

REVIEW ARTICLE

Objectives and applications of phenotyping network set-up for livestock

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ABSTRACT

Providing phenotypic information, which is accurate, reliable, repeatable and comparable across countries or laboratories, is critical to gain a better understanding of the relationship between genes and phenotypes. So far, it is indeed extremely difficult to combine different sources of phenotypic data from multiple origins, partly because of the variability in the methods of phenotyping. The phenotyping program of livestock involves the definition of complex phenotypes obtained from data integration at different levels (from molecules to herds), the implementation of the latest technologies to accurately characterize at high speed and low cost, the greatest number of animals in a better characterized environment, and the development and sharing of large databases for data analysis and modeling. Such a program also involves the construction of a coordinated network of research and professional facilities and a common language with shared definition of unambiguous animal traits and of methods to assess them. To this end, it will build on the 'Animal Trait Ontology of Livestock' (ATOL) project with the objective of defining precisely the phenotypes of interest for farm animals. Then, it will be necessary to combine an environmental information system related to animal husbandry and associated methods to capture the phenotypic differences between animals.

Key words: genomics, livestock, phenotypes.

INTRODUCTION

The organization and delivery of high-performance tools used to determine animal phenotypes, together with the acquisition and sharing of the resulting data, are major challenges currently viewed as key obstacles to the furthering of knowledge, whether in terms of genomic selection or precision livestock farming. The phenotype concerns one or more observable characteristics of an individual and depends on an individual's genotype, i.e. the expression of its genes, in

addition to – or in interaction with – the effects of its environment.

Fine-scale high-throughput phenotyping has therefore been identified as one of today's key

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challenges (Herpin 2009). It is one of the priorities of researchers working in the animal livestock breeding sector (Barbat *et al.* 2010) and is also rightly being promoted by technical institutes and professional livestock production organizations (Hocquette *et al.* 2011a).

The development of precision livestock farming, the access to ever more effective functional exploration techniques, the deployment of current (genomic selection) or future (nutrigenomics) innovations in the genomics sector, the diversification of the selection traits to take into account to meet the expectations of livestock producers, industrial food-processing companies, distributors, consumers and citizens (environmental criteria, animal welfare, etc.), are all issues that justify the organization of a large-scale program targeting precise high-throughput phenotyping of farm animals. The need for such a program has already been identified by the scientific and professional communities in order to meet the new challenges facing the animal husbandry sector (Hocquette *et al.* 2011a).

After having reviewed the latest challenges in terms of science and animal husbandry, we will develop the concept of high-throughput phenotyping and its impacts in terms of the standardization and sharing of data, and also in terms of the organization of the research sector.

NEW CHALLENGES IN THE FIELD OF LIVESTOCK BREEDING

The sustainable development challenges now facing our societies are increasingly linked to environmental protection, to consideration of ethical concerns, particularly those relating to animal welfare, while maintaining a high production of resources needed to counter the impacts of rapid growth in the human population. Against this background, animal husbandry research is focusing on the selection of animals that are: (i) efficient in terms of the processing of food resources to limit their use at the maximum and to reduce emissions to the environment; (ii) robust and adaptable toward climate change and a wide range of livestock breeding methods; and (iii) able to generate a high yield of quality products to meet consumer needs in health and nutrition. In its strategic vision of farm animals of the future, the European technological platform FABRE has effectively described tomorrow's animals as being healthy, robust and adaptable (FABRE 2006).

Controlling the metabolic conversion of meat, eggs or milk feedstuffs by animals is essential to limit emissions of environmental pollutants (nitrogen, methane, phosphorus etc.) and reduce animal feed costs (that represent over half of the operating expenses of a livestock farm, especially in the pig and poultry sectors), while substituting fish oil and meal with veg-

etable protein and oil in fish farming, and making the best use of forage resources for ruminants or of new resources such as the by-products generated by the plant production sectors (biofuels, etc.). Robustness is the property that enables an animal to adapt to or withstand changes in its environment, in particular, climate changes that are becoming increasingly frequent with higher amplitude; resistance to pathogens is another form of robustness, with the need to limit the use of antibiotics in the various animal sectors. An animal's response to environmental variations (and therefore the assessment of its robustness) requires high-frequency measurement of specific traits, hence the importance of high-throughput phenotyping (Friggens *et al.* 2010). Robustness assessments are based on a set of physiological functions of interest and involve the measurement of diverse characteristics such as animal health, reproduction, behavior and life span, in addition to their ability to withstand stress (Mormède *et al.* 2011) and grow normally.

