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An Embryo Quality Assessment Application for ART Laboratories

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Resumo

Nesta dissertação é descrito um sistema que visa atender as necessidades de gestão da informação em laboratórios de Procriação Medicamente Assistida (PMA); é igualmente proposto um modelo de avaliação embrionária com base em uma norma triangular. Uma das consequências indesejáveis mais comuns de tratamentos de PMA é a ocorrência de gravidez múltipla. Portanto, reduzir o número de embriões por transferência é de suma importância. A fim de melhorar as taxas de gravidez, reduzindo a incidência de nascimentos múltiplos uma avaliação precisa da qualidade do embrião é essencial. Os principais objetivos do sistema sintetizado são dois: (i) a recolha e gestão de todas as informações necessárias para realizar a avaliação do embrião e (ii) o desenvolvimento de uma ferramenta que pode servir de ajuda para realizar essa avaliação com precisão e consistência. A aplicação aqui apresentada cumpre estes dois objectivos. A análise dos requisitos do processo de avaliação resultou em um modelo de dados flexível, usado no protótipo apresentado, apoiando o processo de tomada de decisão na transferência selectiva de embriões.

Palavras-chave

Avaliação embrionária, Tomadas de Decisão, Engenharia de Software, Procriação Medicamente Assistida

Resumo Alargado

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A análise dos requisitos do processo de avaliação resultou em um modelo de dados flexível, usado no protótipo apresentado, apoiando o processo de tomada de decisão na transferência seletiva de embriões. De forma algo simplista podemos dizer que o modelo proposto visa essencialmente poder conseguir distinguir diferenças na qualidade de embriões que, seguindo os modelos de classificação actuais, são classificados com uma mesma avaliação.

O modelo de avaliação proposto, baseado em uma norma triangular, é plausível para a avaliação precisa da qualidade do embrião. Por isso, pode ser usado como uma ferramenta eficaz para apoiar a tomada de decisão no processo de transferência seletiva de embriões. Os resultados da avaliação produzidos pelo algoritmo implementado trazem consigo alguma subjectividade na medida em dependem dos pesos (da importância relativa) de cada um dos parâmetros fixados pelo especialista do domínio de aplicação.

Este trabalho produziu uma ferramenta que permite ao administrador determinar os parâmetros que devem ser monitorizados durante as várias observações do desenvolvimento do embrião e registrar esses dados. Depois disso, esses dados estão

disponíveis para serem analisados e os embriões podem imediatamente ser classificados de acordo com os critérios ASEBIR, mesmo nos casos em que a informação disponível é incompleta (perante a ausência da recolha de algum dos parâmetros necessários).

Esta ferramenta tem como fator distintivo a capacidade de acompanhar a evolução e mudança contínua numa área de aplicação com investigação ativa e com constante inovação. Também a independência de um critério específico vai permitir que os utilizadores autorizados (por exemplo, o chefe do laboratório ou clínica) escolham os critérios de avaliação de acordo com a sua experiência.

Neste trabalho, para além dos pontos principais atrás referidos, é oferecida uma revisão bibliográfica sobre os mais comuns modelos de avaliação embrionária. Esta é complementada com um "estado da arte", julgado pertinente para o problema em questão, versando a arquitectura de software. É apresentado o modelo conceptual de dados e casos de utilização bem como diagramas de sequência. São igualmente apresentados testes efectuados com a aplicação. O documento principal termina com as conclusões obtidas e estabelecendo novas metas para desenvolvimentos futuros.

Para poder acompanhar melhor o processo de síntese da ferramenta desenvolvida em anexo são apresentados os diagramas de casos de uso, o diagrama de classes, exemplos de diagramas de sequência, um exemplo do ficheiro tipo *json* usado na aplicação, matrizes de rastreabilidade, uma tabela com os resultados de um conjunto de embriões cujos dados foram considerados para teste da aplicação, e um artigo que resultou deste trabalho e foi publicado numa conferência internacional com arbitragem científica.

Abstract

In this work it is described a system that aims to meet the needs of information management in Assisted Reproductive Technologies (ART) laboratories; it is also proposed an evaluation model of embryos based on a triangular norm. One of the most common undesired consequences of ART treatments is the occurrence of multiple pregnancies. Therefore reducing the number of embryos per transfer is of paramount importance. In order to improve pregnancy rates while reducing the incidence of multiple births an accurate embryo quality evaluation is essential. The main objectives of the synthesized system are twofold: (i) the gathering and management of all the information needed to perform the embryo evaluation and (ii) the development of a tool that can serve as aid to carry out that evaluation with precision and consistency. The application herein presented accomplishes these two objectives. The analysis of the requirements of the assessment process has resulted in a flexible data model, used in the presented prototype, supporting the selective embryo transfer decision-making process.

Keywords

Embryo Assessment, Decision Making, Software Engineering, Assisted Reproductive Technologies

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Acronyms

ART - Assisted reproductive technologies

IFV - In Vitro Fertilization

ICSI - Intracytoplasmic Sperm Microinjection

CRUD - Create Retrieve Update Delete

MVC - Model View Controler

MVVM - Model View Viewmodel

TDD - Test Driven Development

1. Introduction

1.1. Motivation & Objectives

The In Vitro Fertilization (IVF) is the main technique for assisted human reproduction. In 2009, more than 500,000 IVF cycles were recorded in the EIM European register and it is estimated that during that year, in Europe, one cycle per 1000 inhabitants occurred [1].

The assisted human reproduction is characterized by the formation and culture of embryos in the laboratory. Normally, per cycle, a greater number of embryos are produced than the number transferred to the uterus in order to achieve pregnancy. So it is important to choose the most well fitted ones in order to maximize the chances of success. Moreover, if our system of embryo assessment were very accurate we could reduce the number of embryos transferred per cycle to just one, so it would drastically reduce the occurrence of the most common complication, multiple gestations.

Assessing the quality of embryos is done mainly through the observation of their morphological characteristics. The choice of morphological parameters used for this evaluation, as well as the specific weight of each, varies greatly and leads to the development of many embryonic assessment systems. Recently there has been an effort to reach a consensus on the morphological categorization of the embryos [2, 3]. Ultimately this characterization is reduced to the definition of a discrete number of morphological categories in which the embryos are grouped with similar degrees of viability and probability of implantation.

In the routine practices of an ART laboratory, the embryos are examined under the microscope, measuring different morphological characteristics. These values are then integrated into the existing classification system at the laboratory. The integration of all the values displayed by embryos for each of the observed parameters is complex and sometimes is not easy to do it with enough precision and speed to make clinical decisions about assessed embryos.

Having a tool that, given the values of the morphological parameters, assigns each embryo to a certain category would be an important step in eliminating subjective factors in the evaluation of the embryos. Thus, it would facilitate the transmission of accurate information, regarding embryo quality, between ART centers in order to reduce dependence on the criteria of the observer.

1.2. Synthesis of the state of the art

Worldwide, it is estimated that one out of every six couples experience some form of infertility[1] problem at least once during their reproductive lifetime [5], and it is also estimated that 6.6 to 26.4% of women in more developed countries have a lifetime prevalence of infertility [6]. According to the European IVF-Monitoring (EIM) Consortium for the European Society on Human Reproduction and Embryology (ESHRE) lately there has been a steady increase in the number ART cycles per million of inhabitants. Table 1 presents the summary of the results of the studies by ESHRE on ART in Europe, for the years 2007 to 2009 [1, 7, 8].

In 2009 the Portuguese Society for Reproductive Medicine (SPMR), conducted a joint study with Keypoint[2], aiming to quantify and characterize the type of infertility existent in Portugal. According to this study there are at least 120.000 couples facing infertility problems, and 9.7% of women under 25 have problems in conceiving [9, 10].

In recent years the number of couples resorting to ART has increased considerably [11], consequently the amount of in vitro fertilization clinics has enlarged worldwide and the need to improve IVF techniques has become a major endeavor.

Table 1. Overview of ART in Europe, triennium 2007-9

Year	# countries where all clinics reported	# cycles reported	Total population (millions)	Cycles per million habitants
2007	18	376971	425.6	886
2008	19	350143	369.8	947
2009	21	399020	373.8	1067

The assisted reproductive technologies have grown in importance medically, socially and economically. The number of ART units available keeps increasing both in the public and private sectors. Although this is a field with enormous potential there are gaps in some areas including that of information technology (IT).

[1] According to the World Health Organization, Sterility is defined as the "inability to fertilize the ovum with a spermatozoan" while Infertility refers to "the inability to ensure that the fertilized ovum develops sufficiently for the birth of a viable child" [4]. In this paper we will use the word "infertility" to describe both situations since the type of diagnosis associated with reproductive problems will not have an influence on the current work.

[2] Keypoint Scientific Consultancy

The available ART units are multidisciplinary units that cover three different fields: medical, nursing and laboratory. Despite their importance and complementary character, the laboratory component has proven to be of particular importance [12, 13]. After infertile couples are diagnosed most of the process of becoming pregnant is largely dependent on the embryology lab.

Several ART techniques are applied in the embryology lab, namely In Vitro Fertilization (IVF) [14] and Intracytoplasmic Sperm Microinjection (ICSI) [15, 16]. Daily view of oocytes and embryos under an inverted microscope is required in both techniques for a period ranging between 2 to 5 days. Several morphological parameters are assessed during these observations in order to determine the embryo quality and implantation rate. These parameters are later used to determine which of the embryos are transferred or frozen. Evaluation should be continuous, systematic and reducing the variability between observers [17].

Since it directly affects the chances for success, the different techniques used in reproductive medicine embryo assessment are of enormous importance. One of the main problems concerning embryo assessment is the lack of a single evaluation criterion, although several efforts have been made to obtain a consensus [3]. The need to compare results makes it imperative to achieve some sort of standardization.

1.3. Main contributions

The main contributions of this research work can be summarized across three main threads.

a) A state of the art study was made, presenting a brief bibliographical review of the most common models of embryo evaluation. The workflow of an ART unit is also explained with enough detail so that people outside the area can understand better the work on these units.

b) The proposal of an alternative assessment algorithm [18] more flexible and generic than the existing ones and that gives a sound base of work for further improvements.

c) The development of a software prototype that using parameters previously defined by the administrator performs an a-prori embryo classification, following not only the common practice models but also the proposed algorithm, and with the possibility of embedding new future models. This application also allows keeping track of the medical history, related to the area, of a given couple.

1.4. Organization of this document

The remaining part of this document is organized as follows. Section 2 establishes the common background necessary to the understanding of this work. It is presented a brief review of related works, and also an overview on some state of the art software architecture that was taken into account during the implementation. Section 3 briefly discusses the major system requirements. Section 4 proposes a model for the embryo quality assessment based on a prior review of some of the current assessments that are used today by different associations and laboratories.

Section 5 presents some design choices and the data conceptual model that were considered in the application development. Section 6 discusses some results that have already been obtained by the tool, applying the proposed assessment model. To end the main body of this document Section 7 draws the conclusions and pinpoints future lines of work.

In Appendix 1 several use cases that were considered for the implementation of the project are presented. In Appendix 2 it is presented the full Class Diagram. In Appendix 3 is possible to observe two examples of sequence diagrams that were considered good examples for what was the expected application behavior. In Appendix 4 a table with case studies that were considered for tests can be found. In Appendix 5 is presented the *json* file that was formed to test the application in producing evaluations following the ASEBIR criteria. Appendix 6 presents the traceability matrices that were produced during the test phase of this project. Finally, in Appendix 7 reproduces a paper reporting a part of this work, which was presented at WorldCist 2014 conference [18].

2. Background

2.1. ART Software Overview

The available software consists mainly of small applications usually created from generalist tools, like MSAccess, Filemaker, or even MS Excel files, for personal (laboratory) use. Moreover, the existing commercial programs are best suited for the medical component. These are general purpose tools adapted for patient management, assisting in the patient diagnose, recording the medical history, managing gamete bank and lab data storage amongst other specialized tasks. The fact that these are multifaceted programs makes them of little use in the laboratory, being used more often than not as a simple tracker of the results obtained in the several cycles that were performed during a period of time.

Nevertheless there are good integrated equipments commercially available. Arguably the most distinguishable one is the EmbryoScope™ Embryo Monitoring System, developed by Unisense FertiliTech, a built-in gas incubator that is controlled by an embedded PC [19]. This system allows uninterrupted observation of embryo development in a stable controlled environment. It features a camera that collects images of the embryos. The software associated, the EmbryoViewer™, allows to review, annotate and compare development of selected embryos using data files acquired by the EmbryoScope; it also allows a retrospective analysis of the embryo development, and helps the embryologist to easily assess several parameters for embryo selection [20]. Unfortunately these are costly systems, too expensive for most national laboratories or even in the Iberian scale.

There is also software that combines multiple images taken at different focus distances (focal plane merging and z-stacking) allowing the observation of the 3-dimensional morphology of an embryo, particularly a 4-cell. This Image Analysis software operates on a series of digital images acquired at different focal planes (acquired either by means of a common microscope equipped with a digital camera or by specialized hardware) and finds the boundaries of blastomeres as closed contours with regular shapes [21].

The Artemis™ from Medialogic is software that helps to manage, track and report several reproductive techniques. Its main focus is storing and reporting data related to the patients and the embryo cycle itself [22].

In recent years there are studies being made on the prevention of multi-pregnancy, taking into consideration the embryo quality. The main objective is the ability to select the best embryo for transfer [23, 24], thus avoiding the transfer of more than one embryo

that could lead to an undesirable multi-pregnancy. In some countries the current legislation is very stringent on transferring and freezing embryos, for example in Germany no cleavage embryos can be frozen, so all embryos that reach this stage must be transferred, this leads to a high rate of twins and triplets [25].

There are also studies, that tried to used mathematical models and combinatory, e.g. [26, 27], trying to predict pregnancy, specially multiple pregnancy rates, but these take into consideration the selection of a "good embryo", this is obtained by the morphological evaluation of the embryo that will allow identifying a good embryo for transfer. A lot of work is being done in this area with several embryologist associations coming up with rule-sets to classify the embryos. In 2011 several of these associations gather in an attempt to come up with a consensus to standardize the "language" used by embryologists all over the world and compare different rule-sets on the morphological evaluation of an embryo [3].

2.2. Software engineering and Architecture

The ISO/IEC/IEEE Systems and Software Engineering Vocabulary defines software engineering as "the application of systematic, disciplined, quantifiable approach to the development, operation and maintenance of software"[28]. On a less formal way it can be said that Software Engineering main concern is the development and maintenance of software systems that have a reliable and efficient behavior, are affordable to develop and maintain, and fully satisfy all the requirements that the costumer has defined.

Software architecture emerged as one of the most important sub discipline from software engineering; it can be defined as the set of structures needed to reason about the software system, which comprises the software elements, the relations between them, and the properties of both elements and relations, roughly it can be said that is "the prudent partitioning of a whole into parts" [29]. This partitioning brings several benefits: not only allows a large and complicated problem to be split into small and easy to solve problems, but also allows that several people can work cooperatively in the resolution of the same large and complicated problem. This is possible because each step of the resolution that corresponds to a block of written software can interact with other steps, which may be written by different persons. This communication is done through carefully crafted interfaces that reveal the exact information that is needed [29]. Design patters are commonly used for this activity, each of them more suitable for a specific type of problem.

One of the main emphasis in Object Oriented Programming is shifting from software programming to software design, this implies that more time is spent in designing an

application than in programming it, this also means that an error in the design usually takes more time to correct than a programming error. This is the reason why normally most experienced programmers should be responsible for the design. The definition of Design Patterns represents an attempt to formalize and share experience with other programmers [30].

Even with the knowledge that every application is unique, the uniformization of the code following design patterns can help to solve and avoid common mistakes and problems that use to appear. These patterns were introduced to try to put some order in the, normally chaotic, universe of architectural design. The goal is always to try to make classes cohesive and reduce the coupling. Cohesion as in each class defines a small set of behaviors and responsibilities unified by a common purpose; while coupling refers to the interdependency between classes [30].

