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## The role of 'omics technologies for livestock sustainability

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**Abstract.** A successful program of food security for a growing population requires production of livestock in the most efficient and sustainable manner possible to ensure the availability of nutritious foods, the overall health and well-being of humans and animals, and protection of the environment. Innovative and technological advancements that enhance all aspects of food production will arise from basic, fundamental research. Notably, the integration of genomics with other 'omics research fields and computational methods will continue to lead to better understanding of biological mechanisms that are responsible for physical attributes, or phenotypes. Examples of several 'omics methods and their applications are described to demonstrate recent advances and how these methods can be applied to livestock. Research breakthroughs in genomics and other 'omics fields can be used to enhance productivity of food animals, meet the increasing demand for animal-sourced foods, enhance high-quality nutrient availability, ensure nutrient safety, mitigate the effects of climate variability, and result in new technologies that provide continued improvement in food security worldwide.

**Key words:** Genomics, Metabolomics, Predictive modeling, Proteomics, Sustainability

## O papel das tecnologias "ômicas" na sustentabilidade do gado

**Resumo.** Um programa bem-sucedido de segurança alimentar para uma população em crescimento necessita de uma produção animal mais eficiente e sustentável para assegurar a disponibilidade de alimentos de alto valor nutricional, e também a saúde e o bem-estar dos humanos e dos animais, e a proteção do ambiente. Inovações e avanços tecnológicos surgirão da pesquisa básica e fundamental. Em especial, a integração da genômica com outros campos de pesquisa "ômicos" e com métodos computacionais possivelmente facilitará o entendimento dos mecanismos biológicos que são responsáveis por atributos físicos ou fenótipos dos animais. Exemplos de vários métodos ômicos e suas aplicações são descritos para demonstrar os avanços recentes e como esses métodos podem ser aplicados para produção animal. Os avanços na pesquisa em genômica e em outros campos ômicos podem ser usados para aumentar a produtividade de animais, atender à crescente demanda por alimentos de origem animal, aumentar a disponibilidade de nutrientes de alta qualidade, garantir a segurança nutricional, mitigar os efeitos da variabilidade climática, e resultar em novas tecnologias que favorecem a melhora a segurança alimentar em todo o mundo.

**Palavras-chave:** Genômica, Metabolômica, Modelos preditivos, Proteômica, Sustentabilidade

### Introduction

The United Nations recently approved draft recommendations regarding sustainable agricultural development for food security. These

recommendations acknowledge animal-sourced foods as especially important for the diets of children, pregnant and lactating women, and

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elderly people, and encourage consumption of these foods for good health and improved nutrition (United Nations, 2016). These recommendations also emphasize sustainable use and management of livestock genetic resources, along with protection of the environment and efficient use of natural resources. Although progress has been made in the past decades, more than  $750 \times 10^6$  people remain food-insecure worldwide, and lack access to adequate safe and nutritious food for the normal growth and development that enables active and healthy lives (FAO, 2015). Projections indicate that world agricultural production must double in order to meet the needs of a world population expected to exceed  $9.6 \times 10^9$  by 2050. Demand for meat will also expand dramatically because of increasing

population, urbanization, and affluence in many countries (FAO, 2011).

Application of new technologies and related research and development applied to livestock species is necessary to catalyze innovation and new solutions so that production of sufficient animal-sourced foods can be achieved with limited existing resources and variable climate conditions in a sustainable, and likely intensive fashion (Tedeschi *et al.*, 2015). During the last 50 years, production of livestock has increased in efficiency. The integration of genomics and other 'omics tools, in conjunction with phenotype data and systems analyses will enable continued improvements that will be necessary for sustainable livestock production in the future.

### 'Omics Technologies

#### Genomics

The genome is the complete set of genetic material present in an organism. The term "genomics" was coined in 1986 by scientists who were naming a new journal (Kuska, 1998), and thus, the era of 'omics began. Somatic cell hybridization techniques were developed and exploited for the construction of gene maps, as reviewed by Womack (1996). Initially, gene map construction was based on the segregation of enzyme markers across panels of hybrid cell lines. As recombinant DNA technology facilitated hybridization-based techniques and polymerase chain reaction methods for localizing genes, denser physical and genetic maps were generated, and served as important framework tools for genome sequencing that followed (Riggs and Gill, 2009).

The human genome project was a massive undertaking to generate the sequence of the  $3 \times 10^9$  base pair human genome, identify all of the human genes, improve technologies and analytical tools, store and transfer the data and technologies, and address ethical and legal issues that could arise with the availability of such data (US-DHS, 1990). During the 13-year period of the project, rapid advancements occurred in technology, and the first draft of the human genome was announced "complete" in 2003. With this progress, animal genomes began to be sequenced. The first bovine genome was published in 2009 (Bovine Genome Sequencing Consortium), opening the door for livestock 'omics.

