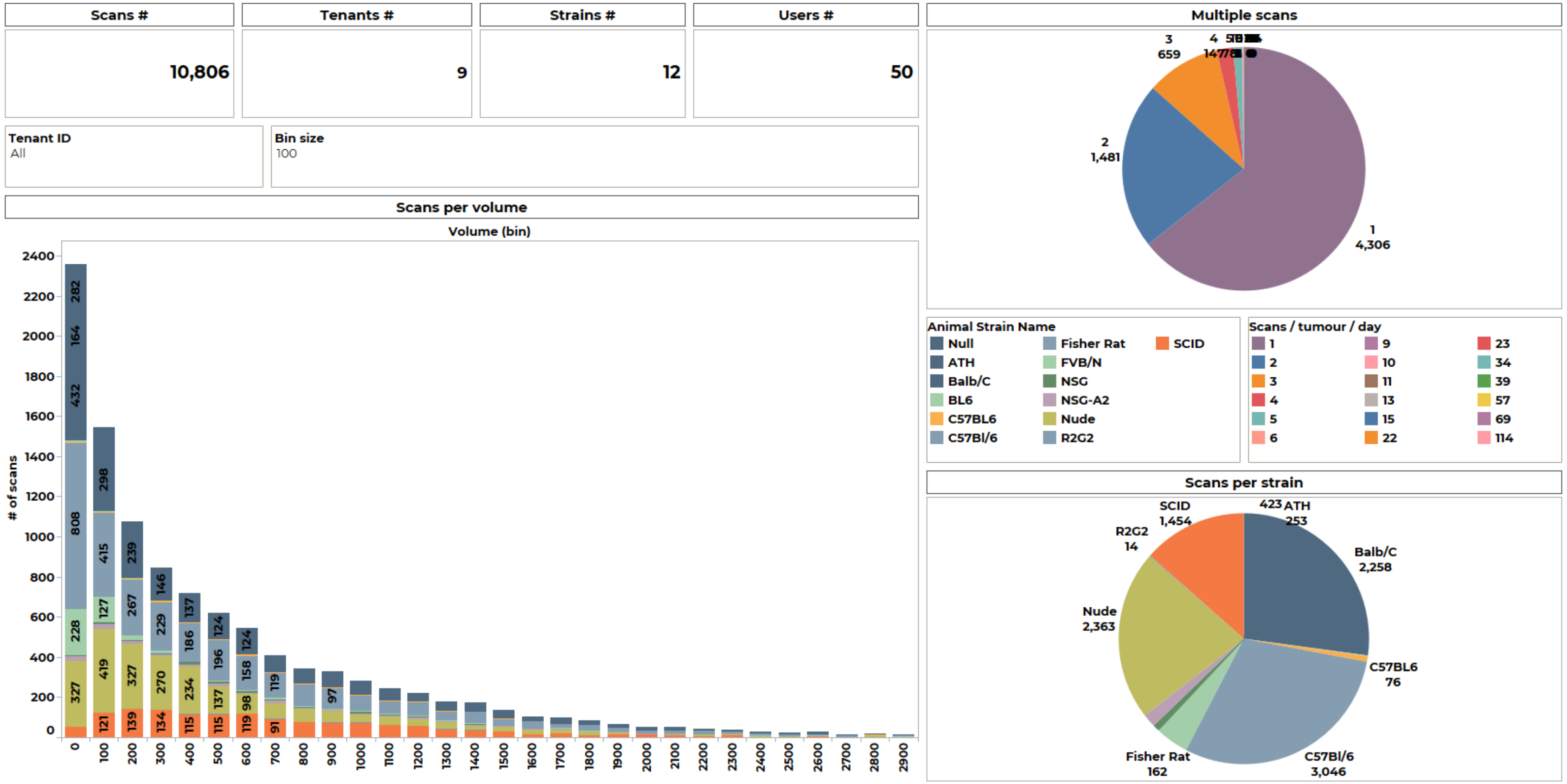
8^{TH} August

Total scans: 8,561

13th September

Total scans:

10,806



Scans #	Tenants #	Strains #	Users #
10,806	9	12	50

Tenant ID
All

Bin size
100

FUEL3D
SHAPING FUTURES

IMPROVING THE SCIENCE THROUGH DIGITISATION AND DATA

BASED ON CURRENT FORECASTS WE WILL HAVE

200

UNITS

IN OPERATION MID-2020

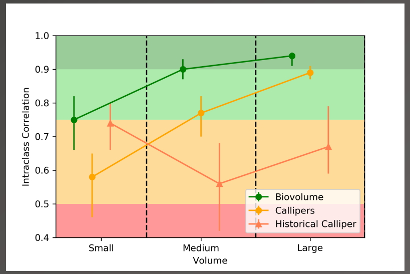
NUMBER OF UNITS	200	
EACH UNIT TAKES	80	A DAY
EACH UNIT USED	5	DAYS A WEEK
UNIT USED OVER	12	MONTHS