2.2.1. Multilayered Architecture

One of the architectural patterns that are recognized is the multilayered architecture, most commonly known as n-layer. Often the names layer and tier are used referring the same thing, although by "layer" it should be understood as a logical group of the functionality and components, whereas "tier" is the physical distribution of the same functionality and components on separate locations (eg servers, computers, networks, etc) [31]. A layer represents a group of modules that offer a cohesive set of services [29]. Layers help in providing and improving not only the changeability as in extensibility, portability, maintainability and/or restructurability; but also in testing [32]. What it's meant is that each layer is developed applying the principle of information hiding, this way only the relevant information, for each operation is shared with the outside. This allows that any change inside a layer is hidden and will not have any impact on any other adjacent layer [29].

The most common layers used are the Presentation or Application Layer, Business Layer and the Data Access Layer. Each of these layers has a well-defined set of responsibilities:

- **Presentation Layer** - it can be any type of user interface; web, desktop or mobile application. It knows how to communicate with the user, but ignores what must happen in order to reply to the user's requests.
    - It is connected to the users: by receiving and dealing with the events, and by presenting the results and replies.

- It is connected to the business layer: by transferring the external events (calls to action), and receiving the replies and results from these actions.
- It is in charge of receiving the users request, validating the data from the request, ordering the execution of actions and communicating the result of the actions to the users.

- **Business Layer** - knows how to execute actions (that can be associated with the user requests), but ignores where and how the data are stored, and how the results of the actions are displayed after. The variables contain the status of the business entities, some are hidden to the outside other have the task to provide the status to the "client" layers.
  - It is connected to the presentation layer by receiving the call to actions, and returning the results and replies.
  - It is connected to the Data Access Layer by requesting the execution of queries to the stored data, and by receiving the replies and results for the requests made.
  - It is in charge for receiving the data related to the action, executing the assigned actions, ordering the execution of queries over the stored data and returning the results and replies of the actions.
- **Data Access Layer** - Know how and where the data is being stored, but ignores how to deal with it. It has the methods that act over the data source, and may also have some minor "business" logic (e.g. max, count).
  - It is connected with the Business Layer by receiving the request for the execution of queries and returning the results and replies of the given queries.
  - It is connected to the databases, or files management system, by passing the queries and data modifications in the appropriate format and language, and by receiving the results and replies.
  - It is in charge of allowing the Business to work without need to understand and know how and where the data are and allowing the information of certain objects of the business layer to persist throughout time.

Figure 1 presents a representation of the 3-layer architecture.

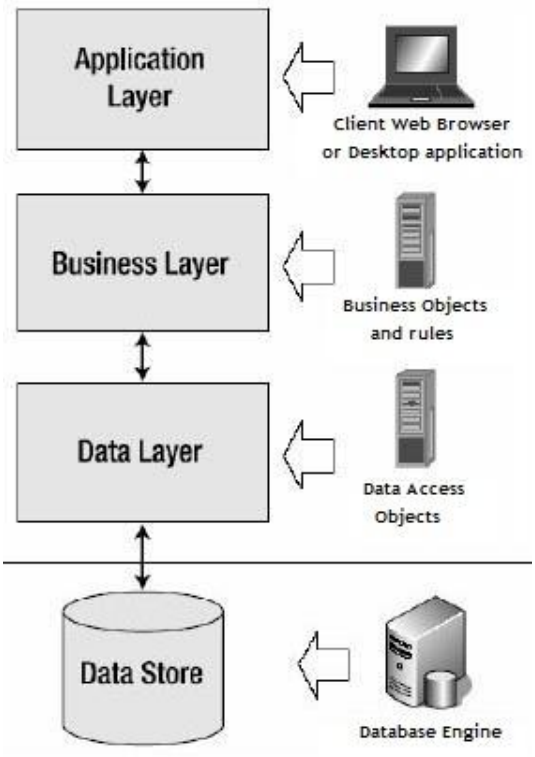

Fig. 1 - 3-layer architecture example. Adapted from [33].

One of the major achievements by using this structure is that if there is a need to change the database, normally it will only affect the Data Access Layer, unless there is a change in the data structure. Also a modification, or even the development of a new user interface, will not affect the Business or Data access Layer, unless there is a need to develop new actions for this new user interface. In the same way a change in the business actions should not create any impact in the other layers [29].

2.2.2. CRUD Methods

CRUD is an acronym for Create, Retrieve, Update and Delete, these are the four basic functions of persistent storage [34]. This approach has the goal of defining a structure that not only supports any and every basic operation that is needed in every software, but also establishes a pattern that will allow that other programmers will be able to understand and use, or re-use, code from other people. So we can consider a good practice that every class in the Data Access Layer should implement these methods.

- **Create** - Method that is responsible for the Insert Operation.

- **Retrieve** – Method that is responsible for the Select operation. On a more accurate approach it should be more than one method, one that return a single instance, and one, or more, that return a collection of instances.
- **Update** – Method that is responsible for the Update operation.
- **Delete** – Method that is responsible for the Delete operation

Of course, different levels of authorization may result in different CRUD cycles, for example a certain user may have authorization to create and/or update some data, only retrieve others, and, also, the delete function may work on different ways, the administrator may have the power to remove the data, as a user may only flag it as deleted.

2.2.3. Model-View-Controller

The Model-View-Controller (MVC) is a software architectural pattern for implementing user interfaces, It was introduced into Smalltalk-76 by Trygve Reenskaug, in the 70s [35, 36], and later used to build interfaces in Smalltalk-80 [37]. MVC divides a software application into three interconnected parts: the application object (Model), the screen representation (View) and the responsible for how these two communicate (Controller). Prior traditional design of user interfaces tend to group these components together, with this pattern the flexibility and reuse increases [37]. The two major benefits from this are: the possibility to attach multiple views to a model providing this way different presentation of the same data, and the possibility to change the way a view responds to a user input without need to change its visual presentation [37].

Although the original aim was to use this pattern in desktop applications, the model has been widely adopted as architecture for web applications in several programming languages; varying mainly on the interpretations on how the responsibilities are divided between client and server [38].

Figure 2 depicts a representation of the information flow.

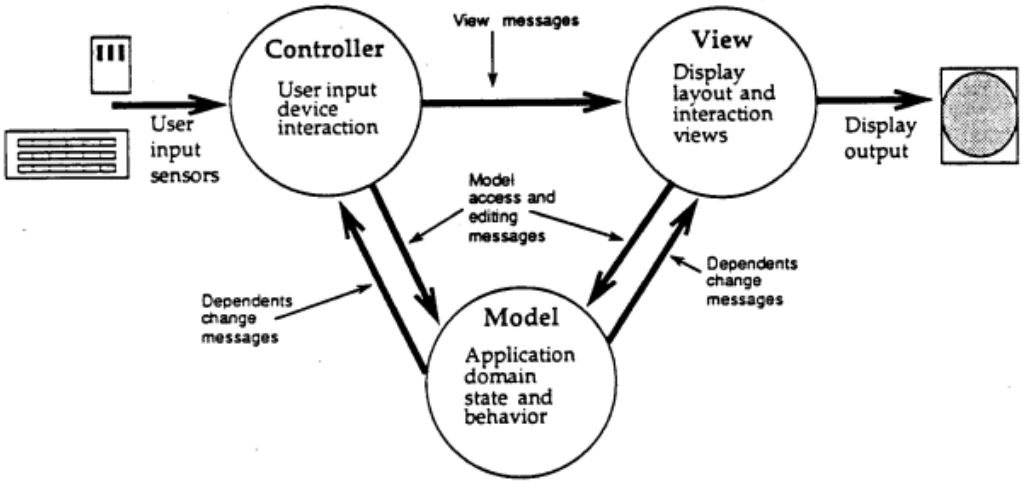

Fig. 2 - Diagram of MVC Pattern. Reproduced from [39]

In its early definition, the *Model* would consist in an active representation of an abstraction in the form of data in a computing system [40], so a model could be a single or a structure of objects. The data from this *Model* updates the *View*, or *Views*, allowing the presentation of one, or more, representations of the *Model*, that the *User* sees [40]. The user should be able to manipulate the data, and these manipulations are possible by using the *Controller* that acts as a link between the *User* and the *Model* [41].

2.2.4. Model-View-ViewModel

The Model-View-ViewModel is an architectural pattern originated from Microsoft. Based on the MVC pattern, it is specifically targeted to the development platforms that support event driven programming in Windows Presentation Foundation [42]. The main goal is to help to separate the business and presentation logic from the user interface. This will help to reduce numerous development and design issues and also make the application much easier to test maintain and evolve [42]. One of the major problems on using MVVM is that it can turn easy work into excessive if it is being used on simple user interface [43]. In figure 3 the main components of the model are presented. These are briefly described below.

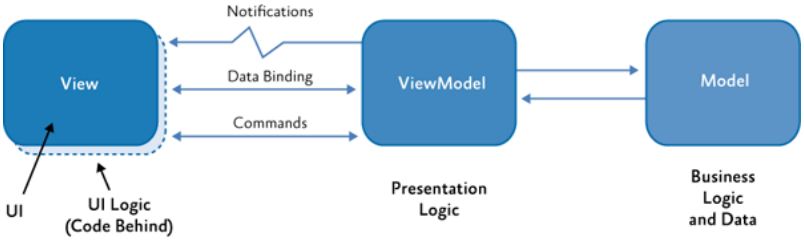

Fig. 3 - Diagram of MVVM Pattern [44]

- **View class** - is responsible to define the structure and the appearance of what the user sees, also it defines and handles the visual behavior of the user interface. It refers the view model through a *DataContext* property. The controls defined in the view are data binded with the properties and commands exposed by the view model. The view may customize the data binding between itself and the view model, by formatting data or do some first-degree validations for example. Ideally the codebehind contains only the constructor, and may contain some UI logic the implements visual behavior or the customizations that were referred previously [42, 44].
- **ViewModel class** - it encapsulates the presentation logic to support the use case, or user task, in the application. It does not refer directly the view, it only implements properties and commands to which the view can bind. This is because one view model can binded with several views. It sends notifications that the view, or views, can capture via *INotificationPropertyChanged* and *INotificationCollectionChanged* interfaces. It also coordinates the interactions between the view and the Model. It may manipulate Data so that it can be easily consumed by the view and also implement some properties that may not exist in the model. It may also implement data validation via *IDataErrorInfo* or *INotifyDataErrorInfo* interfaces [42, 44].
- **Model class** - it is responsible for managing the data and for ensuring its consistency and validity. It does not directly reference the view, or view model, and does not depends on how they are implemented [42, 44].

2.2.5. Unit testing and Test Driven Development

Testing is of major importance, especially on large projects with a very high demand of scalability. These projects have the need of using unit testing, this comprehends the testing of small pieces of the software, most commonly a single function, isolate it and determine if it behaves as expected [45] allowing to detect and resolve a lot of problems early in the development cycle. Of course in most applications this is very difficult because of the strong coupling between the user interface and the code, but with MVC, and MVVM, this can be obtained because the three parts are loosely coupled, and enforce the separation of the business logic from the display logic. As in the two patterns the logic that controls the flow of the application is in the Controller or ViewModel a test of the business logic can be easily executed by just invoking the methods associated with the commands that need to be tested [46].

Test Driven Development (TDD) is a development approach where one writes a test before producing the code to fulfill that test [47]. One of the main goals is to make the programmer think the design before actually write any functionally code [47]. The result is not only the production of clean code, but also a suite of unit tests that can be run at any time to provide feedback that the software is still working [48]. There are two levels of TDD:

- Acceptance Test Driven Development - where a single acceptance test is written, these test represent an expected behavior or specification that the application must conform, and then is produced just enough code to fulfill that test. The goal here is to specify detailed, executable requirements for the solution [46].
- Developer Test Driven Development - where a single developer test is written, that covers a small part of a specification, and then is produced just enough code to fulfill that test [46].

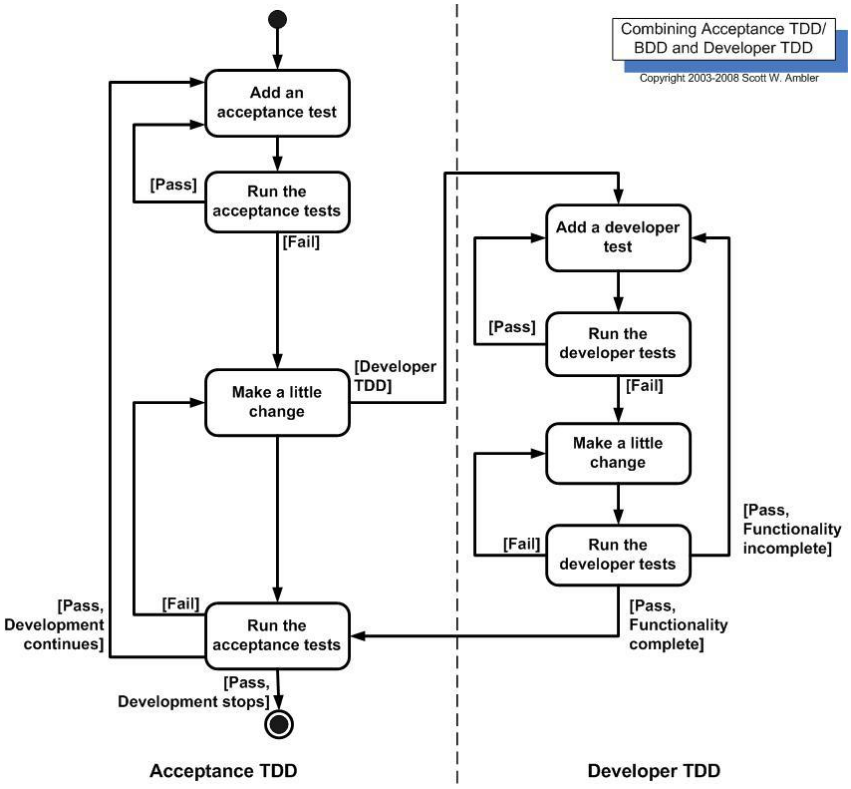

Fig. 4 - Diagram of ATDD working with DTDD [46]

According to the diagram a single Acceptance test is formulated, normally associated with the specification that is going to be developed, then as the code is being produced, before each new step a small test is produced to validate the code that will be developed. This approach is very useful as it provides a constant feedback whereas each previously

developed component is still working, as new components are being developed; it also acts as documentation. Moreover it forces a critical analysis and design, because no code is produced without fully understand what is the expected result, consequence from this is that the software tends to be better designed, loosely coupled, and easily maintainable. It also acts as a regression safety net on bugs; this means whenever a bug is detected, a test should be created to detect and reveal that bug before the correction is made, after this on every run of the tests all previously bug fixes are verified [47]. This way, if by any chance this bug may reappear, due to a new development for example, it will be detected as soon as the tests are executed.

3. System Requirements

3.1. Specifications

The main goal of the application is to be able to collect and store the information related with the embryos, and to be able to assist in the process of decision making. On a first stage the application will be a local standalone application with a local database.

Generally speaking: the application must be able to know who does what. Therefore a module of administration must be implemented, where the laboratory staff can be managed, this will be used to identify who is responsible for which tasks. These people must be identified by their function in the laboratory (medic, or embryologist) each function will have specific tasks. Also not all the laboratory staff will have access to the application; all the persons that have tasks that involve the embryos and/or the couple should be register, so that it can be traced who did what, but it is not necessary that they have access to the application, as their tasks can be inserted, by another certified user (e.g. the medic that accompanies the process). Several laboratories may use this application in the future, so there would be a need to have all the information in a centralized server, so the concept of laboratory must exist, and there must be a way to manage several laboratories.

There will also be a need to have a module where the acquisition protocols behind the observations must be created, so there must be a model module, where a certified user (administrator) must be able to create what readings he wishes to be conducted, in each reading what are the stages he wishes to be observed, and in each stage what are the parameters that should be observed, and how it should be classified.