Furthermore, animal husbandry activities are currently a core issue of several societal debates that partly link up with the challenges described above, and that are fundamental to the future of the livestock production sectors: (i) interactions between animal husbandry and the environment; (ii) regional land planning management aimed at maintaining a significant rural fabric through animal husbandry activities, and at making more attractive animal husbandry activities by improving the way of life of farmers; (iii) and the impact of the consumption of animal products on human health, in terms of red meats in particular, which are often criticized by the medical profession for their high saturated fatty acids content. Our fellow citizens are therefore expecting professionals and researchers to provide answers to these questions, including in particular, better control over the contribution of farm animals to greenhouse gas emissions, along with due consideration of the contribution of livestock breeding farms to carbon storage (particularly through the use of prairies).

Various deliberations have concluded that, despite appearances, these diverse objectives are not necessarily contradictory. In particular, animal products can be produced in both quantity and quality and thereby contribute to feeding humans a balanced diet without damaging the environment (Scollan *et al.* 2011). For example, animals with greater metabolic efficiency would have a greater milk and meat yield, with lower emissions per kg of product (Reynolds *et al.* 2011). Genomic selection, that speeds up progress with regard to criteria that are difficult to improve on using conventional selection approaches (Humboldt *et al.* 2010), and the development of precision livestock farming techniques, are promising avenues for reducing inputs (Bewley 2010), which is a key lever in controlling production costs and cutting emissions of nitrogen,

phosphorous, methane and residues of medicinal products. Research into the development of more robust animals and the fact that livestock farms are now acquiring the equipment capable of a continuous output of large amounts of data on animals (temperature, behavior, feed consumption, etc.), on products (on-line analyses of milk in the milking parlor, etc.), and on the characteristics of the environment at the animal level, should also contribute to improving working conditions on livestock farms and animal welfare.

SCIENTIFIC CHALLENGES

Alongside these societal challenges, research-development projects in biological sciences are taking on ever greater importance with the goal of achieving a more systemic and predictive approach in terms of both genetics and biology. At present, phenotyping is the least developed component of integrative biology, whether referring to plants, animals or humans.

Challenges in genetics

The genomics revolution has pushed forward our understanding of the genomes of animal species through the introduction of pioneering high-throughput technology designed to study DNA and its products (RNA, proteins and metabolites; Hocquette *et al.* 2009; Humblot *et al.* 2010). Genomic selection is a promising way to generate more sustainable animals, and thus scenarios combining genetic progress (even on low heritable traits) and inbreeding rate have to be evaluated within the compass of robustness (Vanraden *et al.* 2011). Currently, one key objective is to establish ever more fine-grained functional relationships between animal genotypes and their phenotypes aimed at developing precision livestock farming that is sustainable over time. In this context, the standardization and accuracy of phenotype measurements are becoming major limiting factors (Monget & Le Bail 2009). Indeed, Barendse (2011) demonstrated that the results of genome-wide association studies (GWAS) differ depending on which phenotypic dataset is used. This author based his research on two sets of values for the thickness of subcutaneous fat (with the same definition) that were fairly closely correlated ($r = 0.72$), but which derived from two separate working groups. It is therefore highly recommended that phenotype values in GWAS experiments should be assessed for their repeatability prior to any analysis. For traits with low measurement repeatability ($r < 0.95$), two or three independent measurements of the same trait should be obtained on the same samples, and individuals should be genotyped solely for strongly correlated traits for independent measurements (Barendse 2011).

Following the spectacular advances made in genetics and genomics, there is a clear lack of knowledge on

phenotypic traits with respect to the highly detailed and accurate data that are available for genotypes and their tissue expressions (transcription products, proteins and, to a lesser extent, metabolic flows). It is vital, therefore, that we develop phenotyping that maximizes the value of genotyping and makes best use of genomics. In other words, 'in the age of the genotype, phenotype is king' (Coffey 2011).

This lack of knowledge derives from a clinical approach to phenotypes and animals. Let's take the example of a human patient consulting his physician for a polyuria polydipsia. A rough clinical analysis might classify this syndrome under 'diabetes' in the broadest sense of the term. However, further investigation might actually classify this syndrome under six possible etiologies: potomania and dyspsomania, which are psychiatric disorders, type I and type II diabetes mellitus, as well as central and nephrogenic diabetes insipidus. Among the latter, we can refine the diagnostic even further by identifying whether, for diabetes mellitus, this is insulin-dependent i.e. type I (young people's diabetes) or non-insulin-independent, i.e. type II (older, fatter people's diabetes). Diabetes insipidus may have a central (defect in the secretion of the anti-diuretic hormone) or nephrogenic (defect in the action of this same hormone) origin. In some cases, the genetic determinism is simple (diabetes insipidus) or fairly simple (type I diabetes), or enormously complex (type II diabetes). In human medicine, the reason for which some syndromes have not been genetically determined for over 30 years, in particular, in the field of fertility (polycystic ovaries, early menopause, etc.) is linked to the fact that anatomical and histological investigations have not made it possible to improve patient characterizations for ethical reasons. Even if the researcher has to follow an ethical approach toward animals, the requirement will never be on the same level with domestic animals.

