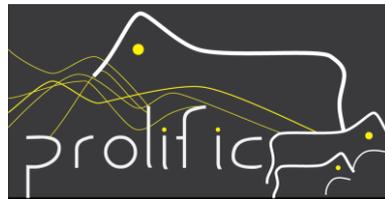


Highlights from PROLIFIC (Pluridisciplinary study for a RObust and sustainabLe Improvement of Fertility In Cows")



August 2016

Collaborative project funded with 3M€ by the european Community's Seventh Framework Program
FP7/2007-2013 under the grant agreement nº 311776
Duration of the project: 1/feb/2013 - 1/feb/2017

www.euprolific.eu

PROLIFIC is a pluridisciplinary project which aims to develop a proactive herd management by providing the farmer with improved tools for on-farm reproductive monitoring and management.

The context

Intensive genetic selection in dairy cattle has resulted in modern cows with very high milk yield but reduced fertility and poor calving performance. The sustainability of dairy cattle farming systems relies in large part on the ability of cows to maintain reproductive performance as they cope with the constraints imposed by environmental conditions and livestock practices. The strategic aim of this project is to unlock the potential for proactive herd management by providing the farmer with improved tools for on-farm reproductive monitoring and management. This will be achieved by a pluridisciplinary approach to eliminate the key scientific/methodological blockages and develop innovative solutions for a robust and sustainable improvement of fertility in cows.

General objectives

Are to eliminate the key scientific and methodological blockage and develop innovative solutions for a robust and sustainable improvement of fertility in cows.

The project will:

- 1) develop models to support on farm decision at different levels: animal fertility, herd management, and socio-economic impact for the farm and the farmer
- 2) identify genes and pathways involved in the adaptation of the reproductive function to different environmental conditions, especially low input feeding systems
- 3) identify the functional quantitative trait nucleotides for days till first luteal activity (based on progesterone measures) and estimate genomic breeding values using whole sequence information on individuals
- 4) study the adaptative response of animals to different feeding systems and management strategies
- 5) demonstrate the applicability of the knowledge and tools produced in the PROLIFIC project at the farm level
- 6) disseminate the knowledge produced in the project to the relevant stakeholders.



Workpackages.

The project is divided in 7 WPs:

WP 1 Multilevel integration and modelling of reproductive performances at different scales

WP 2 Molecular approach for fertility markers

WP 3 From genomics to selection

WP 4 Innovations in farm nutritional management to optimize cow fertility

WP 5 Multi-site demonstration of reproductive management tools

WP 6 Outreach

WP 7 Management

Participants

PROLIFIC is a pluridisciplinary project taking advantage of the skills and expertise (modelling, molecular biology, genomics, phenotypic recording and statistics) of partners from all Europe. Seven research organizations, one industry and four SMEs are involved in the project:



1 INSTITUT NATIONAL DE LA RECHERCHE AGRONOMIQUE (INRA) France

2 AARHUS UNIVERSITET (AU) Denmark

3 CONFEDERACION DE ASOCIACIONES DE FRISONA ESPANOLA (CONAFE) Spain

4 INRA TRANSFERT S.A. IT France

5 TEAGASC - AGRICULTURE AND FOOD DEVELOPMENT AUTHORITY (TEAGASC)
Ireland



6 LATTEC IS (Lattec) Denmark

7 SERVICIO REGIONAL DE INVESTIGACION Y DESARROLLO AGROALIMENTARIO DEL PRINCIPADO DE ASTURIAS (SERIDA) Spain

8 TECHNOLOGIES SRL (ST) Italy

9 STICHTING DIENST LANDBOUWKUNDIG ONDERZOEK (DLO) Netherlands

10 SKANESEMIN EK FOR (SM) Sweden

11 SVERIGES LANTBRUKSUNIVERSITET (SLU) Sweden

12 THE SCOTTISH AGRICULTURAL COLLEGE (SAC) United Kingdom

13 UNION NATIONALE DES COOPERATIVES AGRICOLES D'ELEVAGE ET D'INSEMINATION ANIMALE (UNCEIA called now ALLICE) France

Highlights from WP 1

MULTILEVEL INTEGRATION AND MODELLING OF REPRODUCTIVE PERFORMANCES AT DIFFERENT SCALES

Overall objective of this WP is to develop models to support on farm decision at different levels: animal fertility, herd management, and socio-economic impact for the farm and the farmer.

