AI and Preclinical Animal Research; Better Welfare & Better Data

Introducing AI in Biomedical Science

Computing power, data handing capacity and the ability to automate science have been increasing roughly exponentially since the 1960s [1]. These technological leaps have transformed all areas of society, science, including biology and, of particular relevance here, many areas of drug discovery and development. In the past few years, a key emerging trend in relevant biomedical technology has been the introduction of Artificial Intelligence (AI) as a tool to handle the vast torrents of data and to help discover organising principles hidden within these data. There are already many embodied examples of AI used in healthcare and the diverse spectrum of applications ranges from the development of small, often wearable, devices that recognise, record and monitor physiological biomarkers generated by biological function (e.g. Heart rate, Blood Pressure, Respiration rate & Temperature) and give us indications of our general health status, all the way to AI driven computational platforms that can process thousands of clinical samples in seconds to identify potential pathology in medical images [2].

A brief look at any vivarium today whether academic, biotech, government or pharma shows that these developments are already starting to have an impact on how experiments are designed and performed. Efforts over the last 30 years have seen many elements of computer vision, machine learning and AI deployed for the capture, analysis and tracking of animals in behavioural assays [3][4][5]. However, the application of AI in the area of animal welfare in the vivarium is more limited. Welfare assessment remains predominantly manual and relies on time and resources to check individual animals for health and well-being as frequently as needed. We check for signs of disease, we check for signs of efficacy with specific challenge tests, yet apart from cursory welfare checks and the key experiments, our animals in research studies spend the vast majority of their lives left entirely unobserved in their home cages.

We firmly believe the lack of adoption of AI for automated behavioural analysis represents two broad sets of opportunities that we cannot afford to miss: First, continual, and automated behavioural monitoring removes much of the technical handling required for welfare assessment (reduced stress) while at the same time filling in the gaps that would be unobserved in traditional assessment methods. Second, the same data stream is equally relevant to the study and represents valuable additional data that can be used to test safety and efficacy, perhaps even replacing additional studies entirely.

The Scope of AI — from Databases to Biomarkers

Big tech and big pharma have a history of high profile partnerships and many of these include leading names in AI including Amazon, Apple, Google, IBM, Meta to name but a few, but the key advances appear to be mostly in data handling, mathematical and chemical modelling as well is in the areas of proteomics and metabolomics [6]. The ability of AI to scan vast libraries of compounds and match these with therapeutic areas and specific 3D models of molecular targets is fairly easy to understand. These include areas of drug design [7] and pharmacokinetic prediction [8].

There is little debate on the benefits of AI where it is already used to scan large databases and collate the most up to date information on standards of care and clinical practice, to manage workflows and discover new knowledge. However, how do we take these opportunities and apply the power of AI to the ethical treatment of animals in a preclinical laboratory setting? The application of AI to the home cage provides an unparalleled opportunity to improve welfare and gather orders of magnitude more data points for preclinical research. This is the challenge that the scientists and engineers at Actual Analytics endeavour to answer, and while the value of true Home Cage Monitoring is readily apparent to those already using such technologies [9][10][11][12][13], the vast majority of vivarium staff are only just beginning to see the potential.

A key point of synergy between modern AI techniques, and the longitudinal data produced by continuous monitoring, is the potential to combine diverse streams of complex data to create new compound biomarkers in the digital domain. The use of such digital biomarkers in clinical studies is[IM1] well documented, and all signs are that these are increasingly important in clinical efficacy studies. For example, Phase 2 clinical studies for efficacy increasingly rely on digital biomarkers to track patient locomotion and vital signs throughout the duration of a clinical trial. It has been noted that such digital technology allows study directors to collect important biometric data and also encourages compliance with the study. The ability to collect data in real time or in near real time, and to be able to interact with this has multiple implications ranging from identifying the correct populations for studying the efficacy of a particular drug as well as improving the management of resources during a study. In the preclinical sphere there has been scarce insight as to how and what AI will do to enhance the well-being of the animals we use for in vivo experimentation. However, there is already evidence that AI utilization is being effectively applied to veterinary, livestock and free-living large animal areas [6], [14].

Monitoring the Individual – the Key to Mitigating Risk

Actual Analytics Ltd is a pioneer in the area of Home Cage Monitoring of individual animals in grouped housing. The ability to monitor at a cohort level is integral to preclinical efficacy and safety studies but the ability to monitor individual animals, remotely and at all times through the length of a preclinical in vivo drug trial, is also important. This ability to monitor an individual within a group is a feature that remains largely elusive to other products in the sector – yet it is of crucial importance – especially when one considers the value of translating preclinical observations to the domain of clinical trials, where potential insights hinge on an accurate understanding of the variation between individual participants.