TOTAL DATA COLLECTED **960,000**

FUEL3D
SHAPING FUTURES

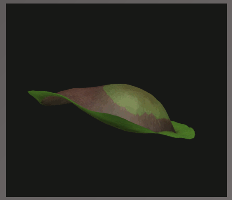
TRANSFORMING THE SCIENCE

Untraceable – single study
Caliper measurements



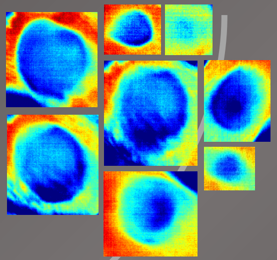
Statistically significant
Improvement in
Inter-operator performance

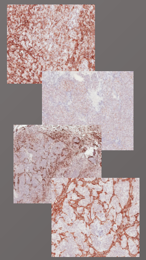
Fully traceable global dataset
Eliminating data and user error



3D analysis of tumour volume

Assessment of tumour condition throughout growth





Assessment of tumour thermal signatures
To understand histology

A fully traceable cloud connect platform is designed to transform the way drug efficacy is monitored and understood

CONTINUOUS LEARNING

ARTIFICIAL INTELLIGENCE EFFORT

USES OF AI AT FUEL3D

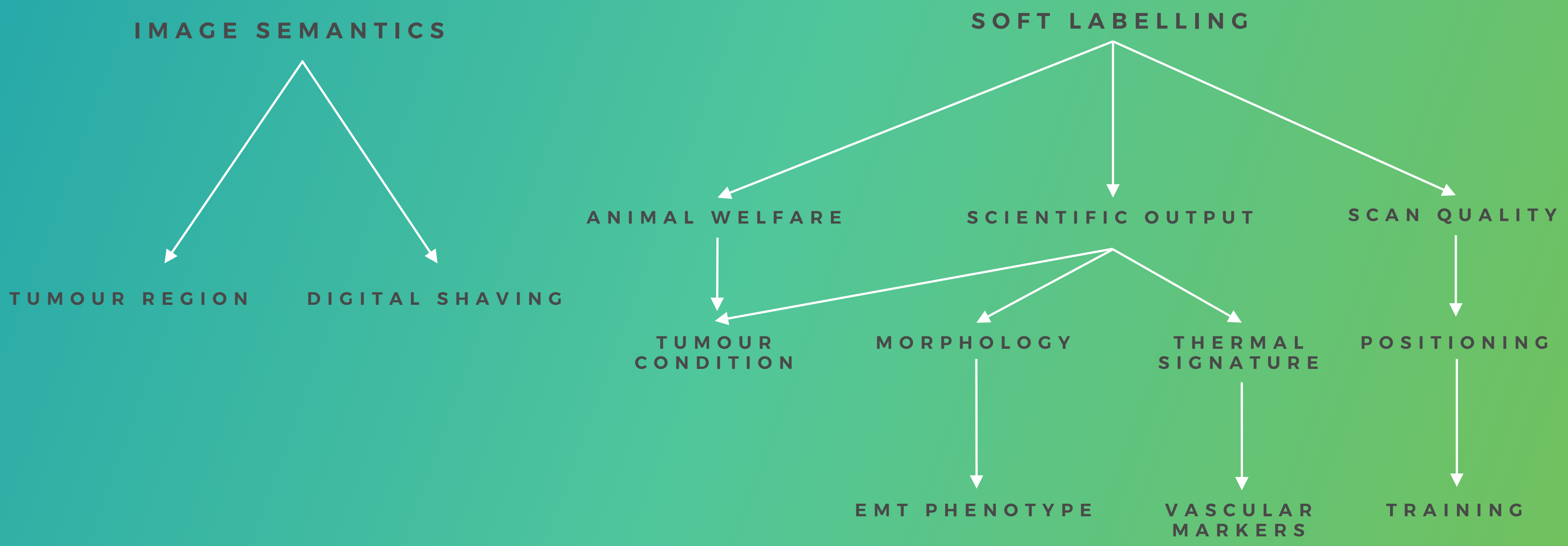


IMAGE SEMANTICS

TUMOUR REGION

DIGITAL SHAVING

SOFT LABELLING

ANIMAL WELFARE

SCIENTIFIC OUTPUT

SCAN QUALITY

TUMOUR CONDITION

MORPHOLOGY

THERMAL SIGNATURE

POSITIONING

EMT PHENOTYPE

VASCULAR MARKERS

TRAINING

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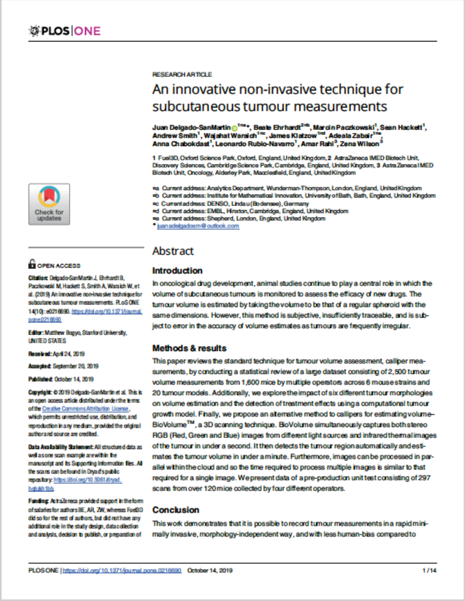
PUBLISHED PLOS 1 – OCT 2019 - An innovative non-invasive technique for subcutaneous tumour measurements



RESEARCH ARTICLE

An innovative non-invasive technique for subcutaneous tumour measurements

Juan Delgado-SanMartin[1¤a*], Beate Ehrhardt[2¤b], Marcin Paczkowski[1], Sean Hackett[1], Andrew Smith[1], Wajahat Waraich[1¤c], James Klatzow[1¤d], Adeala Zabair[1¤e], Anna Chabokdast[1], Leonardo Rubio-Navarro[1], Amar Rahi[3], Zena Wilson[3]

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Check for updates

Citation: Delgado-SanMartin J, Ehrhardt B, Paczkowski M, Hackett S, Smith A, Waraich W, et al. (2019) An innovative non-invasive technique for subcutaneous tumour measurements. PLoS ONE 14(10): e0216690. https://doi.org/10.1371/journal.pone.0216690

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Data Availability Statement: All structured data as well as one scan example are within the manuscript and its Supporting Information files. All the scans can be found in Dryad's public repository: https://doi.org/10.5061/dryad.hqbzkh1bb.