Development of a Reproductive Physiology Model (RPM)

It has been developed a **Reproductive Physiology Model (RPM)** that simulates the hormonal dynamics involved in the regulation of the reproductive success of the cow. RPM is a theoretical model based on state-of-the-art descriptions of the bovine reproductive axis along the different physiological stages of the cow reproductive cycle (anovulatory, cycling, and pregnant). It was done a review of the literature to point out mechanism involved in the central regulation of the expression of oestrous behaviour in dairy cows. The model is based on a comprehensive representation of the key components of the reproductive axis mechanics: hormonal signaling (regulators) and biological units (sustainers of structural support for competence and functional generators of signals). This model simulates the dynamics of main hormones (LH, FSH, Inhibins, Progesterone, Estradiol, PGF2 α , Oxytocin, Interferon τ and Cortisol) and main biological units (follicles, corpora lutea, oocytes, embryos, spermatozoa, placentas, adenohipophysis and neurohipophysis) involved in the reproductive cycle. The model allows simulating the functioning of the bovine reproductive axis at different time scales: hour (e.g., pulsatility of oxytocin and prostaglandin F2 α during luteolysis,); day (e.g., estrous cycle); week (e.g., cyclicity,); month (e.g., lifetime reproductive performance),

By way of modulations of its parameters, the model can generate deviations around the normal behavior and simulate phenomena such as irregular cyclicity, short/prolonged luteal phases, fertilization failure and embryonic mortality. The implementation of this model has been achieved and sensitivity analysis is on track.

Analysis of progesterone profiles

It was analysed progesterone data from a research herd in Denmark. We divided them in five quantiles (Q1-5), and described their shape. It was found that 1) the majority of the progesterone profiles showed a typical profile, including the ones that exceeded the optimum cycle length of 24 days; 2) cycles in Q2 and Q3 had steeper slopes and higher peak progesterone levels than cycles in Q1 and Q4 but, when normalized, had a similar shape. This means that, in this dataset, we did not find many deviant progesterone profiles, and that the deviations that we did find were mostly related to height and length of the profile, not its actual shape.

Predict chance of insemination success

Progesterone data from seventeen Dutch and Danish herds were used to build an equation to predict chance of insemination success. We found that cycle length, parity and milk yield were found to be good predictors for chance of insemination success. Cows with higher milk yield appeared to ovulate later, so they might benefit from later insemination (1-2 d). However, this is (for now) a hypothesis, and needs to be investigated in more depth before we can draw any conclusions.

Key scenarios that are relevant and robust to increasing environmental variability and meet demands for a more sustainable dairy production

It was organized a workshop with the aim to build key scenarios that are relevant and robust to increasing environmental variability and meet demands for a more sustainable dairy production. The target audiences for the workshop were organizations that are partners in PROLIFIC or members of the Stakeholder Advisor Board (SAB), but the workshop was also open to other experts on invitation by partners or SAB-members. The workshop was held in Uppsala, Sweden, between 9 and 10 October, 2013. The main outcome of the workshop is the identification of 7 production systems and 10 management strategies that are relevant to consider in the modeling component of PROLIFIC. However, the ranking procedure pinpointed two in each that were considered the most significant.