It is now well known that careful selection of relevant individuals and active engagement and education of trial participants are important precursors to high quality clinical trials. These steps provide assurance that the participants are relevant to the study, that the test regime is understood and therefore compliance with it will be more likely. In turn this reduces the likelihood that participants drop out of studies resulting in study failure due to being underpowered or because the study is skewed by inappropriate inclusion of the wrong participants. The readiness to enter a clinical trial, the physical condition of the participant and the ability of the participant to be supported by social structures (friends, family, caregivers) are all issues that need to be addressed.

Perhaps surprising to some, there is a preclinical correlate of these preparations where we should be carefully assessing the baseline behaviour of our animals; their physical condition, background circadian rhythm and home-cage dynamics. These should be all be known and where relevant, be within satisfactory levels prior to initiating an in vivo experiment. These parameters can then be followed closely during the experiment and changes from the previous base-line attributed to the research condition. Thus, continuous monitoring of animals before as well as during the study mitigates the risk of experimental failure due to animals that are in bad condition, are not suited to their home-cage grouping and/or not full acclimatized to their test environment or are extreme behavioural outliers.

AI offers a bright future for translational research: It enables a new set of behavioural, histopathological and molecular endpoints produced from preclinical studies that can be more readily reconciled with the biomarkers provided by the clinical stages of drug development. We can therefore expect a more direct translation between the clinic and the biomarkers of disease and of drug efficacy at the preclinical stage. This will reduce the risk and cost associated with drug development and allows for less subjectivity in the trial process. How these methods are implemented is vitally important: While measuring average cage level events is certainly useful, one must recognise the risk in averaging across individuals: It is easy to imagine a scenario where three animals, one ‘normal, one ‘hyperactive’ and one ‘hypoactive’ appear, when averaged, as all normal. Moreover, recovering and tracking the individual identity allows us to extract pair-wise social interactions (see Figure 1) which are powerful biomarkers for both welfare and efficacy.

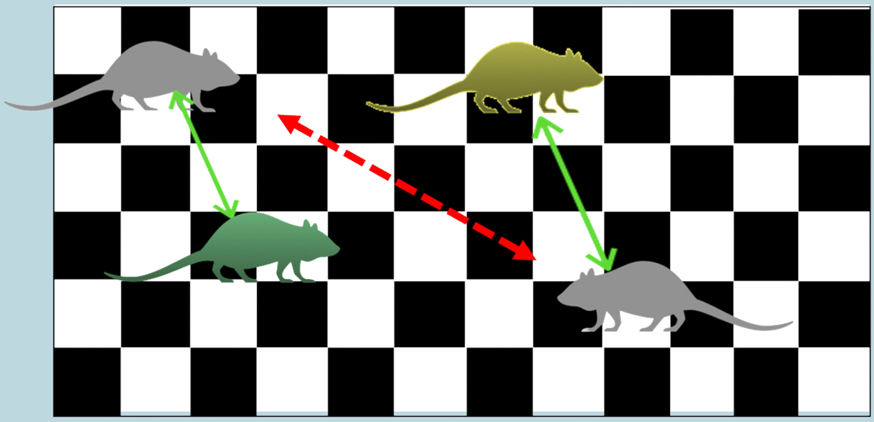

Figure 1. Examination of social separation in the home cage. Spatiotemporal data, such as those measured by ActualHCA, allow the operator to focus on each individual animal over long periods of time. In the example above extreme changes in social distancing by an individual within the group can be used as a possible indication of depression, anxiety, unsettled home cage dynamics and a possible general lack of wellbeing for that individual animal. Mitchel et al. demonstrated the power of this approach in identifying a measurable effect of PCP treatment on the social behaviour of rats [15]and used a similar approach to quantify social effects in a mouse model of Autistic Spectrum Disorder [10]

Enabling Ethical Research – Addressing the 3Rs

The 3Rs (Replacement, Reduction and Refinement) provide the ethical framework for the treatment of laboratory animals and underpin the modern approach to developing experimental studies involving animals [16][17]. Using AI and machine learning to track and check the wellbeing of animals in the system goes beyond simple locomotor activity monitoring and extends to include eating and drinking behaviour, measurement of stereotactic and social behaviours all of which are indicative of quality of life. The ability to have an incident, or a set of incidents, recorded with a time stamp allows the scientist to go back to the scene of the incident and observe what was happening in the cage at that time. This allows us to remotely view, without handling or otherwise disrupting the animals, the individual events and social relationships in the home cage. A unique identifier for each animal allows us to quickly discern the nature of the problem and where required intervene or look for external sources which may include noise, light and operator behaviours in the vivarium.

