Proc. Assoc. Advmt. Anim. Breed. Genet: 24: 10-13

MEASUREMENT ENABLED PRECISION INTERVENTIONS: A FUTURE OPPORTUNITY FOR LIVESTOCK FARMING

M.R. Hutchinson [1,2]

[1] Adelaide Medical School, University of Adelaide
[2] Australian Research Council Centre of Excellence for Nanoscale BioPhotonics

SUMMARY

When the opening ceremony of the 2032 Brisbane Olympic games is televised, it will be the first time an Olympics will be viewed by humans on Mars and the Earth's moon. Technological advances that will enable us to become a multiplanetary species, and to sustain and feed a long-term moon base are happening at such an extraordinary rate and enabling truly amazing feats of humanity. Whilst these may, at first glance, seem far-fetched ambitions, the scientific advances that are enabling these endeavours have immediate relevance to farming practices that will bring new efficiencies, productivity, new products, and ultimately new value to the producers who adopt them, and societies who purchase them. An example of these innovations will be in the explosion of measurement enabled precision interventions, based on the generation of decision enabling data. Critically, these advances will occur in human medicine before they are tested in livestock. However, the fundamental biological discoveries are still relevant and therefore innovations in human medicine can be rapidly translated to livestock. This measurement enabled understanding is extremely relevant to livestock production, where knowledge of the "mind and body" state of a dynamic and living organism is crucial. Here, a short summary of the types of technologies and biological breakthroughs they afford will be provided, with specific focus on humanities greatest health burden: PAIN.

INTRODUCTION

Diseases of the central and peripheral nervous system account for more than three quarters of the years humans live with disabilities (Institute for Health Metrics and Evaluation 2020). These diseases do not always result in death. However, disorders of the brain and spinal cord account for the greatest societal burden of disability because patients live a long time with these disorders in chronic pain or with mental health problems. Why is it that medicine and the scientific research that advances the quality use of medicines have failed to address these problems of the brain and spinal cord? The simplest and yet most important answer is that these disorders are very complex and involve multiple physiological systems. These disorders arise from developmental adaptations and involve a complex presentation of gene and environment interactions. As such, we currently lack knowledge of the "mind and body" state of the dynamic and living organism in humans. Sound familiar? We face the same shortcomings in available technology to quantify optimal strategies for livestock care and production.

Unfortunately, the acceleration of the use of precision medicine in fields like cancer which are allowing for personalisation of treatments based on measurements (mechanistic biomarkers) have not yet developed for complications of the brain and spinal cord. Some advances have been made, such as the use of advanced imaging platforms such as fMRI, PET and measurements from EEG. However, despite these isolated advances, most diseases of the central nervous system are still approached with subjective diagnosis and empirical treatment selection. Moreover, even for human medicine, these complex imaging approaches will not economically scale to diagnose and manage three quarters of the world's human population who are afflicted by disorders of the central nervous system. Let alone translate to farm based, livestock production tools. Therefore, new methods and solutions are needed that create measurement enabled precision interventions that have translational, and scalability engineered into them from the beginning.

Let’s take PAIN as an example where future innovations are needed. In livestock production, acute pain is experienced due to management procedures, such as castration and tail docking, injuries from fighting or housing conditions, diseases such as mastitis or other infections, and at time of birth. These acute injuries and acute painful experiences can transition into the persistence of pain, which has a profound impact on the wellbeing and resilience of the animal that cause increased costs and reduced productivity. Pain in animals is an experience that we are unable to reliably diagnose or quantify. Even when animals in pain are identified we are still left ineffective in verifying the success of interventional treatments. These limitations arise from our inability to objectively measure pain. This means that opportunities to add beneficial chronic pain resilience genetic traits to breeding values have yet to intentionally begin. We still use old medicines based on empirical data for the management of acute pain associated with injury, illness, and husbandry practices. We need new measurement data of the “mind and body” state of the dynamic and living organism to advance the management of pain in livestock.