These were: *Average productivity and input* and *High technology, high production, large herds, low grazing* for production systems and *Tailored voluntary waiting period* and *Heat detection/improvement methods* for management strategies. These should thus be the first priority to be included in the PROLIFIC project

Methane emission model

We have implemented a methane emission model in the SimHerd model. With the new model it was simulated various herds and scenarios focusing on reducing methane emission through reproduction and culling management. Simple scenarios of improved estrus detection rate and pregnancy rate resulted in increased methane emission per kg milk. This was mainly explained by increased young-stock herd. Reduced methane emission was simulated as a result of reproductions management scenarios where beef semen was used for the lowest producing cows in the herd. Such strategies require an overall good reproductive efficiency in the herd.

Highlights from WP2

MOLECULAR APPROACH FOR FERTILITY MARKERS

Objective: The identification of genes and pathways involved in adaptation of reproductive function to different environmental conditions, diet and pathogens. New findings on phenotypic and genetic markers for fertility could be used as tools to be included in selection schemes

Planned experiments and analysis aims to:

- identify from "*in vivo*" models molecular markers differentially expressed in relation with diet and/or Negative Energy Balance in fat and reproductive tissues.
- investigate in "*in vitro*" models changes induced by well known pathogens in uterine tissue.

Four types of outcome

1) New inputs in modelling: General information on mechanisms regulating reproductive function to be included in future simulations to optimize WP1 models has been produced. This includes new insights on the impact of diet on reproductive tissues, and how Negative Energy Balance potentially impairs uterine function which relates to some of the abnormal progesterone profiles and fertility issues under study in WP1.

2) Functional information to orientate future genetic studies: Both results from *in vivo* and *in vitro* models already show genes and network of genes differentially expressed / deregulated under metabolic imbalance or exposure to pathogens. This represent a functional information which can be used to reinforce the choice of candidate genes/regions potentially influencing fertility identified through WP3 and which could represent interesting targets to be studied more deeply in the future to optimize genomic selection.

3) Information to design new diagnosis and prognosis tools: Results which may be useful to design future diagnosis and prognosis tools have been generated. This includes for instance a list of genes and proteins modified by bacterial components which may be used to develop future tools dedicated to the diagnosis of persistent inflammation in the endometrium or predictors of pregnancy success. This includes also a list of candidate proteins / genes identified in fat tissue from pre-partum cows which could be predictive of fat mobilization/ metabolic disorders in lactating cows. Present work should be followed by development activities “post Prolific”.

4) Basic information for future research on Health and Resilience: Results have been produced from *in vitro* models showing a strong impact of metabolic imbalance on uterine tissue. This information and corresponding know how will now be used to develop un-invasive models to study how various factors affects health and resilience of uterine tissue in dairy cows.

Highlights from WP3

FROM GENOMICS TO SELECTION

The objective of this workpackage is to identify the functional mutations for days till first luteal activity (based on progesterone measures) and estimate genomic breeding values using whole sequence information on individuals. The fertility of dairy cows has decreased due to strong genetic selection for milk production. Currently more attention is given to fertility in breeding programs and the negative genetic trend is reversing resulting in an improvement of fertility, but availability of new fertility indicators could speed up this process.

New phenotypes

Traditional fertility traits based on calving and insemination records might be biased by farm management decisions, and endocrine measures based on progesterone profiles might be a better indicator of fertility status of the cow itself. For the Prolific project milk progesterone records have been collected for 5,770 lactations from Holsteins at experimental herds but also at commercial herd equipped with the Herd Navigator (Lattec I/S, Denmark). The raw progesterone measurements have been translated into endocrine fertility traits like commencement of luteal activity (CLA), luteal phase length etc.

New trait: commencement of luteal activity (CLA)

The heritability for CLA ($h^2=0.12$) was somewhat higher than the traditional fertility traits (calving interval and calving to first service) and some of the endocrine traits have a higher repeatability over lactations. CLA has higher repeatability ($r=0.29$) than calving interval ($r=0.09$) and calving to first service ($r=0.13$). Noteworthy, CLA had a lower correlation with milk production than calving interval and is thus a good trait to select for improved fertility whilst improving yield simultaneously.