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Abstract

Introduction

In oncological drug development, animal studies continue to play a central role in which the volume of subcutaneous tumours is monitored to assess the efficacy of new drugs. The tumour volume is estimated by taking the volume to be that of a regular spheroid with the same dimensions. However, this method is subjective, insufficiently traceable, and is subject to error in the accuracy of volume estimates as tumours are frequently irregular.

Methods & results

This paper reviews the standard technique for tumour volume assessment, calliper measurements, by conducting a statistical review of a large dataset consisting of 2,500 tumour volume measurements from 1,600 mice by multiple operators across 6 mouse strains and 20 tumour models. Additionally, we explore the impact of six different tumour morphologies on volume estimation and the detection of treatment effects using a computational tumour growth model. Finally, we propose an alternative method to callipers for estimating volume–BioVolume™, a 3D scanning technique. BioVolume simultaneously captures both stereo RGB (Red, Green and Blue) images from different light sources and infrared thermal images of the tumour in under a second. It then detects the tumour region automatically and estimates the tumour volume in under a minute. Furthermore, images can be processed in parallel within the cloud and so the time required to process multiple images is similar to that required for a single image. We present data of a pre-production unit test consisting of 297 scans from over 120 mice collected by four different operators.

Conclusion

This work demonstrates that it is possible to record tumour measurements in a rapid minimally invasive, morphology-independent way, and with less human-bias compared to

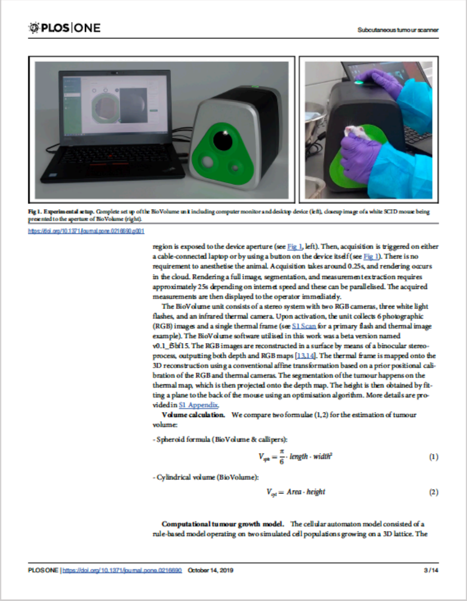

Fig 1. Experimental setup. Complete set up of the BioVolume unit including computer monitor and desktop device (left), closeup image of a white SCID mouse being presented to the aperture of BioVolume (right).