In this module, there must also be a way to manage other things like the families of externals that is used. Anything that is used in the laboratory, that enters in contact with the embryo during its incubation phase and that may influence his normal development is considered as an external. There are three kinds of external that may be used: equipments (incubators for example), consumables (several type of gases) and disposables (e.g. pipettes). There must be a way to define these types, so that it will be easier, in the next module, to define each one of these equipments more easily.

With the bases defined in the two previous modules the next and last module should be the one that will be used more, it is the laboratory management. In here a user will be able to register the couples that are being submitted to ART processes. The process associated, or processes in case of they had already been submitted to ART treatment, and

its subsequence information. Each process of course will have embryos, which will be following a reading schedule, defined on the previous module, with its associated stages and subsequent parameters. By using the data that was collected the application should be able to give the score for the embryos. This classification cannot be static, meaning that, it should be possible to obtain rankings following different sets of rules. Also there must be the possibility of, in case an observation is not performed, the application must be able to predict what value would be observed and, based on this value, be able to return an approximate evaluation. The application must also be able to keep track on post-transfer status, following the pregnancy evolution.

Other important points in the Laboratory model, the identification of the externals that were used, and that entered in contact with the embryo; also there must be a way to manage the several kind of medications that can be used during the process, this way it will be easier to declare them in the process and prevent misspelled names or different names for the same medication.

Laboratories, personnel, and Couples have in common the need to have a series of contacts, of several types associated (telephone, mobile, emails), and also, at least one address.

3.2. Administration Management Module

The Administration module must allow managing the following two groups of information, and its related data.

3.2.1. Manage laboratory

It must be possible to manage a laboratory, with all the necessary data related.

- **Manage contacts** - manage the contacts associated with the laboratory.
- **Manage addresses** - manage the address, or addresses associated with the laboratory.

3.2.2. Manage personnel

It must be possible to manage a person with all the related information.

- Identify which is the laboratory to which he is associated.
- Identify function in laboratory (medic or embryologist). Different functions are associated with different tasks.
- Identify if it is a user or not and be able to create a login.

- **Manage the contacts** - manage the contacts associated with the given personnel.
- **Manage addresses** - manage the address, or addresses associated with the given personnel.

3.3. Model management Module

The Model Management is where the Laboratory administrator manages the way he desires the observations to be made, for that (s)he must be able to manage the following groups of information, and its related information.

3.3.1. Manage parameters

It must be possible to manage a parameter definition, to give its theoretical information.

3.3.2. Manage stages

It must be possible to manage a stage definition.

- **Manage the parameters in the stage** - Associate parameters to stage.
    - Identify range of possible observed results for each parameter in the given stage.
    - Identify what should be the value for a parameter in the stage in case of the reading is not performed.

3.3.3. Manage readings

It must be possible to manage the reading definition.

- **Manage stages in reading** - Associate stages to a reading
    - Identify order of stages in that reading
    - **Manage the parameters in reading stage** - the reading may only demand some of the parameters as mandatory.

3.3.4. Manage Category

An embryo maybe categorized in several stages (in study, cryopreserved, etc) these categories maybe important in a future work.

3.3.5. Manage types of external equipments

Define the type of externals that may exist in the laboratory.

3.4. Laboratory management module

The laboratory module is the most used part of the application in a day-to-day basis. It should allow the user to manage the following group of information, and its subsequent data.

3.4.1. Manage couples

It must be possible to manage the couples and all the data associated with them.

- **Manage the contacts** – manage the contacts associated with the couple.
- **Manage the addresses** – manage the addresses associated with the couple.
- **Manage the Processes** – manage the process or processes that are associated to the couple.
    - **Manage the embryos** – Manage the embryos associates to the process.
        - Select what reading will be performed on the specific embryo
        - **Manage the reading** – record the results of the parameters for each of the stages according to the previously selected reading.
        - Calculate the result, or results, for the embryo according to the reading and a selected rule set.

3.4.2. Manage the externals

It must be possible to manage the several externals that are used in the laboratory and relate them to what type, as defined previously they belong.

3.4.3. Manage the medications

It must be possible to manage the medications names and its role in the process.

The evaluation rule sets must not be an integrated part of the application. It must be possible to pass them from one instance of the application to the other without the need to a new installation.

There will be three levels of authorization:

- **Application administrator** - Full access over the application
- **Laboratory administrator** - Can manage personnel from his laboratory; can manage the model module, and the laboratory module
- **User** - can only manage the laboratory module. This level of authorization could later be sub-divided in more groups, for example: the "laboratory user" that only has power over the couples and its subsequent data; a "laboratory responsible" that, besides the "simples user" level can also manage the externals that exist in the laboratory; also the "medic user" that as the simples user can only manage the couples information, but only consult the reading data; and a "Medic responsible" the besides the "medic user authorization also manages the medication data.

3.5. Use-Case Diagrams

UML is a language for specifying, constructing, visualizing and documenting an information system [48]. The Use case diagram describes a relation between actors and use cases of given system. This gives a global and high-level vision of the system being fundamental to the correct definition of its range of application [48].

The Diagrams of use cases of the 3 modules are next with a brief explanation on them. These are very general use cases, more detailed diagrams can be found on Appendix 1. The concept of "manage" stands for the operations of listing, creation, update and delete.

3.5.1. Administration management module

In figure 5 is presented the Use-Case diagram for the Administration Management Module.

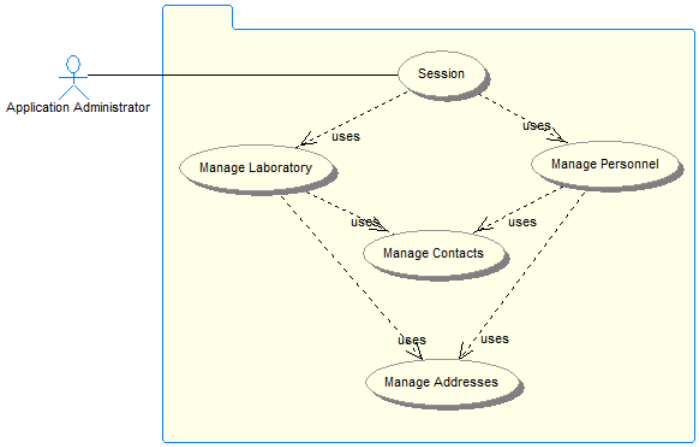

Fig. 5 - Administration management module Use-Case Diagram

First the current user, being either an administrator of any lever or a simple user, must be authenticated in the application, thus creating a session. From here (s)he can manage (create, update or delete) a Laboratory, if a laboratory already exists, or right after its creation, (s)he can manage its contacts, and its addresses. The same way (s)he can manage the personnel, where (s)he can manage their function, and if they will have, or not, access to the application giving them authorization. As in the laboratory the administrator can also manage the personnel contacts, and addresses.

3.5.2. Model management module

In figure 6 is presented the Use-Case diagram for the Model Management module.

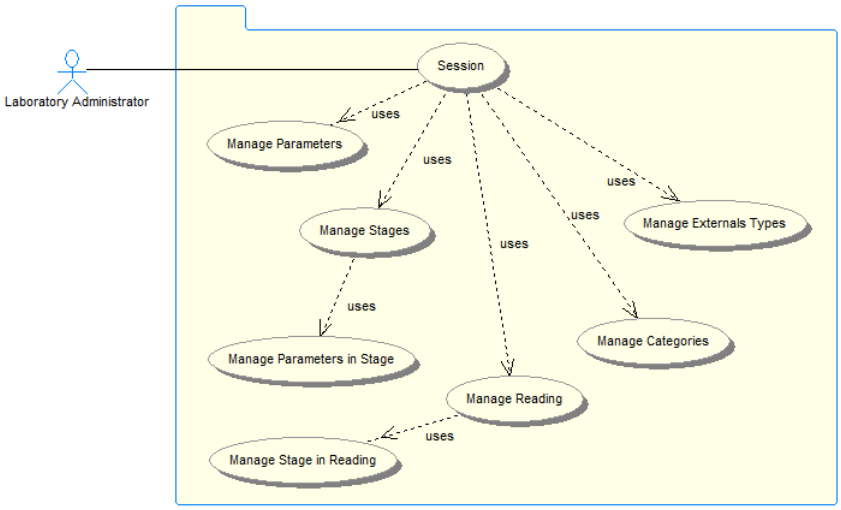

Fig. 6 - Model management module Use-Case Diagram

As in the previous diagram, the user must be authenticated before start using the application. After this (s)he can manage the Parameters, (s)he can manage the stages, and in each stage (s)he can manage what parameters, from the ones already existing in the application, must be associated with the given Stage. (S)He can also manage the readings, and for each reading manages what stages must be taken in consideration. (S)He will also have the tools to manage the categories of embryos, and the external types.

3.5.3. Laboratory management Module

In figure 7 is presented the Use-Case diagram for the Laboratory Management module.

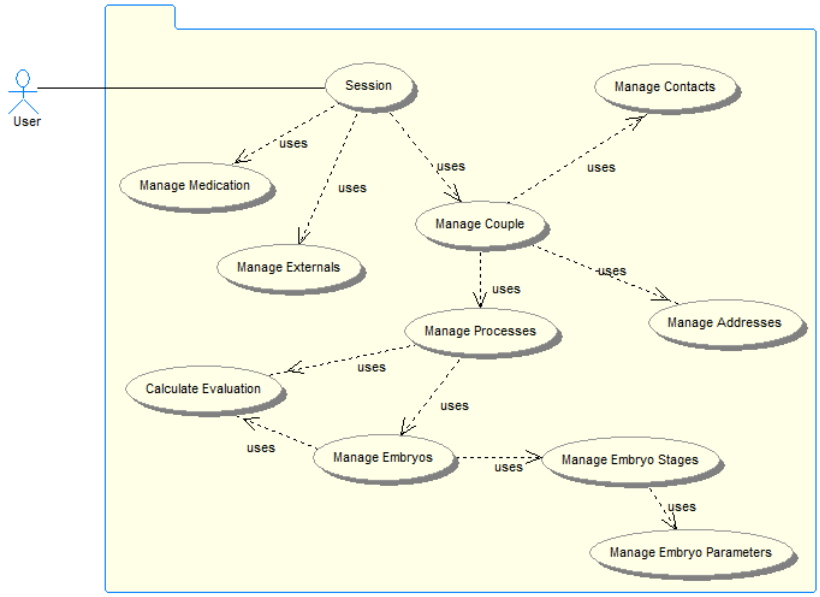

Fig. 7 - Laboratory management module Use-Case Diagram

As in the other two situations the user must perform the authentication before starts using the application. After this he can manage the couples and, as in the cases of laboratories and personnel, manage the contacts and addresses associated to them. Each couple will have one or more processes, this will be the result of previous ART processes, and these processes can also be managed. Each process will have several embryos associated, and each will pass several stages where several parameters will be evaluated. These stages and parameters will be, of course, defined in the reading (defined on the Model module) that was associated with the embryo. From the process and from the embryo must be possible to calculate an evaluation according to a chosen set of rules. It will also be possible to manage the externals, according to the types defined in the Model module, and also manage the medications.

4. Proposal for embryo quality assessment

4.1. Current evaluations

As was referred in the Introduction, there are several variations in the grading of oocytes and embryos, and this turns to be a major obstacle for the purpose of inter-laboratories comparisons. Nevertheless, in 2011 in Istanbul, there were defined some "common grounds" mainly in what should an embryo "look like" in order to be classified as a good embryo [3]. The Meeting group was small to allow consensus to be obtained, formed by recognized experts to support the credibility of the consensus. Following the experts recommendations only three mainstream assessment models were taken into consideration and analyzed during this workshop: ASEBIR[3], ACE[4] together with BFS[5], and SART[6].

The ASEBIR system includes all stages from gamete to blastocyst. On the oocyte and on the zygote although there are some parameters that are taken in consideration there is no evaluation process.

As is shown in the correspondent tables, the embryo is evaluated in 7 morphological parameters on d2 and d3 stage (see Fig. 8), and 6 parameters on the blastocyst stage (see Fig. 9). It is given a classification from A (an embryo with optimal quality and the best implantation potential) to D (a poor embryo with low chance of implantation).

ACE, and BFS have developed and published practice guidelines [50] that include embryo morphology assessment (see Fig. 10). For blastocysts, a three-part grading system is used, based on an original work from David K. Gardner and William B. Schoolcraft [51, 52], with modifications by Emma L. Stephenson [53].

The embryos are evaluated in 3 morphological parameters, and it is given a classification from 4 (Best) to 1 (Worst).

[3] Asociación Española para el estudio de la Biología Reproductiva

[4] Association of Clinical Embryologists

[5] British Fertility Society

[6] Society for Assisted Reproductive Technology

Grade	Day	Cell number	Fragmentation (%)	Symmetry	Multi-nucleation	Vacuoles	Zona Pellucida
A	2	4	<10[a]	Even	No	No	Normal
	3	4(d2) →7–8 (d3)	<10[a]	Even	No	No	Normal
B	2	2 or 5	<26[a]	Even	No	No	Normal
		4	11–25[a]	Even	No	No	Normal
	3	4(d2) →7–8 (d3)	11–25[a]	Even	No	No	Normal
		4(d2) → ≥9 (d3)	<26[a]	Even	No	No	Normal
C	2	2–6	26–35[a]	Uneven	No	Few	Abnormal[b]
		3[c] or 6	<35[a]	Uneven	No	Few	Abnormal[b]
	3	2, 4, 6 (d2) → >7(d3)	26–35[a]	Uneven	No	Few	Abnormal[b]
		6(d2) → >8 (d3)	<35[a]	Uneven	No	Few	Abnormal[b]
		2 or 4 (d2) → 6(d3)	<35[a]	Uneven	No	Few	Abnormal[b]
		3[c](d2) → >6 (d3)	<35[a]	Uneven	No	Few	Abnormal[b]
D	2	1 or >6	>35		Yes	Many	Abnormal
		3	>35	Even	Yes	Many	Abnormal
	3	1 or >6 (d2) → any number of cells (d3)	>35		Yes	Many	Abnormal
		Any number of cells (d2) → <6 (d3)	>35		Yes	Many	Abnormal
		(d2) → (d3), only one additional cell	>35		Yes	Many	Abnormal

[a]Large fragments (i.e. not dispersed throughout the embryo).
[b]Without assisted hatching.
[c]One large and two small blastomeres.

Fig. 8 - ASEBIR Embryo Assessment criteria D2+D3 [3]

QUALITY	Blastocyst organization	Zona pellucida	ICM	ICM size*	Trophectoderm	Blastocoele Expansion**
Blastocyst A	At D+5	Thinning at D+5	Oval and compacted at D+5	3800μm²-1900 μm²	Homogeneous epithelium Eliptical cells	Blastocoele occupies the whole of the volume of the embryo.
Blastocyst B	At D+5	Thinning at D+5	Oval and compacted at D+5	3800μm²-1900 μm²	Irregular epithelium	
Blastocyst C	At D+6			<1900 μm²	Homogeneous epithelium Eliptical cells	
Blastocyst D	At D+6			<1900 μm²	Irregular epithelium Few cells	

*3800 μm² is comparable to the size of a blastomere of a 4-cell embryo. **Collapsed blastocyst: This is a natural mechanism which takes place at the blastocyst stage, and if it happens the blastocyst will need to be observed again. This will not change the category assigned to the embryo.

Fig. 9 - ASEBIR Assessment criteria for blastocysts [2]

SART is an organization of professionals dedicated to the practice of IVF, or assisted reproductive technology that represents the majority of the ART clinics in the United Kingdom. The criterion followed by SART is represented in tabular format in figure 11.