Figure 2. A) In ActualHCA, each individual animal is assigned a unique identifier (from its RFID tag) which allows a scientist to go back to the time of any event (as defined by the data) in the home cage and focus on the behaviours and functions of that specific animal. AI allows us to simultaneously track complex behaviours in the home cage but also allow us to single out one animal and potentially define alarms for if/when this animal deviates from an expected “normal” in the home cage. B) The architecture of the Actual Analytics system supports remote viewing. This allows for a referral to scientists, technicians and veterinarians as well as other collaborators through a live, remote video connection and also through the exportation/sharing of all processed video and analogue data in standard open formats.

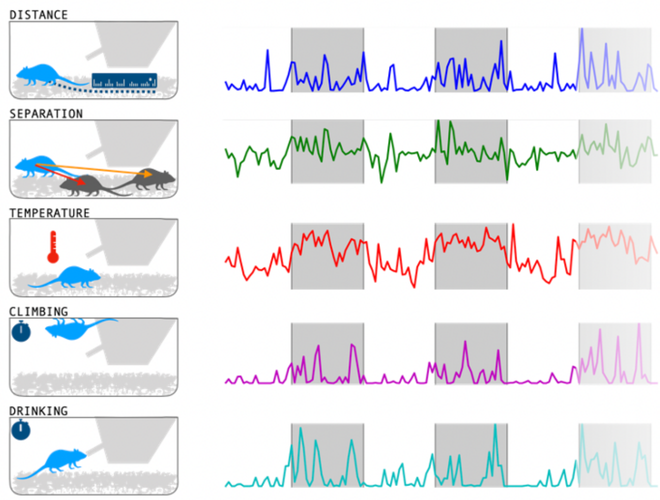

Figure 3. Examples of some key home cage functions and behaviours measured by ActualHCA. These measures can all be used singly and used to monitor each animal within the social group or can be combined to form more complex digital biomarkers which can track quality of life for welfare monitoring or in different combinations may be used to track efficacy.

In a similar vein, the monitoring of an individual in a human clinical trial is of primary importance to the success, or the failure of that trial. This monitoring is important in terms of compliance as well as the ability of trial operators to pick up any previously unsuspected safety issues with the test article. Failed clinical trials, often show, in retrospect, the unsuitability of certain individuals in clinical trials [18] – especially when the trial has become under powered due to patient drop out [19]. Given the importance of the individual in the clinic it is surprising that individual animal data in pre-clinical in vivo testing stage appears to be frequently overlooked. The development of AI methods in this area offers a credible solution, but this in turn requires high-quality data streams capable of revealing subtle behavioural variations.

Recognising its potential in underpinning a new generation of pre-clinical models, Actual Analytics has pioneered the longitudinal monitoring of rodents in their home cage. ActualHCA provides comprehensive longitudinal data streams from group housed rats or mice during the in vivo phases of safety and efficacy studies. The ability to monitor spatial position and locomotor activity and derive metrics from this which can be analysed are inherent within ActualHCA, as they are with other similar products with the major difference being that ActualHCA measures these with respect to each individual within a social group. The contribution of other behaviour parameters provides a unique insight into each animal in the cohort and the dynamic changes that happen during studies.

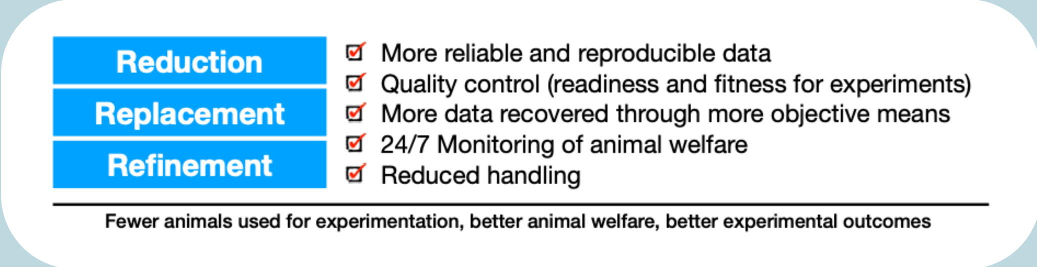

Figure 4 The 3Rs principles and the benefits of continuous automated home cage monitoring

Conclusion

Home cage monitoring already offers clear and convincing 3Rs benefits while enhancing data quality and quantity. The story is not complete, and a promising future lies ahead. AI methods such as those discussed here provide the potential to monitor new behavioural biomarkers, delivering new capabilities and even to be expanded to permit the integration of new data sources. It is the explicit intention of Actual Analytics and its partners to disrupt, elaborate and improve on the science produced in the preclinical phases of drug development using AI applied through the ActualHCA platform.

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