As sequence data became available, high-throughput arrays for detection of single nucleotide polymorphism (SNP) variations across individuals were developed, and are now widely used, especially for genome wide association studies (GWAS). The

physical traits, or phenotypes, that are of great interest for animal production often occur as the cumulative result of many different genes, each with small effects. The regions of the genome associated with specific measurable phenotypes are known as quantitative trait loci (QTL). A few traits are greatly affected by a single, major gene, such as the myostatin mutations that result in double muscling (Grobet *et al.*, 1997). In the case of the leptin gene, the combination of the genotype for two leptin SNP with backfat phenotype was described as a means to improve identification of high-quality grading cattle under feedlot conditions (Lusk, 2007). However, many traits of interest, such as meat tenderness, are affected by the DNA sequence composition at multiple locations across the genome, presenting more complex computational challenges. To map the QTL for traits of interest, one needs a population of animals that expresses variability for a quantitative trait, accurate records, a genetic map for the population, and a roadmap of markers (SNP) distributed evenly and densely across the genome. Analytical approaches that combined linkage and linkage disequilibrium (association) methods in a single analysis (Meuwissen and Goddard, 2002; Uleberg and Meuwissen, 2007) have helped broaden the application of QTL mapping.

As the tools and instrumentation associated with genome sequencing continue to improve, information generated from the whole genome sequencing of certain animals has been used to make available commercial assays of thousands of SNP markers for food animal species. Costs for sequencing have dropped significantly, but sequencing the whole genome of an animal is often not practical, and

requires substantial computational support. However, the commercial SNP arrays can be used to provide a genome snapshot for animals within a herd at a manageable cost. The analytical methods that incorporate information from multiple markers on the SNP array into selection decisions that capture the majority of genetic variation in traits of interest are the next challenge. Genomic selection, or marker-assisted selection on a genome-wide scale (Meuwissen *et al.*, 2001), was implemented with the idea that the prediction of accurate breeding values for young animals would lead to increased genetic gain for traits for which selection is difficult. Greenwood *et al.* (2013) analyzed the molecular value prediction (MVP) of economically important traits of *Bos indicus*, and reported that marbling MVP was highly associated with marbling scores and intramuscular fat. Thus, a promising application of genomics might be its integration with nutrition models to improve the prediction of cattle performance and their carcass composition and to provide decision support to optimize profitability in feedlots. Tedeschi (2015), for example, identified commercial SNP panels to improve the predictability of days on feed (DOF) to reach a desired United States Department of Agriculture grade, using a growth model (Tedeschi *et al.*, 2004) and molecular breeding value (MBV) scores that were computed from SNP panel arrays. Tedeschi (2015) showed that MBV for ribeye area was strongly correlated with key variables of the growth model, suggesting its predictability could be improved when combined with certain MBV scores.

The greatest gains from genomic selection in cattle have occurred in the dairy industry. During a seven-year period, dramatic improvements were made in generation interval, as well as lowly-heritable traits such as years of productive life (Garcia-Ruiz *et al.*, 2016). In part, these remarkable gains in American Holstein cattle have been made because of the availability of many decades of phenotypic records, the use of artificial insemination, and widespread industry adoption of this technology. Across the livestock industries, application of genomic selection has taken different paths as reviewed by Van Eenennaam *et al.* (2014). Structural differences in the beef industry have slowed adoption of this technology, but opportunity remains for integration of whole genome sequencing and genome-wide SNP data into genetic improvement programs for beef cattle.

### Transcriptomics

The genomic DNA serves as an organism's genetic code that is transcribed into the messenger RNA which is then translated into proteins. Other

RNA transcripts serve functional roles in the translation machinery (rRNA and tRNA), or as regulatory molecules (e.g., miRNA, lncRNA) whose important roles are the subject of active, current research. As whole genome sequences become more readily available in various meat animal species, the use of genetic road maps along with profiling of transcribed RNAs can help researchers begin to explore the interactive networks of genes that underlie the biological mechanisms responsible for specific livestock phenotypes. Like SNP arrays, expression microarrays can return a profile of known gene expression in a tissue or cell.

