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Where Next for Livestock Innovations?

There is no doubt that the tremendous developments in the biological sciences will provide many opportunities for innovation in livestock farming. Innovations currently underway include speeding up the process of selective breeding and delivering new and better diagnostics and vaccines. We have already seen development of GM farmed species and some of these are likely to get to market somewhere in the world in the next few years. In the medium-term there will be innovations from combining cell and genomic technologies. The developments we see today are just the beginning of what will be possible and are unsophisticated in comparison to what will be possible in the longer-term. Biology and biotechnology (with a little help from the disciplines of engineering) offer practically unimaginable potential to improve the efficiency of food production from livestock; to reduce environmental impact per unit food produced; to reduce the impact of disease; improve animal welfare; to enhance product quality and nutritional value, and to safeguard human health.

Innovations in livestock farming will be needed to address the growing global demand for animal protein from a growing and more affluent population and to address the other challenges of the ‘Perfect Storm’ [1]. The research and development to deliver these benefits does of course take time (in some cases decades), but in Europe the speed at which these innovations will be delivered is, in the short-term at least, likely to be more a function of politics and policy than the ability of science to deliver innovative solutions.

Recent innovations

Looking back at recent decades we can see that global livestock production has already benefitted from a wide range of innovations (see Table 1 for some examples).

Table 1 Application areas and example innovations

Breeding and genetics	Reproduction	Animal health	Growth modifiers	Nutrition	Other biotechnologies	Post-farm gate
Breed substitution	Oestrus synchronisation	High-health stock	Hormone implants	Formulation to requirements	Multiple ovulation and embryo transfer	Meat quality standards
Within breed improvement	Induced parturition	Improved diagnostics	In-feed growth modifiers	Synthetic amino-acids / micronutrients	Semen sexing	HACCP
Wider use of breeding values	Wider use of AI	New and better vaccines	Injectable productivity enhancers	In-feed enzymes	Vaccine immune-modulators	Novel processes & packaging
Use of DNA diagnostics	Embryo transfer	*Salmonella* vaccination		Pre- and pro-biotics	SCNT cloning	Traceability systems
Genomic selection in dairy cattle	Pregnancy scanning	Selection for disease resistance		Modified product composition via diet		

Overall these innovations have helped deliver considerable improvements in the productivity of many livestock systems. Indicative progress between the 1960s and the early part of this century was reviewed [2] and is summarised in Table 2. Several innovations contribute to the improvements seen, but it is generally accepted that the largest single factor is the impact of improved genetics (breed substitution and selective breeding).

Table 2. Improvements in livestock productivity over the last 40-50 years

Species	Trait	Indicative Performance		
		1960s	**2005**	**% Change**
Pig	Pigs weaned/sow/year	14	21	50
	Lean meat %	40	55	37
	Feed conversion ratio (FCR)	3.0	2.2	27
	Kg lean meat/tonne feed	85	170	100
Broiler chicken	Days until 2 kg are reached	100	40	60
	Feed conversion ratio	3.0	1.7	43
Layer hen	Eggs per year	230	300	30
	Eggs/tonne feed	5000	9000	80
Dairy cow	Kg milk/cow/lactation	6000	10000	67

Modified from van der Steen et al. (2005)

These improvements in production efficiency in turn provide other benefits. We recently used the Life Cycle Analysis (LCA) models of UK agriculture developed by Cranfield University to estimate the effect of past selective breeding on the emissions from UK livestock production. Genetic trends from breed improvement programmes were fed into the LCA model along with estimates of the uptake of improved breeding stock [3]. The results show that the intensive poultry breeders have reduced emissions (in terms of Global Warming Potential) by over 1% per year for the last 20 years. These improvements are from selection for efficiency and are not from any direct selection for reduction of emissions. Pig and dairy industries are not far behind these reductions, but beef cattle and sheep production has changed little in the genetics of emissions per unit product. This is in part due to the biology of the species (longer generation intervals and fewer progeny per male), but also reflects the facts that feed efficiency is not a measured trait in these industries and that the uptake of improved stock by commercial producers has been poor.