Within the Australian Research Council Centre of Excellence for Nanoscale BioPhotonics we have established a decadal research program to meet this challenge. To create scalable, and hence economical fast solutions, we have harnessed light-based imaging and sensing tools to capture information from biological processes. The advantage of light based measurements is that it is capable of adapting over scales ranging from events occurring at the single molecule (nano), through to secondary and tertiary biological structures (micro) to subcellular and cellular anatomy (macro) (Hutchinson 2020). Moreover, light can be safe and non-destructive and is therefore uniquely positioned to be able to provide the desired measurement and imaging outcomes. The breakthroughs that are allowing the new use of light in these measurement technologies is afforded through optimisation of the technologies that enhance the light matter (in this case biology) interactions, creating customised light, sculpting how the light enters or interacts with matter, making structures and surfaces that allow sensing of events to occur when and where we want them and of course imaging beyond where light normally can go was needed (Hutchinson 2020). Given the brain and spinal cord are classically viewed as “dark”, the measurements and imaging here can be conducted on very low background noise. Finally, the cost to scale these technologies are rapidly decreasing and therefore they are becoming increasingly accessible to a broader range of scientists right through to handheld technologies in the field with producers.

This measurement enabled innovation is not new to the red meat industry, with the Meat and Livestock Australia implementing the Meat Standards Australia many years ago. As of mid-2021 the Meat and Livestock Australia have called for proposals on how to develop and implement the Lifetime Animal Wellbeing Index. It is critical to start efforts to improve outcomes in complex traits like pain and wellbeing from a basis of excellence in measurement. Without the development and implementation of measurement tools, significant efforts and resources can be expended that ultimately achieve suboptimal outcomes (i.e. a waste of time and money). The recent human medicine equivalent of this has been the greater than 5000% increase in opioid use in the management of pain states that have proven to be non-responsive to opioids. In fact, the Centres of Disease Control have defined opioids as contraindicated for all chronic pain (non-cancer pain) conditions owing to the substantial worsening of the individual’s quality of life and concerning fatality rates.

Unlike human medicine, many experiences of livestock husbandry care are highly standardised. This makes for establishment of a quantified best practice highly achievable. An example of a potential routine trigger for the classical presentation of a persistence of pain in animals is amputation. Whilst on the decline in livestock, surgical removal of body parts is still widespread. This practice itself causes pain, resulting from the resection (cutting) of peripheral nerves and the possible formation of traumatic neuromas and causes significant ongoing sensitisation at the level of the brain and spinal cord to mechanical stimuli. Light touch transitions to a painful response. Imagine grass blades running across sunburnt skin. The parallel amputation and the associated changes in brain and spinal cord function in humans is considered to be significantly painful (Hutchinson and Terry 2019). We cannot ever know what an animal feels or thinks and therefore we avoid anthropomorphising these states. Instead, we can use a reductionist scientific approach to examine at the molecular and cellular level events and anatomical structures of the sensory system in animals. We can then use comparative histology and classical biology to infer possible functional consequences. Using these approaches, it is possible to see the hallmarks of chronic pain in animals. This can be seen in cellular adaptations in both the injury site and within the brain and spinal cord. Importantly, these same changes are associated with the phenomenon of residual stump pain and phantom limb pain in humans. This is a prevalent experience as painful symptomatic neuromas following amputations are observed in up to a quarter of amputees. These types of measurements are now afforded through high volume and rapid light based sensing equipment, or alternatively cheap and disposable field based assays that can use light and cameras on mobile phone devices (Orth *et al.* 2018).

It is important to also realise that the field of medical neuroscience is rapidly evolving. The international effort that the opioid pandemic has triggered has resulted in thousands of new studies that have identified hundreds of previously untested targets that could provide chronic pain solutions for humans. And of course, because of the highly conserved nature of these systems, many have the potential to be applied to livestock. One major area of growth has been the realisation that a solely neuronal or electrical view of brain and spinal cord function is wrong. We now view the brain and spinal cord as capable of immune functions, literally speaking the molecular language of the immune cells that circulate around our body. This has triggered a revolution in the pain field, as pain which was once thought of as solely a neuronal wiring problem has given way to an integrated neuro and immune hypothesis of exaggerated pain (Hutchinson and Terry 2019).