Clearly, it was the highly accurate clinical characterization of bovines presenting with type I versus type II muscular dystony that enabled the Michel Georges laboratory to identify the genes and mutations involved (Charlier *et al.* 2008).

Challenges in biology

Generally speaking, research has often been based on using the easiest traits to measure rather than directly the traits of interest when these are difficult to understand and to record. For example, it is now standard practice to estimate beef tenderness by measuring its shear force which is correlated to tenderness.

High-throughput phenotyping approaches involve: (i) the definition of new traits (predictors of phenotypes of interest) or complex phenotypes, such as robustness or fertility, obtained by integrating data at several different levels (gene, tissue, animal, herd); (ii) the deployment of the latest high-throughput methods

and technologies in order to provide a cheaper but more accurate means of characterizing the largest possible number of animals; and (iii) the development and sharing of large databases designed to summarize data and modeling procedures.

Predictive biological approaches stand at the interface between integrative biology and modeling. Integrative biology connects research on molecules (DNA, RNA, proteins and metabolites) with research on individuals and populations (Hocquette *et al.* 2009). Modeling makes it possible to represent and better understand complex biological phenomena and the way they interrelate, and to point out the areas of lack of knowledge. It is underpinned by advances in high-throughput analysis techniques that provide significant quantities of data, especially on genes, their expression and their regulation in relation to their environment. These new approaches and mathematical models are now enabling researchers to explore how animals respond to variable environmental conditions and to develop predictive tools in fields as diverse as ecosystem control, plant growth, tracking of the spatial distribution of animal species, animal health and behavior, their metabolism and production.

HIGH-THROUGHPUT PHENOTYPING

Definition

High-throughput phenotyping of farm animals appears to be essential given the new societal and scientific challenges that will have to be faced to ensure sustainable animal production. It can be defined as: 'a method of determining phenotypes that can be subject to rapid, repeatable and automated measurements that generate significant volumes of data' (Hocquette *et al.* 2011a).

For example, mid-infrared spectrometry (MIR) is an alternative method that has been used routinely for a number of years already in order to measure protein and fat content in milk. This technique has been refined in order to estimate the fatty acid composition of ruminant milk, following the development of prediction equations based on MIR spectra, which provide greater insight into a product's nutritional characteristics. These estimated phenotypes are then compared to animal genotypes to gain a better understanding of the fine composition of milk and its control (<http://www.phenofinlait.fr/spip.php?rubrique11>). This type of approach is often referred to as horizontal phenotyping as it corresponds to measurements that are easy to take on a large number of animals. Another way to collect large amounts of data is achieved through many 'Precision Dairy Farming' technologies, including daily milk yield recording, milk component monitoring (e.g. fat, protein and SCC), pedometers, automatic temperature recording devices, milk conductivity indicators, automatic estrus detection or calving monitors, and

daily body weight measurements, already being utilized by dairy producers (Bewley 2010).

Vertical phenotyping corresponds to the measurement of several phenotypes on an increasingly fine grain relating to a family of phenotypic traits concerning a small number of individuals but with a large amount of measurements. For example, in the beef quality domain, simultaneous measurements are taken of carcass traits (conformation, fat cover), sensorial meat quality criteria (tenderness, flavor, juiciness), fine muscle composition (type of fibre, collagen and fat content, fatty acid composition) together with the expression of the genes and proteins involved in determining beef quality (European ProSafeBeef program, FOOD-CT-2006-36241; <http://www.prosafebeef.eu>). More generally, the accumulation of intramuscular fat is the subject of active research in all meat-producing animals with search for molecular markers of carcass fatness, marbling, activities of enzymes involved in lipid metabolism and expression of their genes (Hocquette *et al.* 2010).

In the field of reproduction, vertical phenotyping has made it possible to study several key events relating to fertility: post-partum cyclicity, gamete quality, early embryonic development and implantation, in particular, according to livestock breeding conditions (Ponsart *et al.* 2008, 2011a,b,c; Mansouri-Attia *et al.* 2009; Thelie *et al.* 2009; Gad *et al.* 2011). Vertical phenotyping may therefore bring into play a number of complex techniques, such as ovum pick-up and embryo-related biotechnologies, including genotyping (Guyader-Joly *et al.* 2008; Humblot *et al.* 2010; LeBourhis *et al.* 2011) together with imaging, functional genomics, metabolomics, etc., aiming to better understand the crosstalk between an embryo and its maternal environment coming in a range of a space-time continuum, and thus including functions involved in pregnancy success or failure.

The third dimension of phenotyping results from the diversity of the new challenges to animal breeding as explained before. Indeed, multiple phenotypes need to be recorded in the same animals that should, at the same time, be food efficient, leave a reduced impact on the environment, deliver high-quality products, meet the criteria for satisfactory welfare, and be profitable to the breeders.

Methodologies to be developed

According to the above definitions, high-throughput phenotyping clearly involves the use of equipment and methodologies that generate a large amount of data based on measurements that are often automated.