Genomic predictions for CLA

CLA would be a good trait to select on without impairing milk production as strongly as selection for traditional fertility traits, but CLA is not recorded population wide. Therefore, it is being studied the accuracy of genomic predictions based on this reduced set of phenotypes. Prediction equations generated based on this studies, could be easily applied to SNP databases.

Identifying functional mutations for CLA

With this purpose, it is being studied the associations between the endocrine fertility traits and variation on the genomes of the cows, as most of the cows with progesterone records were also genotyped. At the moment it is being performed genome-wide association studies to search for genetic variants associated with endocrine fertility traits. The regions have been fine-mapped using whole-genome sequence data. Detected variants could be used in breeding programs to enhance genomic selection, but could also be used in farm management tools by developing optimal management and treatment protocols for the specific genetic background of the cow.

Optimal breeding strategies

Optimal breeding strategies will be evaluated by determining optimal selection criteria and the associated achievable genetic progress in terms of fertility traits.

Highlights from WP 5

MULTI-SITE DEMONSTRATION OF REPRODUCTIVE MANAGEMENT TOOLS

Objectives:

- To deploy, and evaluate, on commercial farms decision support tools that will allow the farmer to better target reproductive actions at individual cow and herd level, according to the livestock system he/she finds himself in.
- To demonstrate the feasibility of transferring new fertility bio-markers into an in-line on-farm measuring system. moving towards a pre-market stage the new knowledge and innovation developed in the project

Deployment of Insemination prognostic tool

The insemination Worth Predictor (IWP) is a decision support tool that describes the chance of successful insemination at a given oestrus.

- The IWP equation has been developed and is based on data derived from progesterone measurements in milk (Herd Navigator©). The length of the cycle ending at the oestrus, milk yield and parity are included in the equation.
- The model has been developed based on sixteen farms with a milk yield around 8,500-9,500 kg milk per year per cow.
- The preliminary evaluation of the model showed that the model is working well on farms with a milk yield around the level where the model was developed, but it needs further evaluation on farms with higher yield.
- Data from cows from 10 high yielding farms (between 9,500-12,500 kg milk per year per cow) will be used for further evaluation and calibration of the IWP equation.

Deployment of a reproductive management timing optimizer (RMTO)

The Reproductive Management Timing Optimizer (RMTO) is a decision tool that describes the (expected) effects of a change in fertility management in a herd.

- The RMTO relies on a herd-level simulation model, RPMherd, which is developed in WP1. The model is nearly finished and will soon be operative.
- RPM herd is able to simulate a herd and predict fertility performance and demography of the herd over time, using a set of predefined rules about culling, heat detection, insemination, and heifer management. These rules are either default (farmer chooses between fixed systems, e.g. low input, seasonal), or filled out by the farmer.
- Using questionnaires in Sweden, France and Ireland, default rules for each system were derived from farmers. Farmers and technicians in Sweden and France were gathered in focus groups, to ask them for their expectations and wishes for a tool. This was done to prevent that we build a tool that is not worth using in practice.
- In may and june a prototype of the tool will be shown to farmers and technicians, to ask for their opinion about the tool.

Deployment of a progesterone-based benchmarking tool (PBT)

The Progesterone Benchmarking Tool (PBT) is a decision tool that compares progesterone profiles from Herd Navigator© farms to a benchmark progesterone profile, and flags profiles that are deviant from the benchmark.

- The PBT relies on a herd-level simulation model, RPM herd, which is developed in WP1. The model is nearly finished and will soon be operative.
- On seven Swedish Herd Navigator© herds, cows were scored for body condition score at calving and at first AI, and this data as combined with available data from the national cow database and progesterone data. This dataset will be used for validation of the PBT.



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Her primary role is to represent the Consortium towards the EC as well as to be the promoter and supervisor of the overall technical and scientific workpackages of PROLIFIC.

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