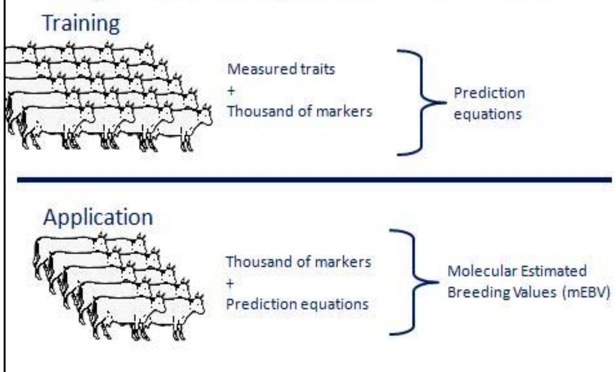
Table 3. % change in gaseous emissions and global warming potential achieved through genetic improvement (1988-2007)

	Methane	**Ammonia**	**Nitrous Oxide**	**GWP_{100}**
Chickens – layers	-30	-36	-29	**-25**
Chickens – broilers	-20	10	-23	**-23**
Pigs	-17	-18	-14	**-15**
Cattle – dairy	-25	-17	-30	**-16**
Cattle – beef	0	0	0	**0**
Sheep	-1	0	0	**-1**

GWP_{100} = the global warming potential over 100 years in CO_2 equivalents

These calculations illustrate that there are win-win scenarios where production efficiency can be improved at the same time as improvements in environmental sustainability. These types of calculations can be done for other innovations; for example, researchers in the US [4] have calculated the impact of using recombinant bovine somatotrophin (Posilac™) to boost milk yield in dairy cows. The 'layman's terms' way of expressing the impact was that for every one million cows treated the carbon footprint of milk production is reduced by the equivalent of taking about 400,000 family cars off the road in the US. Similar calculations might be done for innovations that control endemic disease, for feed additives or even GM livestock.

Figure 1. The Principle of Genomic Selection



Breed improvement

Innovations currently in progress are changing the way that animal breeders undertake breed improvement. Some of these changes are about the quantitative analytical techniques applied to existing trait data; such as taking group effects into account and seeking to select for the best group of animals rather than the best individuals [5]. However, the most dramatic recent changes have come from a technique called Genomic Selection [6] (GS) that is significantly speeding up the rate of progress in global dairy cattle breeding. GS uses a very large number (in the range of 50,000 to 800,000 currently in most species) of DNA markers (anonymous differences in DNA sequence located throughout the genome that in most cases have no known functions) that have been derived from the reference cattle genome sequence.

In dairy cattle GS allows prediction of the genetic merit of young animals (long before bulls will have daughter records available) from statistical associations of these DNA markers with trait measurements on past generations, which is referred to as the 'training' data set (see figure 1). This technology is now being widely applied and has reduced generation intervals in dairy cattle from over five years to under two years. Even though it is less accurate than progeny testing, the faster generation interval is estimated to increase the annual rate of progress by about 60% (for a recent overview see [7]). Faster progress can be beneficial, but it can also result in unforeseen consequences being seen more quickly than would otherwise have been the case. This potential risk reinforces to breeders the need for balanced selection goals that take proper account of fitness traits and the need to be vigilant for unforeseen consequences. If selective breeding does cause unintended harmful consequences then selective breeding is also the means to put things right. Genomic Selection has the added advantage that it results in lower rates of inbreeding than conventional selection (based on information from an animal and its relatives) and provides new information that can be used to monitor, manage and, where appropriate, conserve biodiversity within a population.

One of the disadvantages of GS is that very large numbers (thousands) of animals with trait measurements are needed in the 'training data set' to deliver accurate prediction equations. So while this approach works well for Holstein dairy cattle it is (currently) less feasible or cost effective in other breeds or species with smaller numbers of measured animals. It has great potential for impact in some of those difficult or expensive to measure traits such as meat quality or feed efficiency, but this potential can only be realised by significant investment in trait measurement in large numbers of animals (most likely of each breed and quite possibly also in the relevant environment). Potentially the training of GS can be done for a customer's specific production environment and needs, and sires that best meet those needs would then be selected. This approach is already being considered in dairy cattle.