It is standard practice to distinguish between *ex vivo* methods used to determine traits following the collection of samples (these methods may occasionally be invasive or destructive), and *in vivo* measurements

(often non-invasive), the advantage of which is to enable individual longitudinal tracking of any changes in traits. Concerning sample analyses, the high-throughput issue (corresponding to the large number of analyses that can be performed within a given time) is less important as the samples are processed at a later date, meaning that the analyses can be repeated if the sample size is sufficiently large. For measurements *in vivo* or on the whole organism, the difficulty of the high-throughput approach depends on the technical limitations of the methods used and on the need to ensure that the animals are under normal living conditions, so as to avoid biasing the measurements.

Among the major methodology families enabling the use of high-throughput techniques, we can cite the many optical methods based on reflectance or transmittance measurements taken at various wavelengths (visible, IR, even UV). In the plant domain, they can be applied in the field or in a controlled environment in order, for example, to dose chlorophylls or measure surface temperatures or O₂ consumption (E. Dreyer & P. Gaudin, personal communication). In the animal domain, these methods can be used to estimate feed values (Andueza *et al.* 2011), the traceability of herbivore feedstuffs based on the composition of their products and tissues (Prache *et al.* 2006), or even on the color of their meat, fatty acid composition of milks, etc.

Moreover, the design of a 'multi-sensor, modular and intelligent' system to monitor animals and their environment presents a key methodological challenge aimed at obtaining repeated, multiple information in a non-invasive manner. At present, we can imagine equipping an animal with a multi-sensor onboard system that, in addition to the ID process that is becoming standard procedure (RFID chips), would also reproduce the animal's perceptions and monitor several physiological (temperature, ruminal pH, cardiac and respiratory rate, etc.) and behavioral (travel, lameness, estrus, interactions with other animals, etc.) parameters without disturbing either the animal's behavior or welfare. Fixed-station systems can provide additional back-up through the automatic recording of other parameters, such as weight and conformation, behavioral measurements, or during milking of dairy animals. These measurements are subject to ongoing research (Frost *et al.* 1997; Bewley 2010). It should be mentioned somewhere that, although it is not impossible to do so, difficulties may arise for species of smaller format and/or living in specific environments such as water for fish. Clearly, although some tools (tags) are routinely used in fish or are under test in poultry species, most tools still have to be developed to be able to record individual data in collective rearing conditions, either commercial or experimental ones.

However, over and above the recorded signal, a multi-disciplinary field of research needs to be opened up on data processing and, more specifically, on: (i)

mathematical processing of the signal (filtering, etc.); (ii) establishment of reference measurements (possibly low flow measurements) used to calibrate indirect methods; (iii) validation of the advantages of cumulating data from a diverse range of sources, in particular, those relating to an animal's biological parameters and behavior; and (iv) modeling the balance between the different components of the global phenotype (e.g. feed efficiency vs. robustness, production rate vs. product quality and welfare).

Among *ex vivo* measurements, some techniques aim to quantify biomass (in plants) and the structure of individual subjects (plant architecture, animal morphology and body composition). Some techniques use methods that involve microscopy (for cell-level studies) and imaging (subcellular structure up to the level of the whole organism). One of the bottlenecks in the process is without a doubt the automated processing of image analyses.

Analyses of biological samples (blood, urine, feces and tissue biopsies) also benefit from automated processing that is faster and cheaper, while at the same time, being more accurate, sensitive, reliable and reproducible, thus enabling inter-laboratory comparisons. Groundbreaking advances in metabolomics are also driving forward the achievement of this objective. Studies of the expression of genes and proteins have now reached a level of technical maturity that paves the way for deploying these approaches for high-throughput phenotyping.

All laboratory techniques have the potential to be upgraded in order to perform high-throughput procedures (Fig. 1). For example, histological techniques have recently evolved into 'tissue array'. By analogy with the 'DNA array' used for gene expression studies, tissue array consists in building collections of several tens to several hundreds of tissue cores from blocks of tissues stored in paraffin or frozen. After slicing these blocks into tissue arrays, it is then possible to mount microscope slides containing several tens to several hundreds of tissue slices. These can be used in several different ways, each tissue sample undergoing several tests: standard staining for morphology studies or cell counts, immunohistochemistry, *in situ* hybridization, etc. The tissue array thus forms a novel and effective high-throughput tool that can be used for post-genomics and post-proteomics studies. It is used for cancer research in particular (Radhakrishnan *et al.* 2008). Again depending on species, there are different degrees of technical developments . . . none in some domestic species at present.