https://doi.org/10.1371/journal.pone.0216690.g001

region is exposed to the device aperture (see Fig 1, left). Then, acquisition is triggered on either a cable-connected laptop or by using a button on the device itself (see Fig 1). There is no requirement to anesthetise the animal. Acquisition takes around 0.25s, and rendering occurs in the cloud. Rendering a full image, segmentation, and measurement extraction requires approximately 25s depending on internet speed and these can be parallelised. The acquired measurements are then displayed to the operator immediately.

The BioVolume unit consists of a stereo system with two RGB cameras, three white light flashes, and an infrared thermal camera. Upon activation, the unit collects 6 photographic (RGB) images and a single thermal frame (see S1 Scan for a primary flash and thermal image example). The BioVolume software utilised in this work was a beta version named v0.1_f5bf15. The RGB images are reconstructed in a surface by means of a binocular stereo-process, outputting both depth and RGB maps [13,14]. The thermal frame is mapped onto the 3D reconstruction using a conventional affine transformation based on a prior positional calibration of the RGB and thermal cameras. The segmentation of the tumour happens on the thermal map, which is then projected onto the depth map. The height is then obtained by fitting a plane to the back of the mouse using an optimisation algorithm. More details are provided in S1 Appendix.

Volume calculation. We compare two formulae (1,2) for the estimation of tumour volume:

- Spheroid formula (BioVolume & callipers):

$$V_{sph} = \frac{\pi}{6} \cdot length \cdot width^2 \quad (1)$$

- Cylindrical volume (BioVolume):

$$V_{cyl} = Area \cdot height \quad (2)$$

Computational tumour growth model. The cellular automaton model consisted of a rule-based model operating on two simulated cell populations growing on a 3D lattice. The

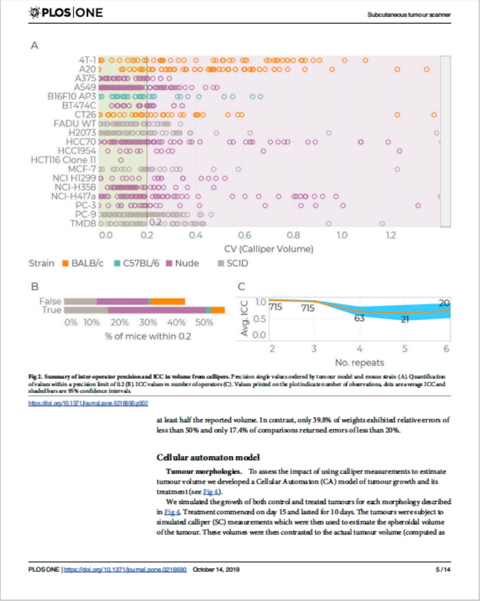

Fig 2. Summary of inter-operator precision and ICC in volume from callipers. Precision single values ordered by tumour model and mouse strain (A). Quantification of values within a precision limit of 0.2 (B). ICC values vs number of operators (C). Values printed on the plot indicate number of observations, dots are average ICC and shaded bars are 95% confidence intervals.

https://doi.org/10.1371/journal.pone.0216690.g002

at least half the reported volume. In contrast, only 39.8% of weights exhibited relative errors of less than 50% and only 17.4% of comparisons returned errors of less than 20%.

Cellular automaton model

Tumour morphologies. To assess the impact of using calliper measurements to estimate tumour volume we developed a Cellular Automaton (CA) model of tumour growth and its treatment (see Fig 4).

We simulated the growth of both control and treated tumours for each morphology described in Fig 4. Treatment commenced on day 15 and lasted for 10 days. The tumours were subject to simulated calliper (SC) measurements which were then used to estimate the spheroidal volume of the tumour. These volumes were then contrasted to the actual tumour volume (computed as

https://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0216690&type=printable

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SHAPING FUTURES

MORE DATA, BETTER SCIENCE: A GREATER ADVANTAGE

- REPRODUCIBLE RESULTS
- GREATER SCIENTIFIC CONFIDENCE
- BETTER TRACEABILITY

INTRODUCING NEW BIOMARKERS:

- TUMOUR CONDITION
- VASCULAR PHYSIOLOGICAL MARKERS

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