Criterion	Grade	Description
Blastomere number		Presented as nc (where n = cell no)
Blastomere size	4	Regular, even division
	3	<20% difference (cell diameter)
	2	20–50% difference
	1	>50% difference
Fragmentation	4	<10% fragmentation by volume
	3	10–20%
	2	20–50%
	1	>50%

Fig. 10 - ACE and BFS cleavage stage embryo grading system [3]

Grade	Cleavage stage: cell number (1 → >8)		Morula/blastocyst: early/expanded/hatching	
	Fragmentation (%)	Symmetry	Inner cell mass	Trophectoderm
Good	0 1–10%	Perfect	Good	Good
Fair	11–25%	Moderate asymmetry	Fair	Fair
Poor	>25%	Severe asymmetry	Poor	Poor
Unknown	Unknown	Unknown	Unknown	Unknown
Not entered	Not entered	Not entered	Not entered	Not entered

Grade applies to all embryos regardless of transfer day.

Fig. 11 - SART embryo assessment criteria [3]

The embryos are evaluated in 2 morphological parameters, on the cleavage stage, that correspond to 1-9 cells on the embryo normally obtained in the interval of day 1 to day 3 after insemination, and in another 2 parameters in the Morula or Blastocyst stage corresponding to day 4 and 5, and it's given a classification from Good to Poor.

The first step for the Istanbul consensus came with the publication of the Atlas of Embryology [54]. The consensus main objective was to start designing an embryo scoring system that can be shared among all embryologists [3]. At the end of the meeting a series of points were produced, these points were, of course, a first set that would need revision at regular intervals. Also, it was stated that these points were "minimum standards" for morphological scoring, and, therefore, the laboratories would not be restricted from performing additional observations or including additional details per observation [3].

4.2. Proposed algorithm

A major concern of this work is to produce a formula that will allow assessment of the embryo and give a quantitative score, all parameters are entered by the administrator of the application, thereby allowing a flexible use that will not require external intervention to rebuild the project whenever a new parameter is considered, or there is a need to change an existing one. Another point is that the evaluation of an embryo in a given day should be conditioned by previous reviews of the same embryo.

The base for the production of this formula will be mainly the ASEBIR criteria, because not also the Istanbul consensus is a minimal standard for embryos, and also because being the ASEBIR assessment an already established criteria with proven results.

Let's start by assuming that the ASEBIR [2] recommendations are enforced by making daily readings, registering the parameters that are indicated in the reading of each particular day. Readings are taken on day 1 after 16-19 hours of insemination, on day 2 after 44-47 hours and on day 3 after 67-71 hours.

The evaluation recommended by ASEBIR is based on the observation of each of the parameters of interest, by reading and assigning a qualitative measure expressed in a partially ordered set of four elements {*A*, *B*, *C*, *D*}. The qualitative overall classification of an embryo, expressed in the same set, cannot exceed the grade of any of the measurements obtained for the different individual parameters. For example, if an embryo has a parameter measurement registered as a *D* then it is classified as a *D* embryo, regardless of the quality of the remaining parameters.

It is our opinion, seconded by some experts in the field of ART, that this scale of four values does not adequately describe the range of different situations that can be found in each of the four levels. For example, let's consider two different embryos, each one being analyzed in the same set of parameters: the first of the embryos with only one parameter rated *A* and the rest as *B*, the second with a parameter rated as *B* rated and the rest as *A*. In both cases a strict classification of embryos would be *B*, but it seems generally agreed that there is a difference in the quality of the two embryos that is not reflected in this rating.

Therefore, without misrepresenting the normative indications from ASEBIR, we propose the following scheme of merit that allows a quantitative description of the changes in quality within each level and, in addition, results in a composite score expressed on a scale of greater granularity that allows observing gradual increases in the expected quality of the embryo.

Consider Pd the set of all the parameters that should be recorded on a given day d. The overall evaluation of the embryo depends on the observations acquired in a time lapse corresponding to a predefined set of days D. Being O_p the observation of any parameter p, the basic result of a daily reading will be defined by:

$$BR_d = min(O_p) \ for \ all \ \ p \ in \ Pd. \tag{1}$$

In the above expression O_p results from the quantification of the 4 qualitative ASEBIR values in any numeric scale that respects the partial order between them, e.g. {4, 3, 2, 1}. Knowing that a reading per day is carried out, assuming MR_d as the maximum observed result in any one of the parameters monitored that day, and $\#P_d$ the number of parameters considered; the daily score can be generalized in such a way that the subtle differences between embryos are apparent:

$$DS_d = BR_d + \frac{\sum_{p \in P} (O_p - BR_d)}{\#P_d * max(1, MR_d - BR_d)} \tag{2}$$

Notice that $DS_d >= BR_d$ but never surpasses the quantitative threshold of a given qualitative ASEBIR assessment. For instance an embryo qualified as C (value 2) can never reach a B (value 3) grade, but it is now possible to shown a relative grading between two C embryos (e.g. values 2.25 and 2.75).

The final score must be obtained by considering all the days:

$$FS = min(DS_d) \text{ for all } d \text{ in } D. \quad (3)$$

Where *D* is the set of days on which the valuation is made.

Notice that in this way it is assured that the score on a given day of a given embryo will never be higher than the score of that same embryo the day before, as is a consensual assumption that an embryo is not likely to evolve to become a better embryo than what was expected based on previous evaluations. Instead of the minimum norm (the biggest of all the triangular norms) another triangular norm, such as the product norm (the standard semantics for strong conjunction), could be used to compose the individual daily scores [55].

5. ARTE Tool application design

For a question of organization we divided the project into 3 major modules, these modules are relatively independent, each one is focused on a field of work, although the last module depends on the other two. The first of these modules is an administration module; where it will be possible to manage the users of the application and organize them by laboratories. The second module, model management, is where are defined and managed the several assessment parameters, organized them by stages, and organized this stages by readings; also is where is defined the several types of externals that may be used and interact with the embryo. The last, but not least is the laboratory module, where the real data is managed, the couples, the related processes and all the information that is associated with it, also the medications that will be used and the externals elements. In this chapter we use Class Diagrams as a way to illustrate a set of classes interfaces, collaborations and their relationships regarding general dependency, generalization and association.

The class diagrams are used to model the structure of a system. These models are typically used in three situations: capture the vocabulary of a system; model simple collaborations; modeling and the design of a scheme of a database [49]. The Full Class Diagram is represented in the Apendix 2.

5.1. Administration management

The administration is composed by the class relative to the Personal, these can be Embryologists or Physicians; they can also be registered as users or not. The personal are associated with a laboratory. Both of them can have addresses and registered contact. There is a class, Entity, which gathers the common data between the Personal and the Laboratories.

There are several degrees of authorization that a user, registered personal, can have. These authorizations will indicate what operations a user can or cannot perform.

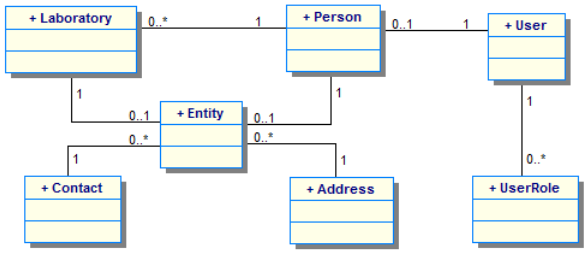

Fig. 12 - Administration management class diagram.

- **Entity** - there is information that may be considered common between the Laboratory and the Person entities, and to allow a correlation between Contacts and Addresses, from the Laboratories and Persons, and as it will be shown later Couples, and its distinction.
- **Laboratory** - the information specific from a laboratory.
- **Person** - The information specific from a person, it's role in the laboratory and if it's a user.
- **User** - specific data from a User username, password, if it's active
- **UserRole** - Specific information from a user role, what the permissions they have.

5.2. Model management

The model encodes the theoretical part of the application. It is composed by the parameter class the stages where this parameter can be evaluated, and the several possible results. Also it has the definitions of the readings that can be made - what stages will be examined, and what parameters in these stages will be taken in consideration. Since the several parameters can be used in several stages, and the several stages can be used in several readings the association between them is a many-to-many relationship.

There is also the external types class, where it is be defined what types of externals interacting with the embryo that will be registered (i.e. incubator, CO2 Gas, etc.)

The Category is be used to register different categories that an embryo may assume, these are status that can be used to register the step where the embryo is and/or its destiny.

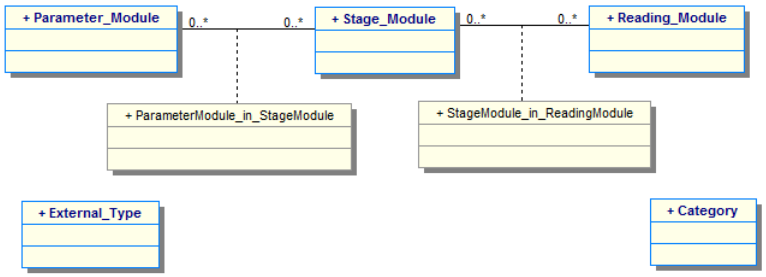

Fig. 13 - Model management class diagram.

- **Parameter_Template** - the specific data of the parameter, its theoretical definition.
- **Stage_Temple** - the specific data of the stage, its theoretical definition.
- **ParameterTemplate_in_StageTemplate** - relation between parameters and stages, what parameter will be taken in consideration in each template, and what it's the possible values the parameters.
- **Reading_Template** - the specific data of a reading template, its theoretical definition.
- **StageTemplate_in_ReadingTemplate** - relation between the stage and the Reading, indicating what Stages must be taken in consideration in a given Reading.
- **External_Type** - the theoretical definition of a External element, being the external a equipment, a consumable or a disposable.
- **Category** - theoretical indication of a condition of an embryo or oocyte.

5.3. Laboratory management

This is where the real data is registered. The Couple class has addresses and contacts therefore, likewise the personal and laboratory; the Couple is also associated with the Entity class. These couples are of course registered in a certain laboratory. These couples have processes that have Embryos associated to them, there is also a class to classify and register the sperm that will be used. These processes have a collection of embryos associated to them, which in turn have a collection of stages. These stages also have a collection of resulting parameters.

These are the results that will be taken in consideration to calculate the evaluation of the Embryo. In order to relate the result of the evaluation with the pregnancy there is also

a class that treats the data related to the transfer and the evolution of the pregnancy. A process can imply several transfers because there is the possibility of cryopreserved embryos to be transferred later; also a single transfer may imply more than one embryo in it.

The Sperm is in a different class as a possibility to be studied in future. In this section there is also place for an external class that will register the specific externals that exists and, may be used, in each laboratory.

There is also a class to register the several medication that can be used in the process, this will allow an easier way to fill the information and reduce the chance of the same medication be inserted with different forms of orthography.

- **Couple** - the specific data of the couple.
- **Process** - the specific data of a process, a couple may have more than one process associated.
- **Sperm** - the specific data of the sperm used on a given process, this may be a point to extend on a future work.
- **Medication** - the specific data on the several medications that are inserted on the system.
- **Mediction_usedin_Process** - relation between the medications and the processes; one or more medication will be used during a process with several conditions.

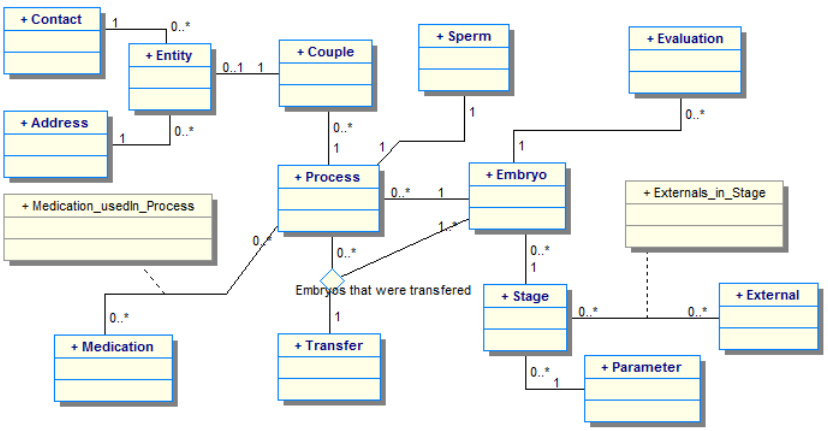

Fig. 14 - Laboratory management class diagram.

- **Embryo** - the specific data of an embryo; several embryos will be associated to a given process.

- **Evaluation** - the evaluation by the user may not be the same that the application gives, even following the same criteria, in these cases the user opinion must prevail and be registered.
- **Stage** - the specific information of the embryo on a given stage.
- **External** - the specific data of an External that can be used.
- **Externals_in_Stage** - relation between external and stage, on a given stage several externals may interact with the embryo.
- **Parameter** - the specific in information of a given parameter on a given stage of a specific embryo.
- **Transfer** - the specific data of the transfer, and the following of the pregnancy, this may be a point to extend on a future work.

5.4. Evaluation

The evaluation should not be an embedded part of the solution, as one of the objectives is the option to create evaluation rules, and be able to share them easily with other installed versions. So the option was to create a template, for *json* files [56] that must be followed by all evaluation files. The files created this way can be deserialized by the application and be used to give the result of a certain reading, or set of readings, of an embryo, or group of embryos. In Appendix 5 is presented the *json* file used for the ASEBIR criteria testing.

5.5. Implementation

The implementation of the application has followed the modulation that was defined on the analysis section. It was decided that, in its current release, it would be a local application, with a central database. The main concern during the implementation was always the scalability of the application due to two main reasons: Firstly, as the field of study is very complex and with several sub-fields, each one of them with its own nuances and specifications, and maybe its own application if deemed appropriate. All these sub-fields are determinant for the final result, a successful pregnancy. Secondly, it is expected that individual components of the application may be reused on future works.

5.5.1. Sequence Diagrams

The sequence diagram is used primarily to show the interactions between objects in the sequential order that those interactions occur. Besides documenting an organization's

current affairs, a business-level sequence diagram can be used as a requirements document to communicate requirements for a future system implementation. During the requirements phase of a project, analysts can take use cases to the next level by providing a more formal level of refinement.

One of the primary uses of sequence diagrams is in the transition from requirements expressed as use cases to the next and more formal level of refinement. Use cases are often refined into one or more sequence diagrams. In addition to their use in designing new systems, sequence diagrams can be used to document how objects in an existing (call it "legacy") system currently interact. This documentation is very useful when transitioning a system to another person or organization [57].