All these methodologies will have to be validated and standardized in order to enable the comparison of data between laboratories, this aspect having taken priority given the very large amount of data generated. The performance characteristics for the analysis methods are: definition of the scope of application, specificity,

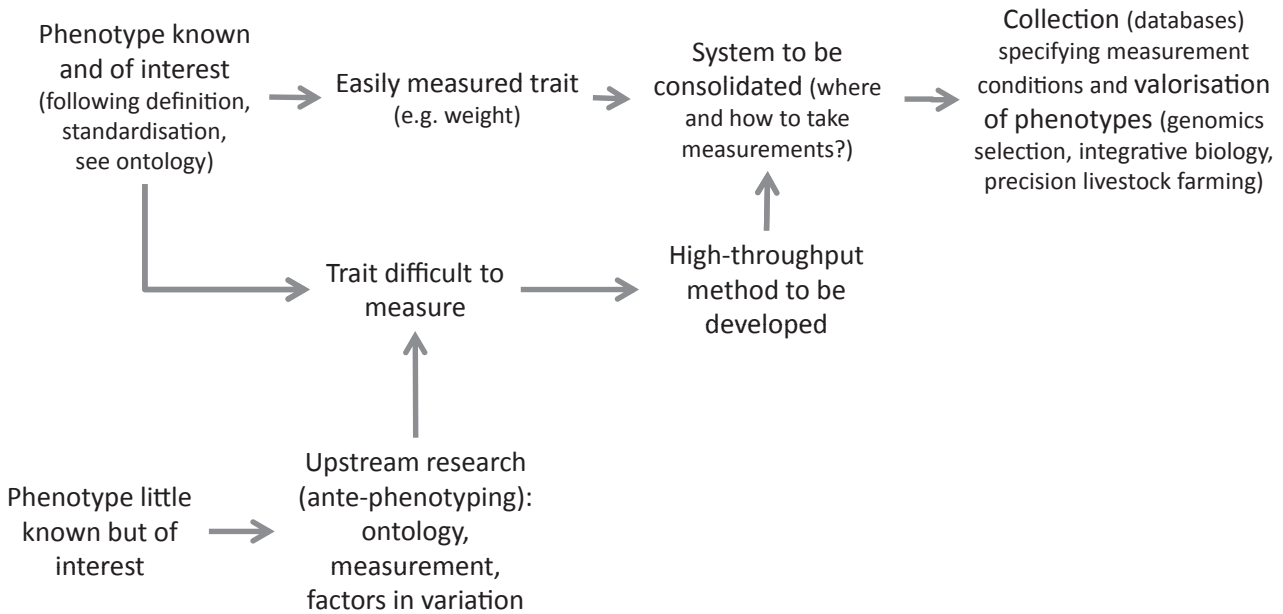


Figure 1 Overall strategy to develop high-throughput phenotyping.

calibration (linearity), accuracy, precision, validity range, quantification threshold, detection threshold, sensitivity, measurement uncertainty and robustness (Huber 2007 and <http://www.labcompliance.com/tutorial/methods/default.aspx>).

THE NEED FOR STANDARDIZATION

In this context of high-throughput phenotyping, obtaining phenotypic information that is accurate, reliable, repeatable and comparable between laboratories, countries or companies, is critical to gain a better understanding of the relationship between genes and phenotypes, and to develop precision livestock farming using robust animals. Up till now, it has been extremely difficult to combine various sources of diverse phenotypic data from databases of many different origins due to the variability in phenotyping techniques (Hocquette *et al.* 2011c) and the absence of any information on livestock breeding conditions.

Research examples

To remedy these problems, various programs have been developed. For example, standard measurements to be set up at commercial farms to estimate a set of 12 criteria relating to animal well-being have been developed that take account of their relevance, repeatability and feasibility (European Welfare Quality® program) (Botreau *et al.* 2009).

Similarly, for horses, and in response to a request by sector professionals, two sets of standardized tests have been developed to provide a rapid and objective estimate of a horse's temperament and its aptitude to take

a saddle, i.e. temperament tests and the assessment of behavior and achievements (Lansade *et al.* 2010).

In the beef quality domain, the 'Meat Standard Australia' program has driven the development of a system for predicting beef quality (Watson *et al.* 2008). The MSA system derives from the constitution and exploitation of an extremely large database (over 500 000 samples), which is continuously being added to, thus ensuring an evolutive approach. It has only been possible to build such a large database by defining and standardizing the measurements taken on animals and meat. This database includes the results of consumer tasting sessions of various meats, based on a number of different cooking methods, as well as data on how the quality of the tasted products (animal, carcass, meat) is put together. This system is a genuine innovation for the meat sector (Hocquette *et al.* 2011b). Another less costly approach is to combine the results of several experiments performed to date in a single database; however, in this case, researchers are hindered by the lack of standardized analysis methods and techniques (Hocquette *et al.* 2011c).

A prerequisite: ontologies

Successful research in the field of high-throughput animal phenotyping requires a common language with shared, unambiguous definitions of traits and their measurement methods (Hughes *et al.* 2008). To this end, the phenotyping program will build on the 'Animal Trait Ontology of Livestock' (ATOL) program developed in France at Inra in collaboration with the Iowa State University, which is seeking to produce an

accurate definition of traits of phenotypic interest (Hurtaud *et al.* 2011).