Glial cells (immune-like cells of the brain and spinal cord), and peripheral immune cells circulating through the brain and spinal cord are now understood to be integral to creating and maintaining the neuroexcitatory states that underpin persistent pain (Grace *et al*. 2021). This has immense implications. Firstly, all the nerve block agents we use to "stop pain" may work to stop the "electrical signalling" of injury, but may do nothing to stop the immune signalling of pain which is able to bypass all nerve blocks and communicate directly to the brain and spinal cord to establish the foundation of chronic pain. Interestingly, the greater prevalence of exaggerated pain in females also appears to have its origins in this neuroimmune involvement, through estrogenic priming of immune functions. We know that male and female immunology differs with females more likely to have autoimmune disease. We also know that women experience up to 12 times the rate of chronic pain (Grace *et al.* 2021). Hence, the persistent pain problem, and the neuroimmune contributors are likely to be even more relevant in livestock owing to the predominance of female animals in production. Therefore, it is critical to understand this immune to brain and brain to immune communication between the peripheral immune, spinal immune and brain immune systems which create and maintain chronic pain states in livestock (Hutchinson and Terry 2019). Moreover, while neuronal processes are critical for the conduction of heightened pain, there is an anatomically distributed immune signal that triggers conduction of the exaggerated pain response (Marsh *et al*. 2021). This breakthrough provides us now with the first opportunity to diagnose pain through a blood sample in livestock. To date, the translational benefits of these discoveries in the fundamental neuroscience of pain have passed directly to the human clinical setting, without changes in animal husbandry practices. This is a critical missed opportunity.

CONCLUSION

We are at the cusp of a measurement science watershed moment, where quantification of "mind and body" state of the dynamic and living organism, such as pain and some emotional states will be possible in humans. Very similar technologies can be used in livestock to make these crucial measurements. However, we cannot wait decades for these innovations to spontaneously occur. If humanity reaches Mars before these opportunities have been translated to livestock production, we will have failed. We need to cultivate specific opportunities, and the relationships that develop from them, to allow for the tough questions to be asked and breakthrough ideas to be tested. If we can accelerate these translational opportunities in the future, then streams of research in neuroscience, immunology, pharmacology and biophotonics will emerge to equip the Australian livestock industry with world-first platform technologies that will be able to, for example objectively quantify pain in livestock. These new technologies will then be used to enhance livestock production practices. For example, it will be possible to rapidly identify new drug targets for their ability to block the persistence of pain, underpin productivity gains and an iteratively improve production and business practices. These capabilities will then all contribute to a greater understanding of how breed selection and defined genetic traits contribute to minimising chronic pain in livestock. Given this futuristic technology is on our doorstep, imagine what the plenary of the 2032 Association for the Advancement of Animal Breeding and Genetics meeting might be… Will we be talking about breeding selection technologies and traits that have be deployed in establishing the first interplanetary transfer of livestock? Only time and your imagination will tell….

ACKNOWLEDGEMENTS

MRH is funded by an ARC Future Fellowship (FT180100565), and research program is funded by the Australian Research Council Centre of Excellence for Nanoscale BioPhotonics (CE140100003), Meat and Livestock Australia, Sheep Industry Fund and the Davies Livestock Research Centre, University of Adelaide.

REFERENCES

Grace P.M., Tawfik V.L., Svensson C.I., Burton M.D., Loggia M.L. and Hutchinson, M.R. (2021)\. *J. Neurosci*. **41**: 855.

Hutchinson M.R. (2020) *Brain Behav. Immun*. https://doi.org/10.1016/j.bbi.2020.04.029

Hutchinson M.R. and Terry R. (2019) *Animal* **13**: 3000.

Institute for Health Metrics and Evaluation (2020) GBD compare data visualization [WWW Document]. URL http://vizhub.healthdata.org/gbd-compare (accessed 1.7.21).

Marsh L., Hutchinson M.R., McLaughlan C., Musolino S.T., Hebart M.L., Terry R., Verma P.J., Hiendleder S. and Whittaker A.L. (2021) *Animals* (Basel) **11**: 2054.

Orth A., Wilson E.R., Thompson J.G. and Gibson B.C. (2018) *Sci. Rep*. **8**: 3298.