Next-Generation Sequencing (NGS) technologies generate sequence data by producing millions of short DNA fragments in parallel; the length and number of the reads vary with the specific technology (Ghaffari *et al.*, 2013). In the application of NGS to transcriptomics, known as “RNA-seq,” the frequency with which each transcript is represented in a sequence sample is counted (Mortazavi *et al.*, 2008). RNA-seq is a technological approach for capturing RNA transcripts present in a sample, without the need for any prior knowledge of the target sequences. Due to the accurate sequencing platforms available today, closely related transcripts can be easily distinguished from each other (Marguerat and Braga-Neto, 2015), making RNA-seq well-suited for identification and quantification of splice variants, fused transcripts, and mutants. During RNA-seq, messenger RNAs are randomly fragmented into small pieces, then converted to library complementary DNA (cDNA) fragments. These cDNA fragments are amplified and sequenced in parallel, resulting in millions of short sequences called “reads.” These reads can then be mapped to a given region of the target genome. For expression quantification, the number of reads mapping to each gene determines a count, which is a discrete measure of the corresponding gene expression level (Ghaffari *et al.*, 2013, Li *et al.*, 2012). RNA-seq has a large dynamic range and sensitivity due to its digital nature, which can be especially important for detection and quantification of highly abundant and extremely low abundant transcripts.

Transcriptomic methods can be used to compare a biological response to different conditions or treatments, or to assess physiological response to pathogens or pests (Brannan *et al.*, 2014). Transcriptome analyses can also demonstrate how gene expression changes across developmental time points, or in response to diet, and ultimately influences phenotypes. When utilized in conjunction with QTL analysis, transcriptomic analysis can help facilitate candidate gene discovery and provide a

better understanding of system-wide gene signaling pathways. For example, Weber *et al.* (2016) identified gene networks based on residual feed intake (RFI, a measure of efficiency) and gene expression measured by RNA-sequencing analysis of five tissues. In this work, growth and RFI phenotypes were evaluated from 8 offspring (steers) from each of two bulls (high RFI bull vs low RFI bull), along with expression analyses. Their methods utilized the integration of multiple sources of genomic and transcriptomic data to demonstrate differentially expressed gene networks relevant for feed efficiency. Other studies that address the regulatory components of the transcriptome, such as microRNAs that regulate characteristics of skeletal muscle (Dawes, 2015), can reveal which expression parameters are also of great importance for understanding the meaning of transcriptome profiles. Finally, in considering genome regulators, one must also consider the epigenome. Chemical modifications, or marks, on the DNA that does not change the sequence are called epigenetic modifications. The marks may be heritable, and most play an important regulatory function. Although an organism generally possesses only one genome, each cell type reflects a different epigenome—a genome that has been modified to suppress or activate genes necessary for the development and function of specialized cell types. Environmental factors, such as diet (Cho *et al.*, 2012; 2014), may also alter the epigenome in ways that affect an animal's life.

Overall, these types of analyses of genome transcripts and other regulatory modifications will form a basis for a further study that will help investigators connect variations in specific genes with these differences in expressions, and ultimately lead to better understanding of important mechanisms that contribute to a feed-efficient phenotype, desirable meat characteristics, or disease-resistant phenotypes. Moving forward toward understanding these mechanisms should enable development of improved methods for selection of breeding animals based on integrated "systems genetics."

### Proteomics

As methods for analyzing nucleic acids—DNA and RNA—have advanced rapidly, improvements have also been made in methods for profiling the proteome—the set of gene products, or proteins, in a sample. Proteomics techniques ranging from well-established two-dimensional gel electrophoresis (2DGE) methods to sophisticated mass spectrometry have research applications ranging from early growth and development to postmortem events important for meat quality (Bendixen, 2005; Yarmush and

Jayaraman, 2002). The entire protein complement of cells of tissue, or from subcellular compartments, is a complex mixture, but can be fractionated to reduce complexity. Differential protein expression and/or protein modification can be identified after comparison of 2DGE profiles from different animals, followed by mass spectrometric analysis for identification of specific proteins.

A mass spectrometer measures (MS) the concentration of ionized molecules at a range of mass-to-charge ratios ( $m/z$ ). MS instruments consist of three modules: an ionization source, a mass analyzer and a detector, which captures the ions and measures the intensity of each ion species. Widely used ionization methods include electrospray ionization (ESI; Hop and Bakhtier, 1997) and matrix-assisted laser desorption ionization (MALDI; Karas and Bahr, 1990). In addition, liquid chromatography (LC) is often coupled with MS to achieve additional separation of peptides and thus reduce the complexity of an individual mass spectrum (Sun *et al.*, 2010). One of the important challenges of proteomics is the identification of low-abundance peptides. Improvements and advancements in sensitivity and sophistication of mass analyzers have led to many variations that enable identification of low-abundance components of complex peptide mixtures. For example, high resolution ion time of flight (TOF) coupled with tandem MS (MS/MS) instrumentation, or orbital trap mass analyzers, along with other variations, enable reliable analyses and identification tools for many applications and integration with other 'omics techniques (Gallo and Ferranti, 2016).