At this stage, it is important to review a few basic definitions.

- A phenotypic trait corresponds to a simple, easily measured characteristic. This may be the animal's weight, its body composition, its milk production, etc.
- This phenotypic trait is linked to a state or value that corresponds to what is actually measured and relates to a phenotype. The phenotype corresponds to the state of a trait of an organism positioned in relation to all the states of this trait found in the animal population. For example, we would say that an animal is large (its phenotype) as its size (the related trait) will be higher than average.

An ontology is a formal, structured representation of a set of objects (in this case, animal traits or measurements), and of the relationships between these objects. In an ontology, the concepts defining the relationships between these concepts are clearly defined. The concepts are organized in a structured manner (often a hierarchical structure). The meaning of a term defining an object is used unambiguously. The terms used must be machine readable (enabling automated measurements or data use).

To date, researchers involved in the ATOL program have focused their efforts on defining traits and the hierarchical structure that exists between them. ATOL covers the majority of farm vertebrates, including mammals (sheep, cattle, pork . . .), poultry (chicken, turkey . . .) and fish (trout, salmon, seabass . . .). Over 1600 traits have been defined so far concerning animal adaptation and well-being (300), nutrition (> 400), growth and meat production (200), milk production (> 400) and reproduction (300) (Hurtaud *et al.* 2011). There are also plans for a reference base for the measurement techniques used with these traits together with an ontology of livestock breeding conditions. The first aims to provide an accurate definition of the measurement protocols according to standards closely aligned with the quality assurance system, the second aims to define the environmental conditions under which the measurements are taken.

Other standardization approaches

The advent of modern genomics techniques, that generate large amounts of information with experiments that can be difficult to reproduce, has on occasion generated standard protocols that the scientific communities have been invited to adopt.

For example, MIAME (minimum information about a microarray experiment) describes the minimum amount of data that is essential to communicate on a transcriptomics experiment in order to enable both the interpretation of the experiment results with the least

possible ambiguity and to contribute to the reproducibility of the experiment (Brazma *et al.* 2001). More recently, some authors have proposed a MIAPE (minimum information about a proteomics experiment) (Taylor *et al.* 2007). This concept has been extended to include fields other than genomics with, for example, the MIBBI (minimum reporting requirements for biological and biomedical investigations) (Taylor 2007).

Similarly, the MIASE (minimum information about a simulation experiment) describes the least amount of information that needs to be communicated on the modeling approaches. The systematic application of MIASE rules should make it possible to reproduce the modeling studies and, therefore, check the results. This level of transparency is needed to provide the best possible assessment of the quality of a scientific activity. This should also make it possible to share simulation techniques, promote joint projects and use models (Waltemath *et al.* 2011).

At present, some scientific reviews have reported that raw experimental data is not sufficiently accessible. In the medical domain, the editor of *BioMed Central* encourages all authors of a published clinical trial paper to contact them to discuss the publication of their dataset in order to share it with other researchers. More specifically, the journal *BMC Research Notes* made a call to encourage researchers to take responsibility for promoting best practices in terms of standardization, along with the sharing and publication of data with the goal of predictive biology (Hrynaskiewicz 2010).

TOWARD A NEW ORGANISATION

Approach

The setting up of phenotyping programs will make it necessary to prioritize which phenotypes are of the most potential benefit and are most relevant according to their endpoints (development of technical itineraries, genomic indexing, etc.) based on the profile of tomorrow's animals that will have to be efficient, robust, adaptable and productive as detailed earlier. It will also be necessary to store environmental data describing the breeding system in which animals are phenotyped. This will help to gain a sound understanding of the phenotypic differences between animals.

In the same way that the development of complex, costly and standardized techniques for sequencing, transcriptomics, proteomics or metabolomics drove the emergence of genomics platforms, high-throughput phenotyping programs also involve the building of a network of coordinated research (laboratories, experimental units) or development (professional experimental farms, animal husbandry networks) facilities with all the latest, appropriate equipment. This is why different proposals are currently under evaluation in response to different

national or international calls for research platforms focused on animal high-throughput phenotyping.

Facilities to be set up for animal production

The collection of phenotypes requires the setting up of a network of phenotyping platforms specializing in animal production. These platforms may comprise the following.