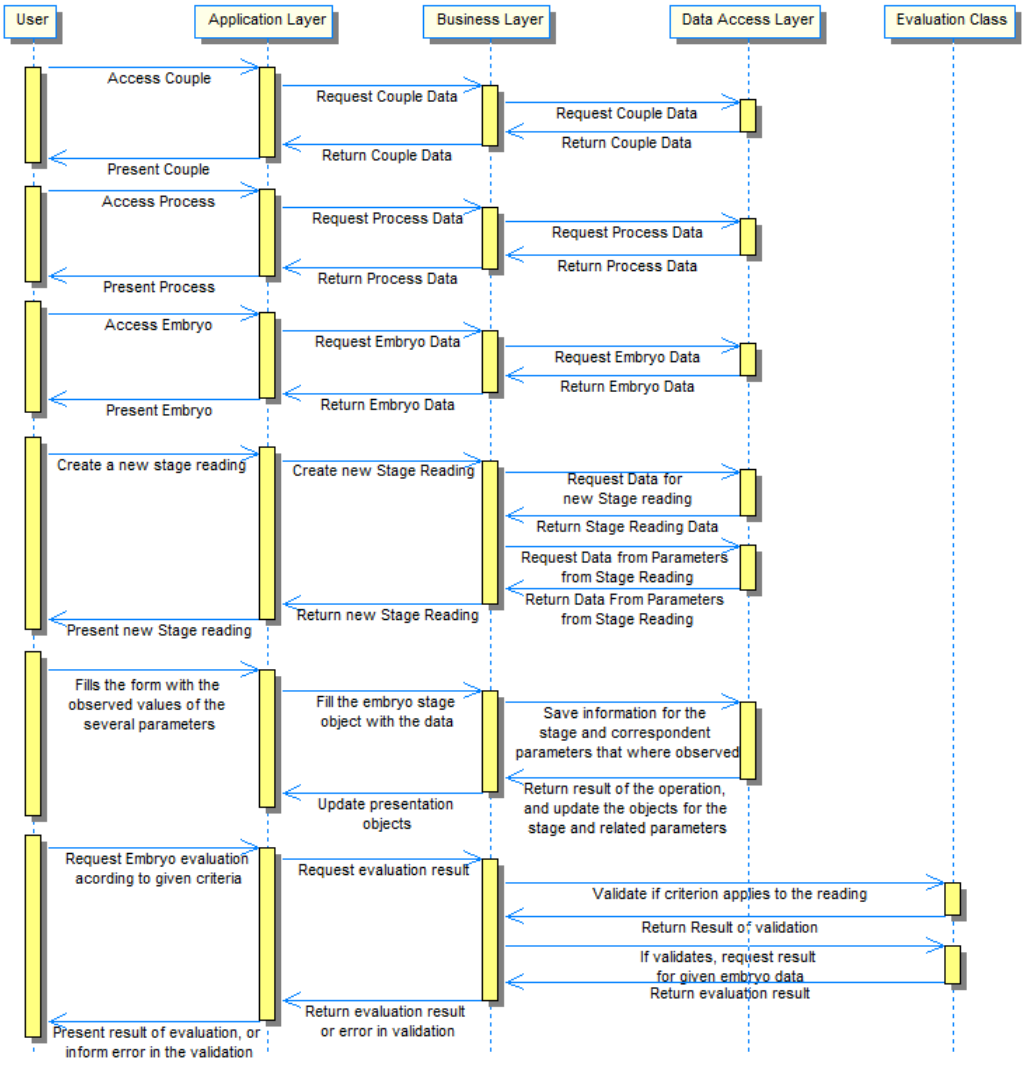

Fig. 15 - Sequence diagram for the reading on a stage followed for an evaluation.

In Appendix 3, a complementary set of examples of the sequence diagrams is presented.

5.6. Database

The database has to respect the laws of standardization, and to be constructed in a way that will allow scalability for future implementations on aspects that are not being addressed in the present moment, for example, a more thorough study of the oocyte or the sperm, or recording more information about why a couple should use ART.

The Database, of course, must be implemented respecting the rules of normalization trying to reduce the redundancy and dependency as much as possible, isolating the data so that the basic operation of creation, modification and removal of a field can be made on a single table and then, using defined relationships, propagated through the rest of the database.

5.7. Solution

This solution is implemented as an Object-Oriented approach following a basic 3 Layer architecture. Data Access Layer: that should be implemented following the CRUD methods directives, and that is responsible to communicate with the Database. Business Layer; the heart and soul of the solution, where most of the operations must take place, and where are defined relations between the different classes and how they interact. Presentation Layer; responsible for the communication with the users

These 3 layers must be implemented independently, this way any change or upgrade on a layer will have a minimum impact on any of the others layers, also it will allow that an entire layer can be reused on future developments of the project without need of re-implementing the architecture, or mixing implementations that may not be directly related; for example the implementation of several User Interfaces, or a need of change in the used database engine.

The several forms that exist in the application can be forms of list, detail, or hybrid, in the case of a certain element also includes one or more lists of other data. Below are examples of the forms of the Application.

First, in figure 16, a detail form. In here the several values that are observed in the embryo on a given day are recorded. On the left side is the menu that allows you to navigate between the three modules, and the top menu is the several parts in which the current selected module is divided.

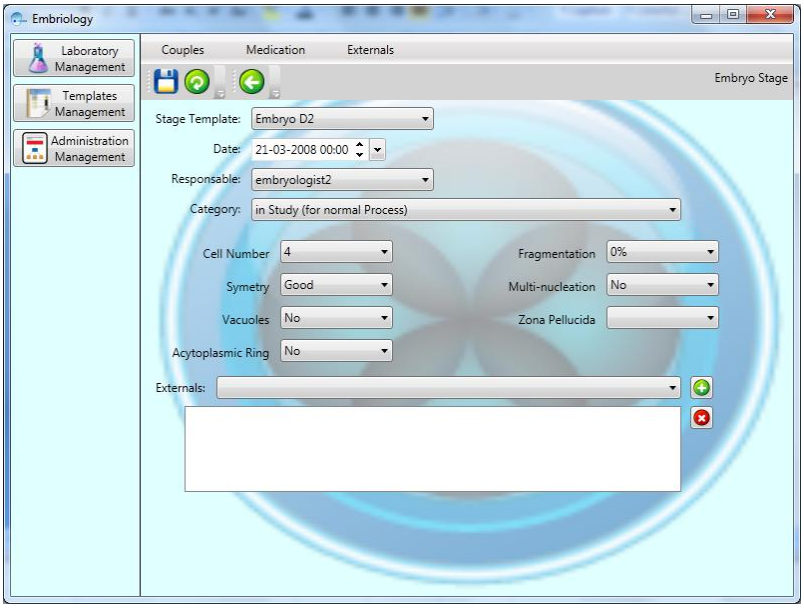

Fig. 16 - Application form: embryo reading detail.

On figure 17, a List form. This is a list of parameters that are defined on the Application. By selecting one of the lines it is possible then navigates to the detail form of the given parameter.

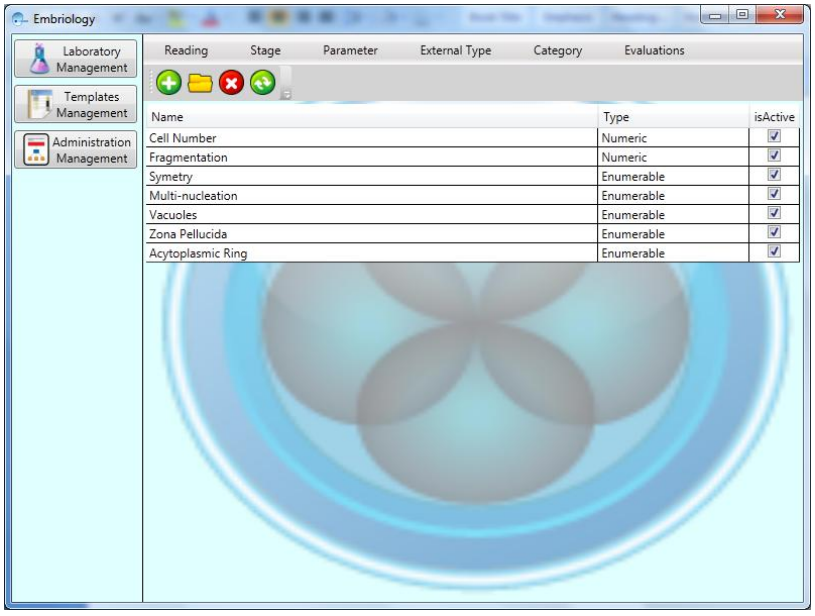

Fig. 17 - Application form: parameters list.

Of course there are situation where there is a need the have a detail and a list associated, for example when looking to a stage template and the list of the parameters that are associated to him (figure 18).

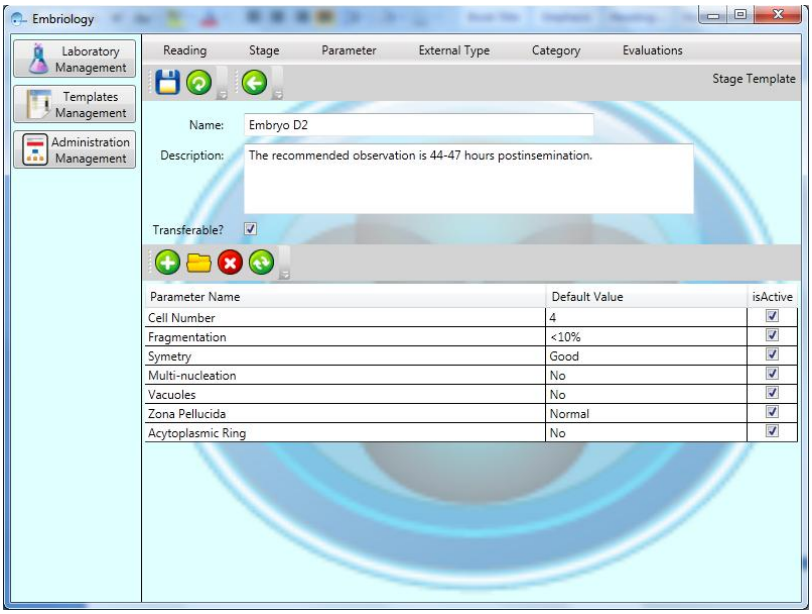

Fig. 18 - Application form: stage template form.

The stage, in the case has several parameters associated to him. In here it is possible to edit the stage data and select one of the parameters and edit the data related with the parameter when associated in the given stage.

6. Case Studies and Tests

6.1. Case Studies

Based on experts analysis of the specialty data [2] a table of importance of parameters was established, but some constraints have to be observed; First, the fact that the two main parameters (number of cells, and symmetry) must be evaluated together; for example, an optimal embryo on the second day after fertilization should be symmetric with 4 cells; so the algorithm proposed for these two parameters is that they should be evaluated as a single one. The same is true for day three after fertilization. Another special case refers to the parameters whose analysis is not cumulative, for example the fragmentation of an optimal embryo cannot exceed 10%. Consider an embryo with 15% fragmentation on day 2, it will have a penalty, and if it kept the same observation on day 3 it will relapse in the same penalty, giving the idea of having worsened, which is not true, so it must be analyzed only the worst value of the two days, and in this case it does not matter what was the selected day.

Following the collected information, seven parameters where identified, namely: number of cells symmetry percentage of fragmentation, existence of vacuoles existence of zona pellucida existence of multinucleation and the presence of cytoplasmic halo. It was also concluded, as mentioned above, the parameters symmetry and number of cells would need to be analyzed together as a single parameter.

Initially it was established the following mapping between the ASEBIR evaluation and the numerical score: *A* - 4; *B* - 3; *C* - 2; *D* - 1. After this a battery of theoretical tests, covering practically every possible case has been established, from this study were obtained the results in Table 2.

Table 2. Ranges of the classification algorithm implemented for each ASEBIR criteria

ASEBIR Criteria	DS(d) Maximum	DS(d) Minimum
A	4	4
B	3,83(3)	3
C	2,83(3)	2
D	1,83(3)	1

The fact that the response A is limited to a single value is understandable because the rules define that only an embryo, graded as optimum in every criteria should be classified as *A*.

After that, a dataset composed of readings from 56 real embryos was tested and the results produced by three different evaluation methods (by an expert, by the ASEBIR criteria, and by the proposed assessment model) were compared.

The objective was to apply the quantitative evaluation algorithm in real cases, and in this way observe the distribution of the various results, comparing with the results from the assessment taken in consideration. In figure 19, we can observe the distribution of the results of actual tests. In the 56 studied cases the experts' opinion matches the ASEBIR criteria. There are cases, although rare, where the expert can supersede this assessment; for instance when the examiners' experience tells him that the embryo will evolve to a better classification than the one that the criteria is giving at that moment.

In Apendix 4 there is a table with the full list of the embryos and their readings.

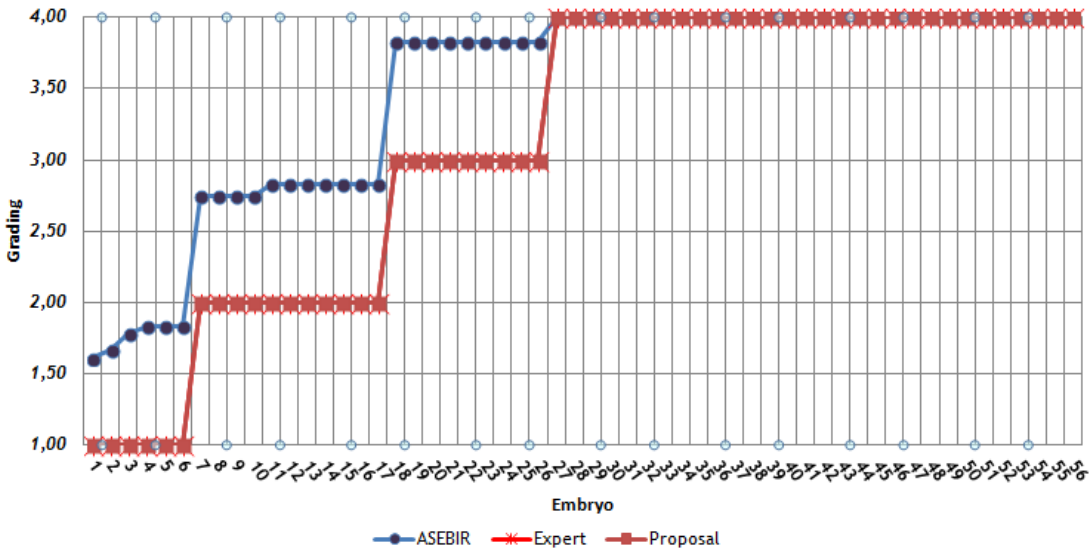

Fig. 19 - Distribution of the results of the evaluated embryos.

The current proposal allows to easily identifying differences between embryos that according to ASEBIR would be equal. For example as we can see in the diagram, the embryos classified between 1 and 2, corresponding to grade D in the ASEBIR, have different grades according to the proposal. This means that for a given class the descriptive power has increased being now possible to represent different degrees of quality.

6.2. Tests

In the development of the application prototype several software tests encompassing unit testing, integration testing and system testing were performed. A traceability matrix helps to correlate and trace business, application, security or any other requirements to their implementation, testing or completion. It evaluates the relationships between different system components and provides the status of project requirements in terms of their level of completion. It is primarily used in software development projects to trace, identify and verify that a specific functionality or component is being developed. Typically, a traceability matrix is a worksheet type document consisting of a table(s). Two different sets of values are compared against each other by placing an identifier for one set in the top row, and the other set on the left column. If there is commonality or a relationship, a mark is placed where the column and row intersect [58]. In Appendix 6 the tests that were made to verify the proper functioning of the several functionalities of the modules of the application are enumerated. For an easier examination these are distributed by three matrices, one for each module.

7. Conclusion

7.1. General Remarks

The selective embryo transfer is necessary in order to optimize efficacy and safety of the different techniques used in assisted reproductive technologies. The accurate embryo evaluation and the up-to-date laboratory workflow management are essential parts of a successful outcome for this task.

The proposed evaluation model, based on a triangular norm, is plausible for the accurate assessment of the embryo quality. Hence it can be used as an effective tool to support the selective embryo transfer decision-making. The implemented algorithm produces evaluation results heavily dependent on the somewhat subjective importance weights provided by the domain specialist.

This work has produced a tool that allows the administrator to determine what should be monitored during the several observations of the embryo development and record these data. After that, these data are available to be analyzed; also it returns the grade of the embryo(s) according to the ASEBIR criteria [2], even in the cases where the available information is incomplete (not all the necessary parameter measurements are collected).

The distinguishing factor that is being aimed is to develop a tool that is ready to keep up with the evolution and continuous change on a field of active research and constant innovation. Also independence from a particular criterium will allow the authorized users (e.g. the head of the laboratory or clinic) to choose and tune-up their favourite evaluation criteria.

7.2. Future Work

On a short-term, additional evaluation criterion are being studied and their interplay being modelled. Another interesting idea is cloud computing, gaining this way all the advantages on that model; on-demand self-service, broad network access, resource pooling, rapid elasticity, measured service [59]. Associated with this idea, it could also be interesting the implementation of several user interfaces. These user interfaces can provide different levels of access, or different objectives of use of the application, or having the same application working on the users most favoured, or practical device (web or mobile devices) but at the same time be able to contribute to the planned management change [60] in the implementation of information systems in health care. We intend to be able to contribute to strengthen the focus on process improvement through the

implementation of multiple models [61]. This guideline has been followed in the development of the prototype presented.