Proteomic methods have been applied widely. One area of interest is vaccine development in beef cattle to protect against infection by microorganisms carried by ticks. Certain surface membrane proteins can induce a protective immune response in cattle exposed to *Anaplasma marginale*, carried by a tick host. Proteomic characterization of these proteins may play an important role in the development of vaccines to provide resistance to infection (Marcelino, *et al.* 2013). Characterization of the complex muscle proteome, both pre- and post-mortem, by emerging tissue MS analysis tools will be of great importance for clarifying mechanisms that determine meat quality characteristics, as discussed by D' Alessandro and Zolla (2013).

### Metabolomics

An emerging area in the application of 'omics tools is in the interrogation of the metabolome – the collection of all the products of metabolism or metabolic intermediates within a cell. Metabolomic tools are being increasingly used to generate an

unbiased global profile of metabolites in samples (*i.e.*, untargeted analysis) or to quantify with high sensitivity a small panel of metabolites (targeted analysis). Such metabolomics analysis can be performed on samples collected from a variety of sources, including the pre and probiotic material, tissues, plasma, intestinal contents, and feces. In a recent example from heat stress analysis of dairy cattle Tian (2016), examined 53 metabolites in milk and plasma and found that metabolite concentration was correlated between the sample sources. This experiment also identified metabolites present in milk that could be used as potential biomarkers of heat stress in the cows. One advantage of profiling metabolic phenotypes is the potential for utilizing samples such as urine or milk that can be obtained non-invasively, unlike blood or tissue. It is also possible to explore the impact of microbial metabolism on intestinal and systemic health by monitoring the production and further metabolism of compounds present in the diet, digesta and plasma (Seidel *et al.*, 2014). The workhorse for most metabolomic analysis is mass spectrometry but nuclear magnetic resonance (NMR) spectroscopy has also been used for metabolomics analysis. Given that the concentration range of metabolites in complex samples such as plasma span several orders of magnitude, analytical methods as liquid chromatography are often used to provide orthogonal

separation and reduce the sample complexity prior to MS analysis.

#### **Metagenomics and microbial profiling**

Metagenomics is an area of considerable research interest, particularly in ruminant animals. Use of genomic sequencing tools to identify the complex structure of the rumen microbiota and their changes in response to diet, in concert with the host bovine genome, may influence a range of phenotypes, including feed efficiency and volume of methane production in the rumen. In addition, systemic responses, such as an inflammatory state in the digestive tract and in the host, result from changes in the intestinal microbiota (Morgan *et al.*, 2014; Ritchie *et al.*, 2015). In another example, indole produced by microbiota of a “healthy gut” was shown to reduce side-effects of non-steroidal anti-inflammatory drugs in a mouse model (Whitfield-Cargile, *et al.*, 2016). In ruminant animals, the complex microbial landscape that exists within the rumen contains bacteria that degrade fiber, species that are responsible for methane production, and organisms that affect overall functional characteristics of the rumen (Denman and McSweeney, 2015). The gut microbiota associated with desirable health and production parameters could potentially be harnessed for feed supplements or other procedures early in an animal’s life to enhance the efficient function of the rumen in adult animals (Malmuthuge and Guan, 2016).

#### **Analytical Tools**

The explosion of genomics and ‘omics tools has generated tremendous quantities of data that require skilled and knowledgeable bioinformaticians, statisticians, and computer scientists. The high-dimensionality of the data, resulting from a huge number of simultaneous measurements, requires the careful application of statistical techniques in order to avoid spurious results. In addition, even more importantly, integration of different ‘omics datasets together to get a whole system perspective of the data, is a key means for pursuing the overall objective of producing livestock to meet demand for food in a world with a growing population and declining natural resources. Mathematical modeling and development of valid decision support systems are crucial tools for managing animals, optimizing animal nutrition, and selecting animals for

reproductive efficiency and thriftiness for their specific environmental conditions or suitability to intensive, sustainable production systems (Tedeschi, 2015).

Ultimately, real gains will come from integrated approaches that utilize all available data sources and lead to breakthroughs in the fundamental understanding of biological mechanisms that underlie phenotypes of interest. As these tools are used to address important physiological mechanisms, creative approaches can be developed and adopted to make gains in efficiency and productivity, so that sufficient animal sourced foods can be produced in an economically-favorable manner that also minimizes resources used and returns value to the environment. This scenario would be a model of sustainable livestock production.

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