- 1) Animal husbandry units at professional organizations or experimental units at research institutes, allows gathering animals under controlled conditions. One of the challenges facing these entities will be their ability to identify all the phenotypes of interest on the same animals in order to perform genuinely integrative biology. At present, the current pattern of dispersal of research bodies means that phenotypes of interest are measured on different animals at different locations, thus making it impossible to analyze the interaction between biological functions. Electronic devices to fully equip animals will help to record a lot of physiological and behavioral information and even basic zootechnical ones, especially for poultry species (or fish).
- 2) Equipment and skills at research laboratories, generally located at or close to these units, capable of performing the measurements on both animals and on the samples received from the various units across the network, as well as from farms or even from downstream sector chains (slaughterhouses, dairies, etc.) as part of major phenotyping projects. This equipment will have to incorporate the latest technological developments, in particular, those developed in the medical research sector (imaging, magnetic resonance, gene expression microarrays, etc.). These analytical platforms will have to base their operations on a set of specifications that meet current quality assurance standards.
- 3) Transfer and storage facilities for raw data generated by specific equipment (sensors, weighing machines, analytical robots, etc.) which will be set up at these various units. The principle behind these data transfers and storage is to focus on the rawest possible data that is as close as possible to the signal generated by the device, bypassing the interfaces that deliver ready-interpreted data, so as to preserve every opportunity for subsequent analysis of biological phenomena.
- 4) Web robot for scanning zootechnical databases that will have to be shared and will be produced by pooled systems for automatic extraction and marking of individual subjects expressing extreme phenotypes, if possible related to fellow members of the species presenting with the same pheno-

typic 'deviances' (family trait). Such a system used for technological intelligence and monitoring of pooled databases would enable the rapid identification of animals of interest (prior to their disappearance) and the collection of the biological samples required for genomics, transcriptomics, proteomics or metabolomics studies.

- 5) Centre for the storage of biological products (meat, milk, blood, miscellaneous tissues, etc.): this involves this network being backed up by resource centres that ensure that phenotypes are traceable and make it possible to find and reanalyze a biological sample with new technology that did not exist at the time that the sample was taken. These collections will be operated according to a specification that covers all the biological resources centres.

Examples of high-throughput phenotyping projects or facilities

A number of pioneering large-scale projects have already been launched in several countries. This is the case, in particular, for the French project QUALVI-GENE. This project entitled 'Detection and validation of beef quality genes in the three main beef breeds in France' was launched in 2003 by involving research bodies and professional organizations. Its aim was to develop a powerful tool for analyzing the genetic determinism of beef qualities vital to the development of selection methods based on molecular information. It has notably enabled the creation of a phenotypic databank for over 3000 animals according to standardized protocols based on use of a system for monitoring beef traits in offspring for calves belonging to the Charolaise (33.3%), Limousine (37.4%) and Blonde d'Aquitaine (29.3%) breeds over a 3-year period (Allais *et al.* 2010, 2011). In the field of reproduction, a sample of 3500 Prim'Holstein cows was monitored during the first third of the gestation period in order to phenotype failed gestations due to early, late embryonic or fetal mortality (Ledoux *et al.* 2011; Ponsart *et al.* 2011b).

Coordinated by Inra and launched on 1 March 2011, the European project AQUAEXCEL (Aquaculture Facilities for Excellence in European Fish Research) aims to set up a new European platform of excellence for aquaculture research and experimentation. The overall objective is to facilitate innovation, sharing common tools and standardized methodologies for phenotyping, in order to develop a high-quality aquaculture production with a negligible environmental impact. AQUAEXCEL is run by a cross-disciplinary team of experts in fish nutrition, physiology, health and welfare, genetics, aquaculture instrumentation and engineering; it is underpinned by ATOL ontology. It will network the highest-performing European aquaculture research facilities (17 partners, 11

countries), covering all production systems, environments, species, scientific expertise and disciplines (http://www.inra.fr/presse/lancement_projet_europeen_aquaexcel).

The PHENOFINLAIT program (<http://www.phenofinlait.fr/spip.php?rubrique11>, Faucon *et al.* 2010) was launched in 2008 and groups all the French actors in the dairy sector. Its aim is to characterize the fine composition of milk (fatty acids, protein fractions) in order to identify and quantify influence factors and their interactions: alimentation, genetic variability, detection of QTL and links with major genes. The expectations of this program are threefold: (i) to implement high-throughput phenotyping methods and 'phenotype' a very large ruminant population; (ii) to lay down the basis for improving the genetics of these characteristics (introduction in a genomic selection); and (iii) to propose a model designed to improve current livestock breeding guidance on the basis of routinely measured profiles of milk fatty acids (in particular). Altogether, 12 000 cows, 4000 ewes and 4000 goats representing seven different breeds, 1500 livestock farms and 26 departments have been phenotyped using milk samples taken 4–6 times per lactation. Samples of blood (genotyping) and milk (additional studies) will also be collected and stored. An important step in this work is the harmonization of milk analyzers for the determination of fatty acid composition in milk of individual animals by Fourier-transformed mid-infrared spectrometry (Ferrand *et al.* 2010; Leray *et al.* 2011).