On the current state of the application, embryos are always related with the couple, a new module that would allow the study of the embryos on a wider perspective, taking advantage of historical data, would be a good idea. In this module there would be the possibility of applying machine learning techniques in order to synthesize classifiers able to better predict the expectable embryo evolution. New assessment criteria could be conceived and tested on the embryos available, without influencing the current assessment results on them.

There is also the objective of introducing in the algorithm more parameters, other than morphological, that will influence the implantation potential of the embryo, such as women's age, number of previous IVF cycles; keeping always in mind, that for the purpose of embryo selection for transfer or cryopreservation, the morphological parameters alone are enough, provided that all other characteristics are common for all embryos of the cohort. Another possible improvement is to extend the embryo assessment process with the inclusion of the data related with the sperm used and the oocyte quality, whenever available. We believe that this information can help to increase the accuracy of the evaluation process.

From the functional side, laboratory management of the external elements can also be integrated on this tool, helping to control the stock of consumables and disposables. Also associated with these externals the implementation of an alarm system that would monitor the relation between the externals and any defective evolution of the embryos.

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Appendices

Appendix 1

Use Cases

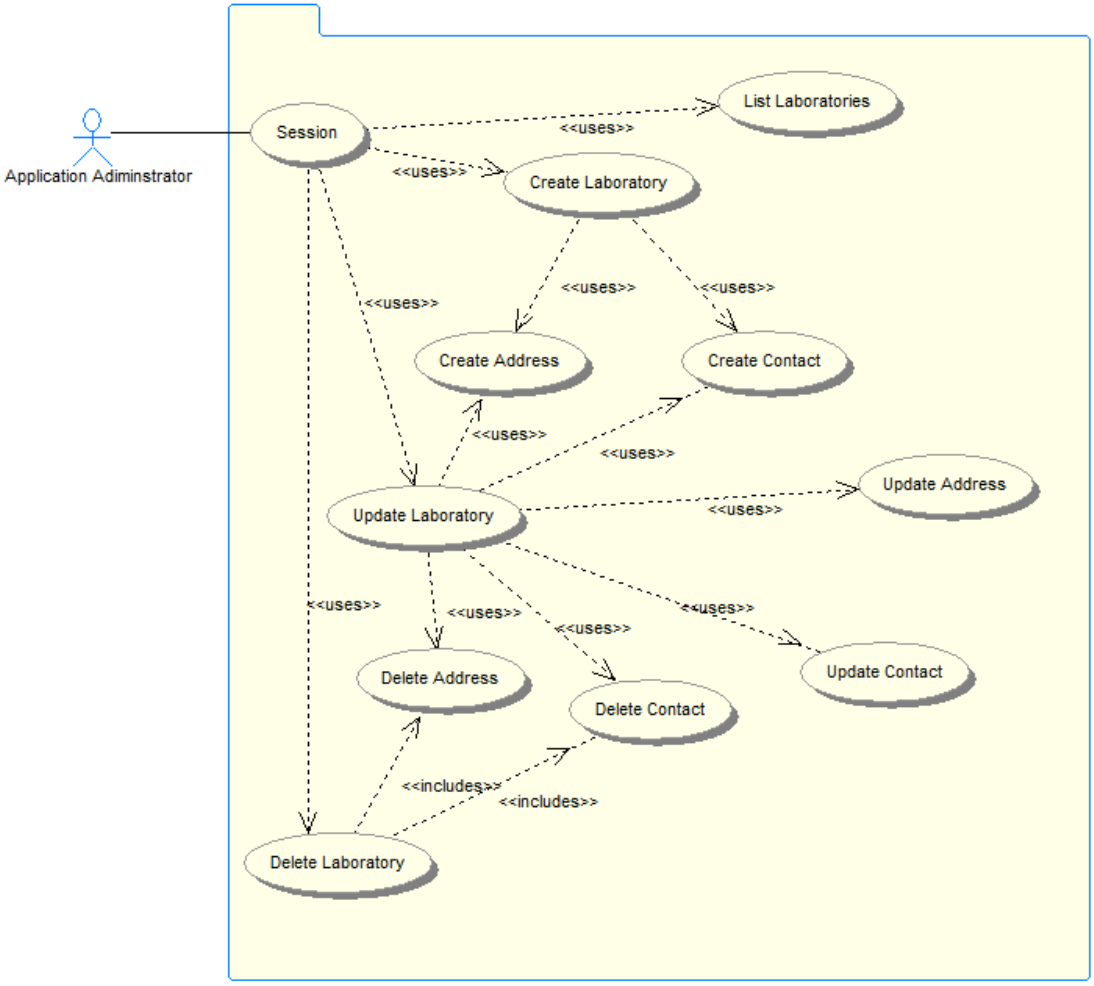

Fig. 19 - Use Case: Application administration for laboratory management.

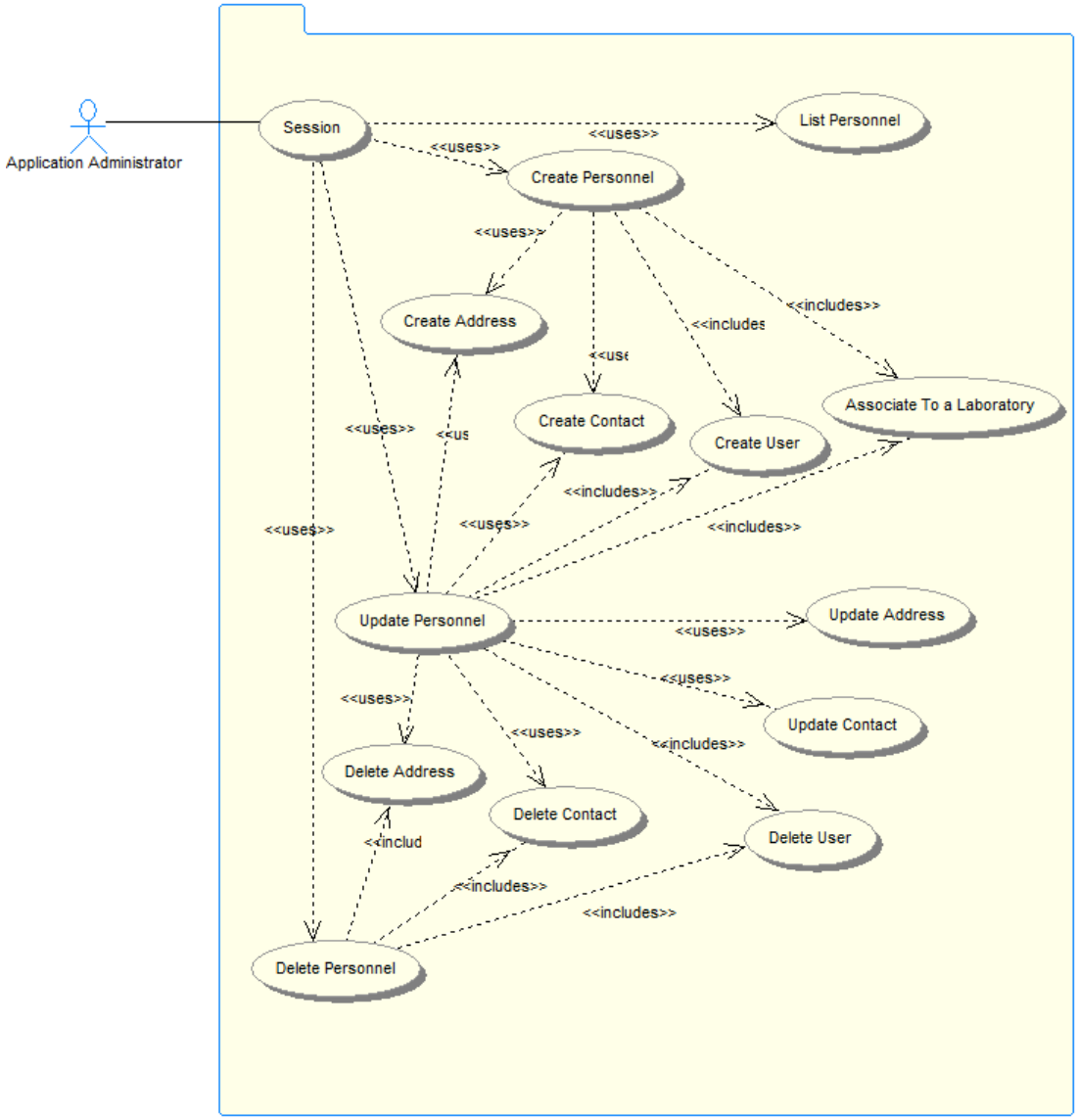

Fig. 20 - Use Case: Application administration for personnel management.

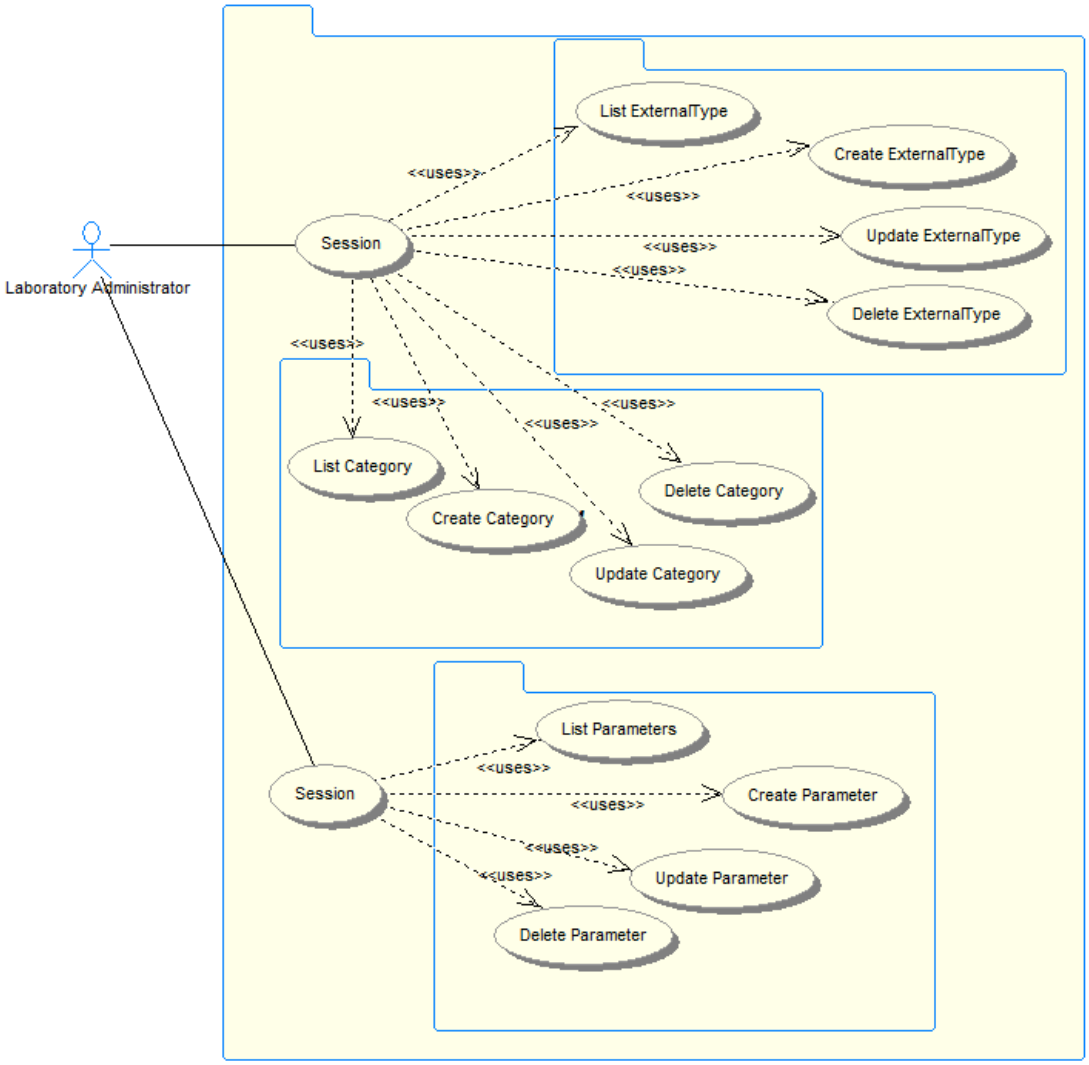

Fig. 21 - Use Case: Model administration for External types, Categories and Parameters management.

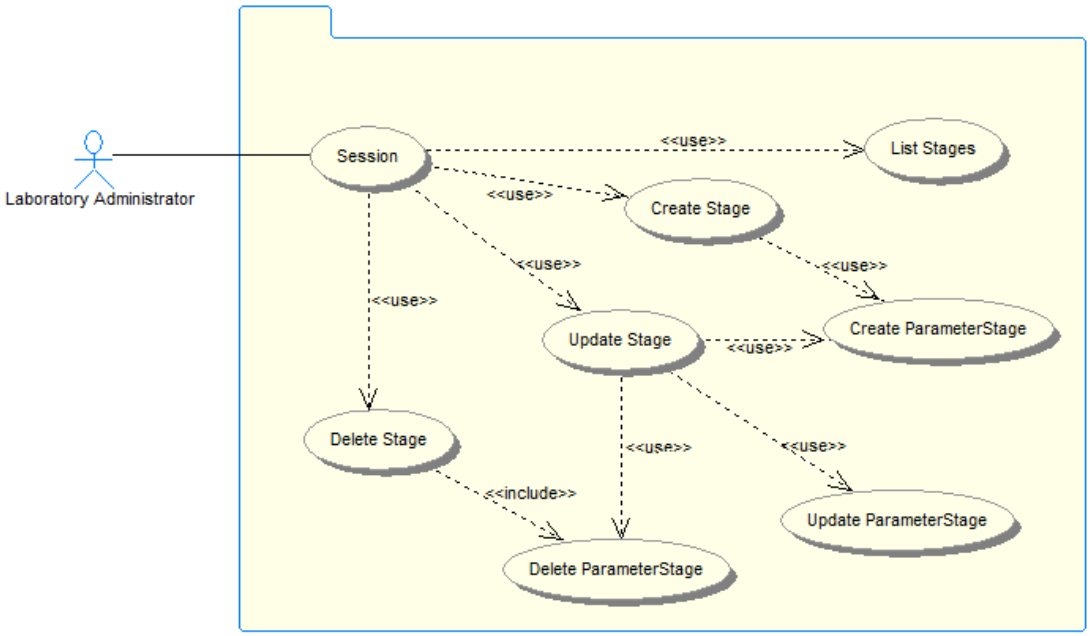

Fig. 22 - Use Case: Model administration for Stages management.