Other opportunities from genomics

There are many other benefits to be delivered for animal breeding and animal health from the availability of reference genome sequences of livestock species (we have all the major species sequenced), the genome sequences of pathogen species, and the ever decreasing costs of DNA analysis. Some examples that will not be considered in any detail in this paper include:

- Improved diagnostics
  - Speed, specificity, sensitivity, quantification
- Molecular epidemiology – e.g. tracking a disease outbreak to its source
- Rational vaccine design
  - Subunit, rationally attenuated, recombinant and DNA vaccines
- Host–pathogen molecular biology
  - Breeding for disease resistance – e.g. scrapie resistance or *E. Coli* resistance in pigs
  - Immune potentiators including improved vaccine adjuvants
  - Optimal breeding stock/vaccine combinations
  - GM disease resistance
- New therapeutics – including the development of performance modifiers
- DNA tools for traceability, parentage assignment/verification and authenticity testing

Advanced reproduction technologies

There is a history of innovations in reproductive technologies that were pioneered in livestock now demonstrating benefits in human medicine; including artificial insemination, embryo transfer and *in vitro* fertilisation. Some of these technologies have had enormous impact on livestock production and others have played only a small part in accelerating selection and dissemination of elite animals.

The same will be true of recent innovations. Technologies for semen sexing (separation or concentration of X or Y chromosome carrying spermatozoa) are already having a significant impact in altering sex ratios. It is estimated that by the end of 2011, 10% of replacement Holstein heifers in the US will be born from sexed semen [8]. There is ongoing research seeking to deliver sex ratio control in pigs and poultry and the potential benefits to sustainability and animal welfare are likely to be substantial.

It is less likely that somatic cell nuclear transfer cloning (SCNT cloning – the "Dolly the sheep" technology) will have a dramatic impact in the short-term. It is however now approved in the US and in use in South America and elsewhere. It has application as: i) an insurance policy to 'copy' very high value individuals such as dairy bulls; ii) a means of disseminating more genes from very high merit individuals (e.g. in pigs where the number of doses of semen from an individual male are more limiting); iii) a way to increase the numbers of animals in highly endangered breeds (it has already been used this way twice); iv) as a means to recover breeding animals from stored tissue or from animals too old or otherwise incapable of breeding (again this has been done); v) an improvement to biosecurity of international trade in genetics (cell lines can carry fewer diseases than imported eggs or semen); vi) potentially some niche uses in breeding programmes e.g. selection for meat quality, and of course, vii) as a research tool. Cloning is not yet possible in poultry and it is likely to be many years before we can contemplate seeing herds or flocks of cloned pigs, cattle or sheep, if ever, largely because the costs of cloning are simply too high. It also needs to be emphasised that animal breeding is a continuous process reliant on variation from which to select. Clones of today's best animals would soon be seen as outdated - as better animals are produced through selection.

Other biotechnologies

Cloning is of course also useful as a way of disseminating GM animals or generating live animals from cells that have been modified, such as through GM. Note however that it might also be possible to select multiple generations of cells *in vitro*, by combining GS with cell technologies [9]. The proposal is that cells in culture might be induced to divide to produce (through meiosis) the equivalent of eggs and sperm, and that fusing these cells in the lab would create new cell lines that might be evaluated by GS to select the best; these would then be induced to generate new eggs and sperm (or equivalent cells that could be fused) and the process would repeat. This could reduce the generation interval of any species down to less than one month. After a series of generations of selection, cloning would be used to produce and evaluate the live animals. There are, of course, a number of risks with this proposed process that would need to be evaluated and mitigated.