Similar projects are also being launched in North America. One large-scale project currently underway in Canada is entitled 'Application of next generation genomic tools in Beef: Addressing the Phenomic Gap'. The aim is to collect a large amount of data (pedigree, performance, carcass characteristics, beef quality, sensorial analysis, etc.) on 2000 animals. A similar project targeting 8000 beef cattle is currently being carried out in the USA. The objective here is to gather genotypic and phenotypic data in order to improve feed efficiency and body composition, and limit greenhouse gas emissions (<http://www.beefefficiency.org>).

Germany launched the PHENOMICS project in May 2010. This involves a network of animal science research units that boast expertise in functional analysis of genomes, veterinary sciences, farm animal genetics, the biology of animal behavior, livestock breeding, bioinformatics and biomathematics. The network is coordinated by the Faculty of Agricultural and Environmental Sciences at Rostock University and includes 19 partners at seven German universities and two independent research institutions <http://www.phaenomics.auf.uni-rostock.de/en-home.html>.

Although not performed under commercial conditions at the production levels, such large-scale phenotyping programs are in fact routinely conducted by the

breeding companies on poultry pure line breeds (but in individual cages). In France, companies have more than 3 million birds presently identified in their data base and over 16 million data. It is in fact also done in fish as only pure lines are being used for the production.

Existing facilities in other domains

Projects run by high-throughput phenotyping platforms currently focus mainly on plant models. Such platforms are generally based on transporting hundreds of plants via conveyors to measurement units that provide irrigation and use optical measurements to monitor plant growth and physiological properties. Setting up a network of such platforms is a major European-scale challenge (see: EPSO: Workshop on Plant Phenotyping, November 2009; <http://www.plantphenomics.com/phenotyping2009>).

In the animal domain, phenotyping platforms have mainly been developed for animal models and are grouped in France as part of the CELPHEDIA network (Creation, Breeding, Phenotyping, Distribution and Archiving of vertebrate models) which develops innovative and standardized technological approaches aimed at speeding up the understanding of the genome and obtaining models of human diseases using animal subjects (<http://www.celphedia.eu/>). There are also several small to medium-sized structures that generally have a transgenesis workshop backed up by a 'rodents' animal house at research centers.

At the international level, a network of high-throughput phenotyping platforms for mutant mice are generating models of human diseases. The world organization for the production of mutant embryonic stem cells (ES cells) now makes it possible to generate series of targeted mutations in just about any kind of gene, which are inducible in time and space. The full potential of this resource is realized when the platforms that generate mutant mice are linked to phenotyping centers capable of exploring the role of each gene. To meet this challenge, several international initiatives have been organized in order to standardize functional tests. The European EUMORPHIA program (<http://www.eumorphia.org>) has created a database, EMPReSS, that has established 150 new operating procedures designed to cover all the major physiological functions, in addition to diseases. This family of procedures is then used in high-throughput phenotyping screens.

A phenotyping program is currently being launched as part of the 'International Mouse Phenotyping Consortium' (IMPC) in order to produce the first standardized and systematic comprehensive functional analysis of the entire set of mouse genes. The introduction of a number of experimental facilities for mice as part of the IMPC will facilitate the comparison of data

between the various laboratories, with the aim of limiting experimental variability sources and research costs, while in no way diminishing their effectiveness (in fact, it may even increase it). More importantly, the use of validated protocols will also make it possible to reduce the number of animals used in research laboratories. The availability of standardized screening programs linked to powerful computing tools and structures will be instrumental in spreading a systematic and rational method for characterizing the phenotypes of individuals. The European initiative Eumodic (European program entitled 'European Mouse disease clinic', <http://www.eumodic.org>) fits perfectly into this domain.

These examples show that the organization of biological research is undergoing profound changes by encouraging the sharing of available experimental means and the setting up of new facilities with standardized and shared methods. While this trend is developing in the plant or medical domain, it is only just beginning in the domain of livestock breeding.

We can learn a lot by looking at other facilities that have been developed for model animals (laboratory mice) in order to develop facilities for our agronomic species. However, the genes of interest regarding our breeding animals will surely differ from those studied in mice and humans (Liao & Zhang 2008), which is why it is important that we develop our own facilities.

Accordingly, the scale of the challenges to be faced in order to generate useful, complete and standardized data for the characterization of phenotypes requires far-reaching measures. The model that is emerging is based on platforms of excellence that specialize in a given physiological function to ensure their efficacy and drive economies of scale. A networked model of integrated centers and specialist hubs would provide a way of achieving such efficiencies but would require solid project management and sufficient computing facilities to enable data pooling and use.

Conclusions

While high-throughput phenotyping has developed strongly over the last few years, mainly with plants and laboratory rodents, high-throughput phenotyping of farm animals is still at the very early stages and, with just a few exceptions, does not yet have clearly identified technological facilities.

Setting up phenotyping research facilities opens up a broad spectrum of issues that range from upstream thinking about which criteria to measure, the measurement tools and methods, the modernization of experimental facilities capable of performing such measurements, etc., up to the acquisition, storage, management, sharing and analysis of the measured data.

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