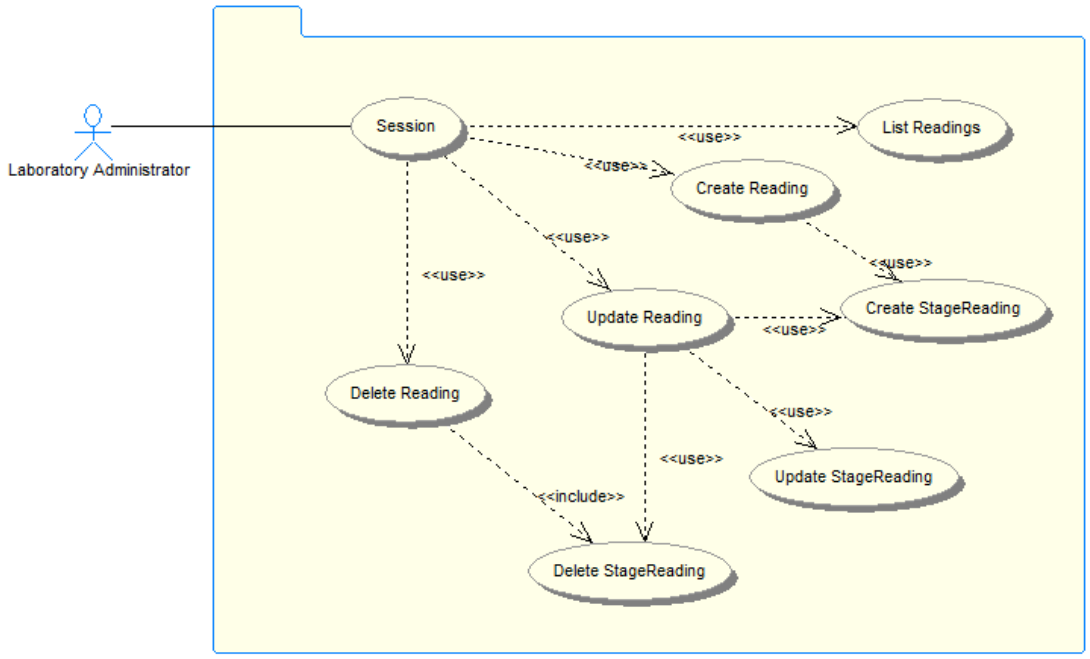

Fig. 23 - Use Case: Model administration for Readings management.

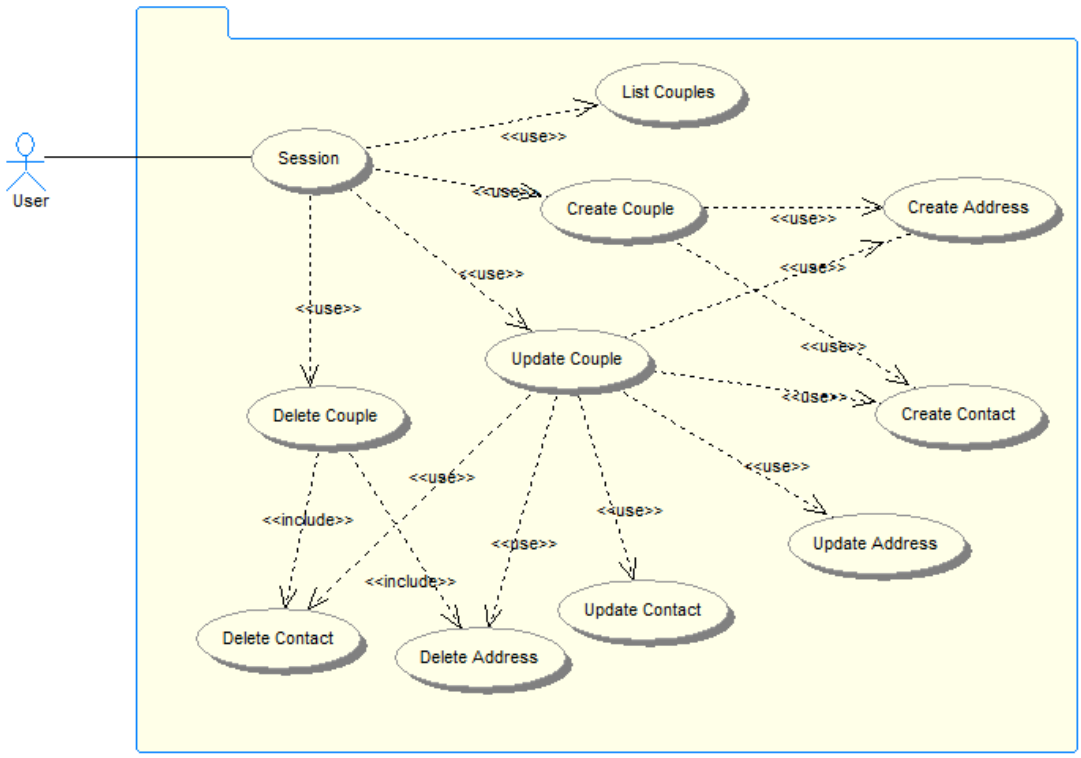

Fig. 24 - Use Case: Laboratory administration for Couples management.

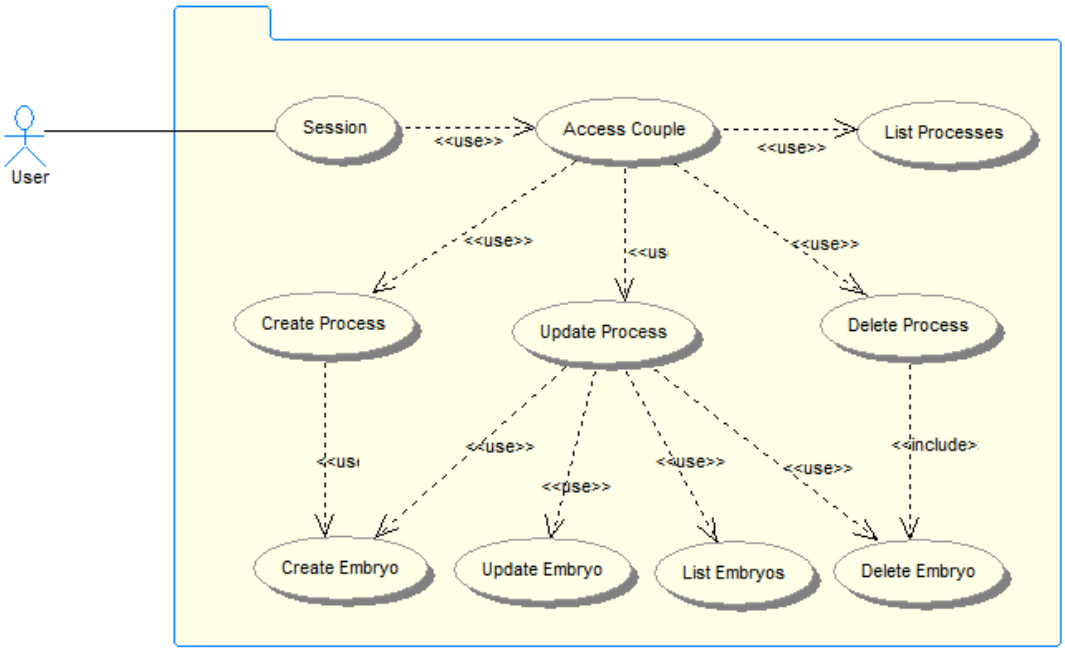

Fig. 25 - Use Case: Laboratory administration for Processes management.

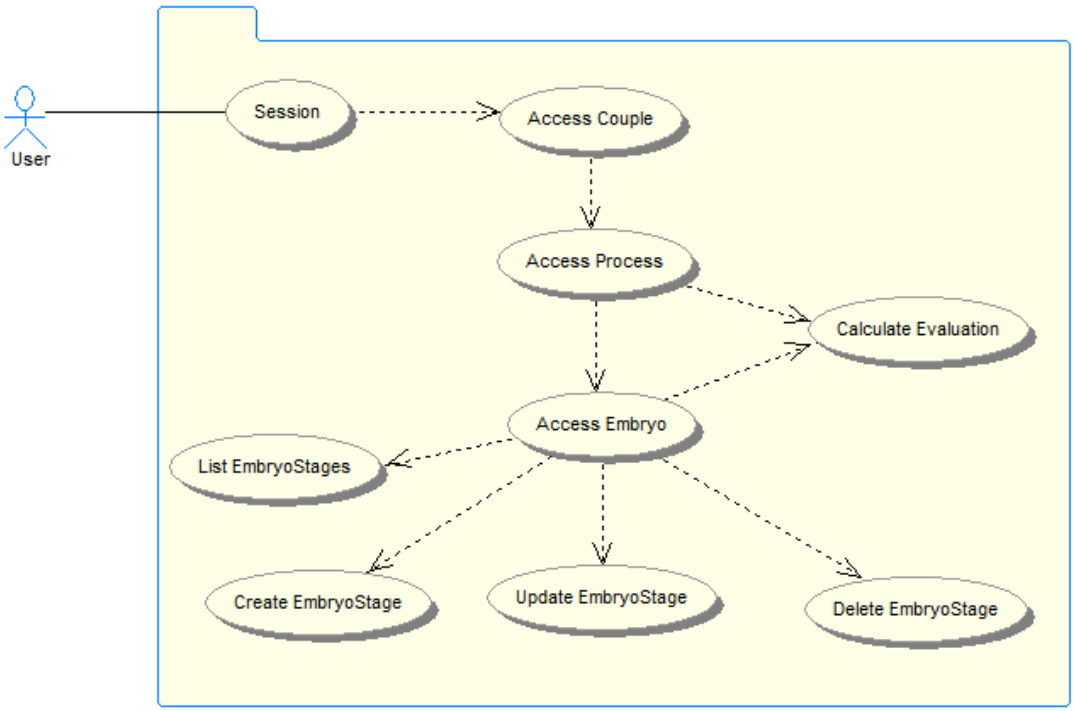

Fig. 26 - Use Case: Laboratory administration for Embryos management.

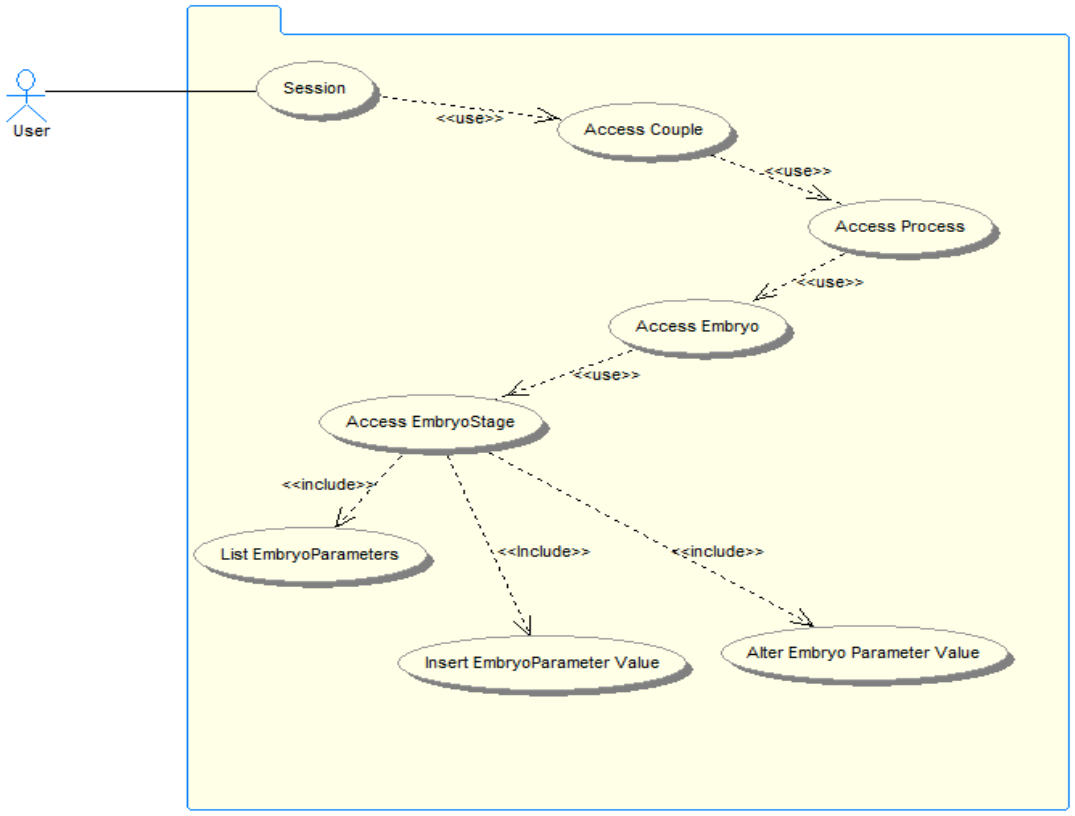

Fig. 27 - Use Case: Laboratory administration for Parameters management.

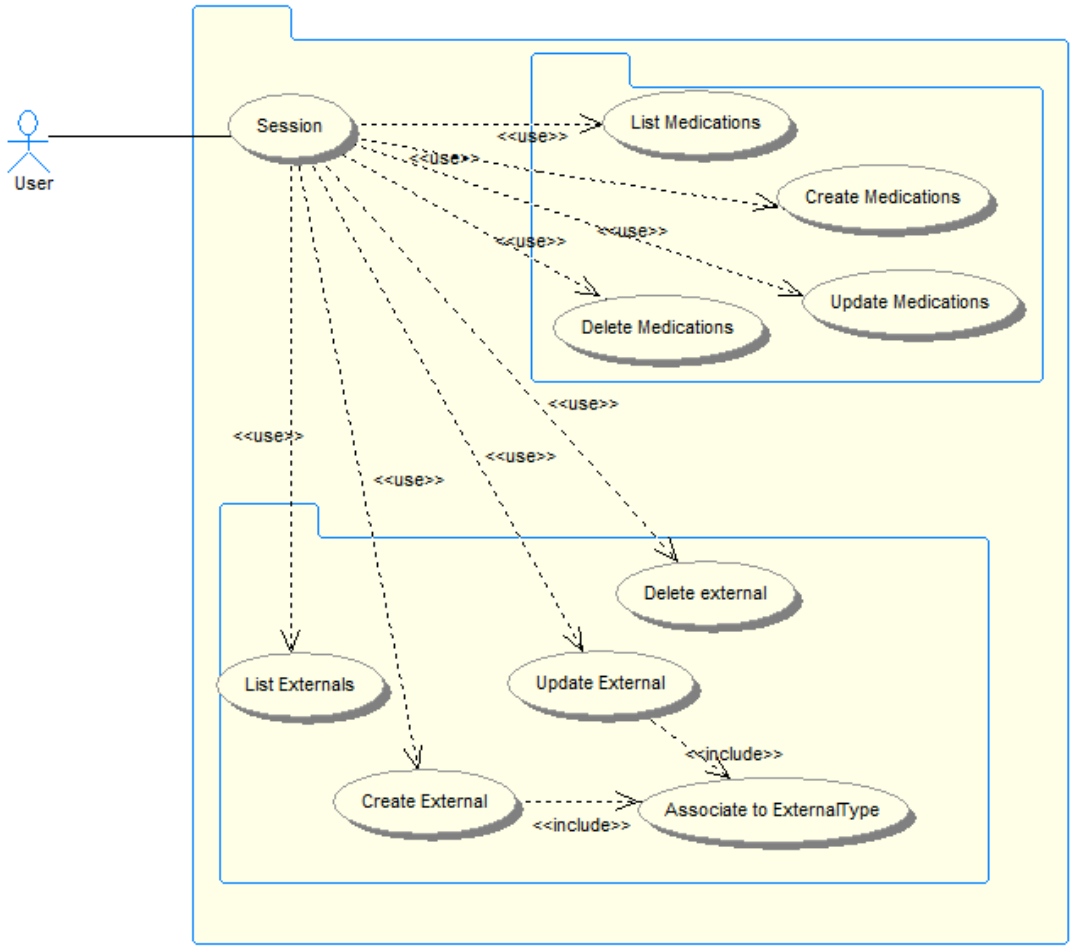

Fig. 28 - Use Case: Laboratory administration for Medications and Externals management.