Perhaps the most dramatic innovations will be possible through genetic engineering and it's more recent offshoot, synthetic biology. Genetic Modification (GM) is often seen as a single technology when in fact it covers a whole spectrum of ways to increase biodiversity in a farmed population. The tools available to the DNA engineer now include the ability to make very small changes in precise locations (Zinc Finger Nucleases [10]). These tools might, for example, be used to correct an inherited defect in an elite family of animals (rather than losing diversity by breeding it out). Technically these animals would still be GMOs, but clearly no foreign DNA has been used so they do not qualify as transgenic.

The term for moving DNA around within species by GM is called cisgenesis (producing cisgenic organisms) and other examples might include: a) increasing the number of copies of a gene (already done for milk protein genes in cattle [11]); b) deleting a gene; c) changing the regulation of a gene so that it is expressed less or more or at different times or in different tissues (or combinations of these); d) moving the location of a gene in the genome to change its expression (for example putting it on a sex chromosome so the effect is different in males and females); e) moving a version of a gene from one breed within a species to another to convey a particular trait variation (much faster than breeding that gene in through multiple generations of crossing), and f) reengineering a gene (for example changing the structure of a protein to alter its function or behaviour). This last example is where biology meets engineering – protein engineering or by some definitions synthetic biology.

Existing examples of transgenesis (moving DNA between species) in livestock include; the Canadian Enviropig™ [12] that has been engineered to express the enzyme phytase (from *E. coli*) in its saliva, thus enabling it to extract more phosphorous from the cereals in its feed and consequently pollute less; and dairy cows that expressed a compound in their milk (lysostaphin - produced by one *Staphylococcus* species) were effectively protected from mastitis infections cause by *Staphylococcus aureas* [13]. There is other research underway on diseases resistance through GM that will be mentioned in the conference talk.

The final technology to mention here is one that it is hoped will have considerable potential in human medicine – gene therapy. Various methods are being explored to change gene expression in target tissues to alleviate or cure disease. These therapies commonly seek to carry novel DNA into cells and get that DNA expressed. In livestock, modified viruses have been used to deliver vaccines, but they have also been modified to deliver gene therapy in the form of additional copies of target-species own genes that then help improve immune function. Development is underway for such therapies for improvement of gut health of pigs and poultry [14], but such products have not yet reached market.

Conclusions

We have been innovating in livestock production since we first domesticated the species we now farm. The main changes we have made are to the animals themselves. Breed improvement and effective dissemination (e.g. via reproductive technologies) has been, and remains, one of the most effective ways to feed more people from the same or fewer resources. Modern biology has accelerated the process of breeding better animals and rapid further acceleration can be expected. In addition, innovations in the way we manage the performance and health of livestock will be delivered by advances in our ability to understand and control reproduction, productivity and health.

Technologies can have both positive and negative effects simultaneously (for example improving disease resistance may improve productivity and welfare, but at some cost to efficiency in the absence of disease) so we need systems approaches that enable us to measure (or ideally forecast) the balance of the impacts – examining benefits, harms, risks and the trade-offs between them. At the same time we must have a rational approach to risk in our regulatory processes – there are, after all, many risks to inaction and stagnation.

Selective breeding technologies in use or near market can deliver a large part of the improved efficiency of food production needed to meet growing global demand for foods of animal origin and do this with fewer resources and lower environmental impact (per unit food produced); and with better animal welfare and human health. Even greater net-benefits will be achieved, or will be achieved faster, in those countries that have an enabling regulatory environment for biotechnologies.

I'm one of those people that believe there is no such thing as a bad technology; it all depends what you do with it and whether the balance of the outcomes (for us, for the animals and for the planet) is good or bad. That is of course, in the end, a value judgement driven by many things; including whether or not you live in feast or famine. It's normal for young technologies to improve with development work and our experience of them. Biotechnology will be no different. I suspect those who were unimpressed with, or even critical of, Stephenson's Rocket (1829) would, had they lived a long time, have been rather impressed by the Flying Scotsman locomotive (1923). Biotechnology developments will, by comparison, be quite a lot faster.

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