Appendix 2

Application Class Diagram

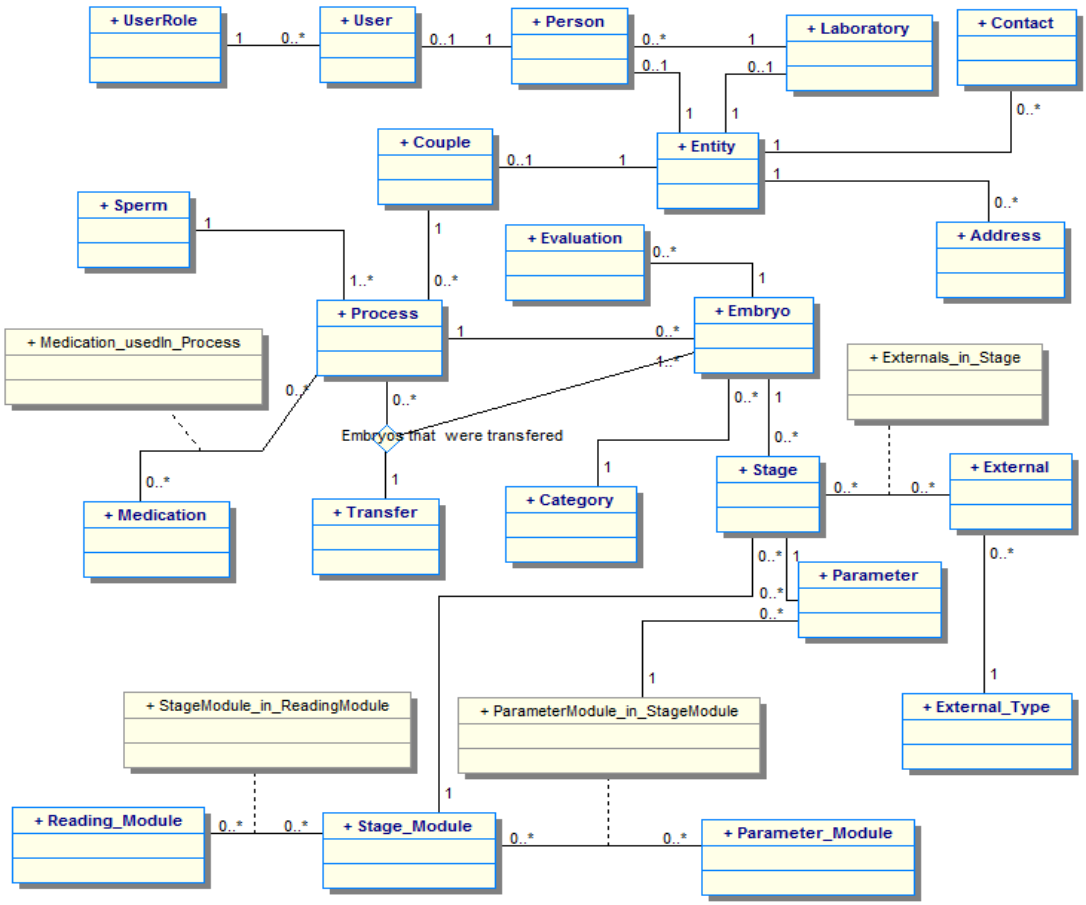

Fig. 29 - Class diagram.

Appendix 3

Sequence Diagrams (selected examples)

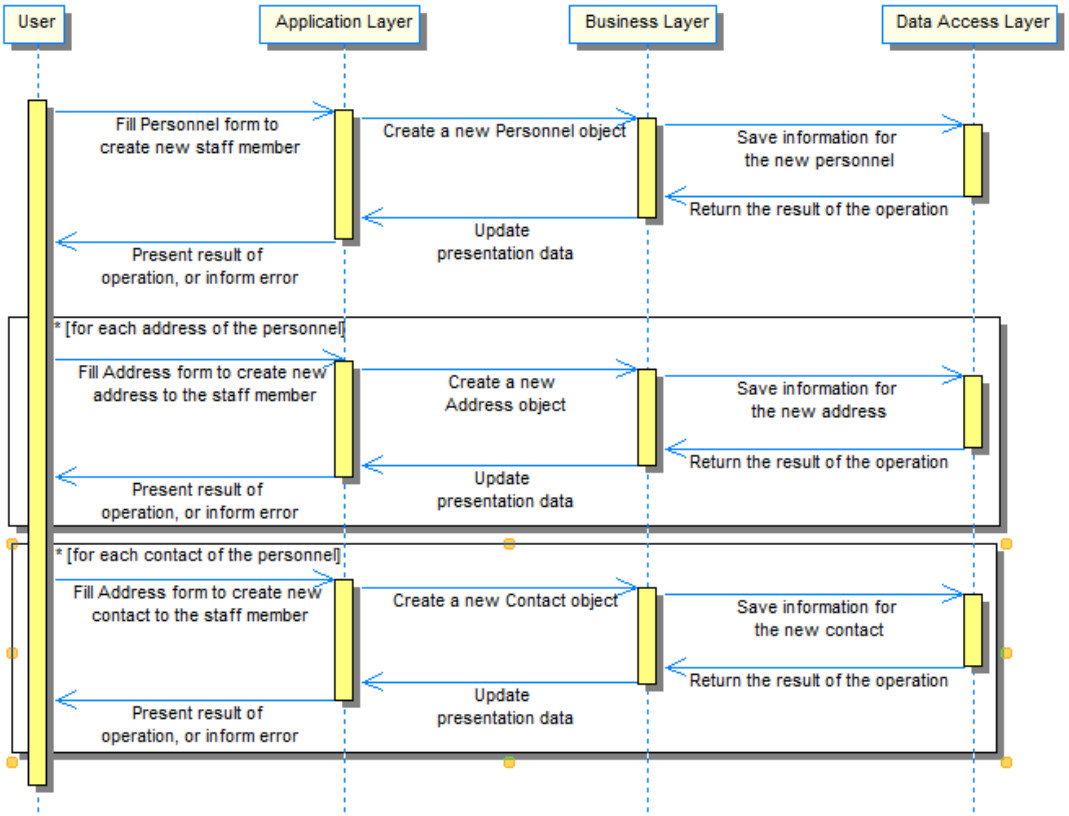

Fig. 30 - Sequence diagram for the personnel.

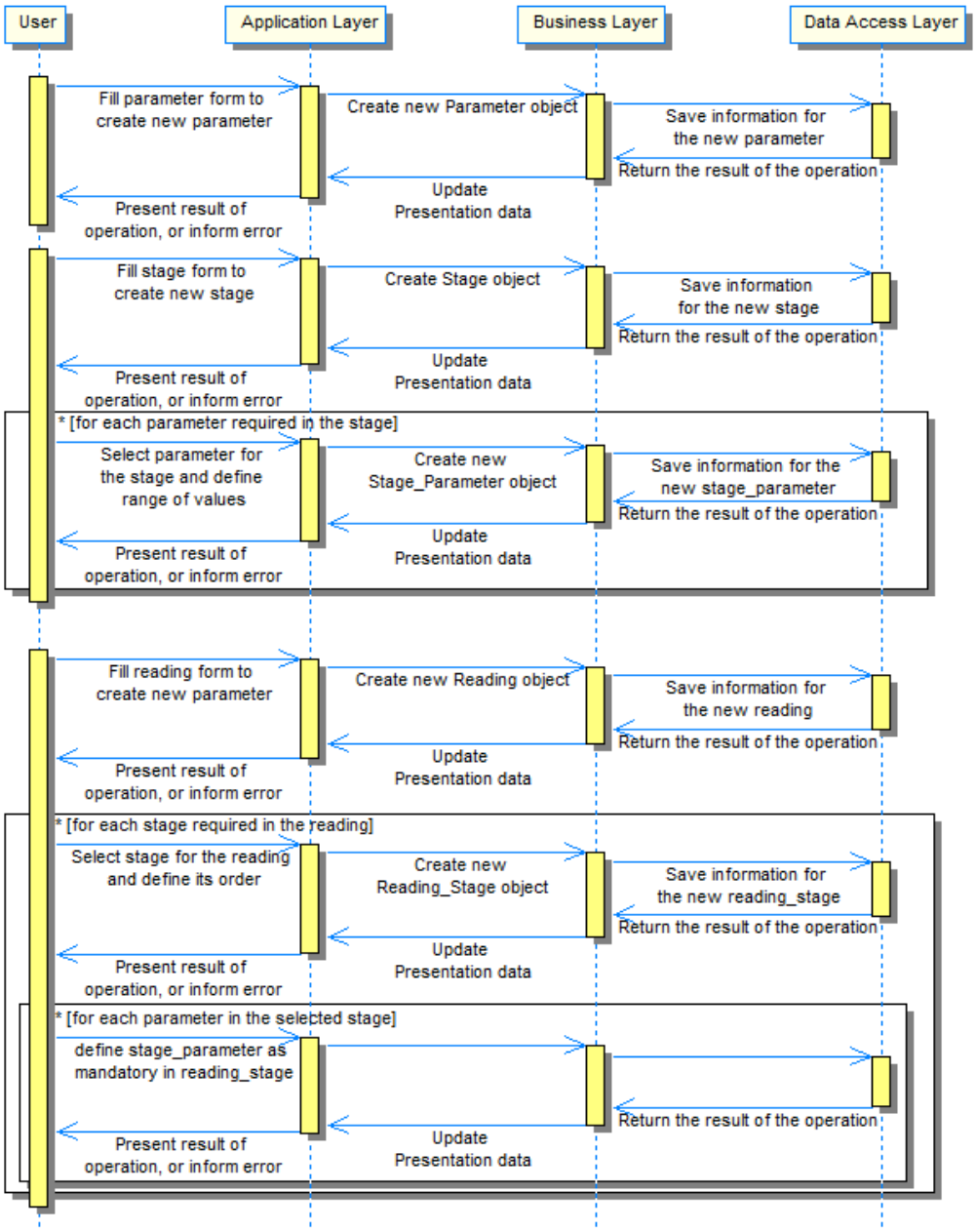

Fig. 31 - Sequence diagram for the process of creation of parameters, stages and readings.

Appendix 4

Case Studies

Process	1617	1617	1629	1629	1637	1637	1682
Embryo Nº	1	2	1	2	1	2	1
Embryo D2							
# of cells	4	4	4	4	4	4	4
Symmetry	0%	11% - 25%	0%	0%	0%	0%	0%
Fragmentation	Even	Un even	Even	Even	Even	Even	Even
Multinucleation	No	No	No	No	Yes	Yes	No
Vacuoles	No	No	No	No	No	No	No
Zona Pellucida	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Acytoplas. ring	No	No	No	No	No	No	No
Embryo D3							
# of cells	8	8	8	7	8	7	8
Symmetry	0%	11% - 25%	0%	0%	0%	0%	0%
Fragmentation	Even	Even	Even	Even	Even	Uneven	Even
Multinucleatio n	No	No	No	No	No	No	No
Vacuoles	No	No	No	No	No	No	No
Zona Pellucida	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Acytoplas. ring	No	No	No	No	No	No	No
Results							
ASEBIR	A	C	A	A	D	D	A
Expert Eval.	A	C	A	A	D	D	A
Algorithm	4,00	4,00	2,75	4,00	4,00	1,83	1,83

Process		1682	1690	1697	1697	1697	1709	1765	1765	18 87
Embryo Nª		2	1	1	2	3	1	1	2	1
Embryo D2	# of cells	4	1	4	4	4	4	4	4	4
	Symmetry	0%	11% - 25%	0%	0%	<10%	0%	0%	<10%	<10%
	Fragmentation	Even	Even	Even	Uneven	Even	Even	Even	Even	Even
	Multinucleation	No	Yes	No	No	Yes	No	No	No	No
	Vacuoles	No	No	No	No	No	No	No	No	No
	Zona Pellucida	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
	Acytoplas. ring	No	No	No	No	No	No	No	No	No
Embryo D3	# of cells	8	4	6	7	8	7	8	9	8
	Symmetry	0%	11% - 25%	0%	0%	<10%	<10%	0%	<10%	11% - 25%
	Fragmentation	Even	Even	Uneven	Uneven	Even	Even	Even	Even	Even
	Multinucleatio n	No	No	No	No	No	No	No	No	No
	Vacuoles	No	No	No	No	No	No	No	No	No
	Zona Pellucida	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
	Acytoplas. ring	No	No	No	No	No	No	No	No	No
Results	Expert Eval.	A	D	C	C	D	A	A	B	B
	ASEBIR	A	D	C	C	D	A	A	B	B
	Algorithm	4,00	4,00	1,61	2,83	2,83	1,83	4,00	4,00	3,83

Process		1911	1911	1918	1919	1927	1927	1980	1980	2062
Embryo Nª		1	2	1	1	1	2	1	2	1
Embryo D2	# of cells	4	4	4	4	4	4	4	4	4
	Symmetry	0%	0%	<10%	<10%	<10%	<10%	<10%	<10%	<10%
	Fragmentation	Even	Even	Even	Even	Even	Even	Even	Even	Even
	Multinucleation	No	No	No	No	No	No	No	No	No
	Vacuoles	No	No	No	No	No	No	No	No	No
	Zona Pellucida	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
	Acytoplas. ring	No	No	No	No	No	No	No	No	No
Embryo D3	# of cells	8	8	8	8	8	8	8	8	8
	Symmetry	0%	0%	<10%	<10%	<10%	<10%	0%	<10%	11% - 25%
	Fragmentation	Even	Uneven	Even	Even	Even	Even	Even	Even	Uneven
	Multinucleatio n	No	No	No	No	No	No	No	No	No
	Vacuoles	No	No	No	No	No	No	No	No	No
	Zona Pellucida	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
	Acytoplas. ring	No	No	No	No	No	No	No	No	No
Results	Expert Eval.	A	C	A	A	A	A	A	A	C
	ASEBIR	A	C	A	A	A	A	A	A	C
	Algorithm	3,83	4,00	2,83	4,00	4,00	4,00	4,00	4,00	4,00

Process		2062	2090	2090	2188	2188	2213	2214	2214	2270
Embryo Nª		2	1	2	1	2	1	1	1	1
Embryo D2	# of cells	4	4	5	4	4	4	4	4	4
	Symmetry	11% - 25%	0%	26% - 35%	<10%	<10%	<10%	0%	<10%	0%
	Fragmentation	Even	Even	Uneven	Even	Unev en	Even	Even	Even	Even
	Multinucleation	No	No	No	No	No	No	No	No	No
	Vacuoles	No	No	No	No	No	No	No	No	No
	Zona Pellucida	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
	Acytoplas. ring	No	No	No	No	No	No	No	No	No
Embryo D3	# of cells	4	7	7	8	8	8	8	8	7
	Symmetry	11% - 25%	< 10%	26% - 35%	<10%	11% - 25%	<10%	0%	11% - 25%	<10%
	Fragmentation	Even	Even	Uneven	Even	Even	Even	Even	Even	Even
	Multinucleatio n	No	No	No	No	No	No	No	No	No
	Vacuoles	No	No	No	No	No	No	No	No	N o
	Zona Pellu cida	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
	Acytoplas. ring	No	No	No	No	No	No	No	No	No
Results	Expert Eval.	D	A	C	A	C	A	A	B	A
	ASEBIR	D	A	C	A	C	A	A	B	A
	Algorithm	2,75	1,78	4,00	2,75	4,00	2,83	4,00	4,00	3,83

Process		2277	2277	2328	2328	2345	2345	2465	2509	2515
Embryo Nª		1	2	1	2	1	2	1	1	1
Embryo D2	# of cells	4	4	4	4	4	4	4	4	4
	Symmetry	<10%	0%	<10 %	<10%	0%	11% - 25%	<10%	11% - 25%	0%
	Fragmentation	Even	Even	Even	Even	Even	Even	Even	Even	Even
	Multinucleation	No	No	No	No	No	No	No	No	No
	Vacuoles	No	No	No	No	No	No	No	No	No
	Zona Pellucida	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
	Acytoplas. ring	No	No	No	No	No	No	No	No	No
Embryo D3	# of cells	8	8	8	8	8	8	8	8	8
	Symmetry	<10%	0%	<10%	<10%	<10%	11% - 25%	11% - 25%	11% - 25%	0%
	Fragmentation	Even	Uneven	Even	Even	Even	Even	Even	Even	Even
	Multinucleatio n	No	No	No	No	No	No	No	No	No
	Vacuoles	No	No	No	No	No	No	No	No	No
	Zona Pellucida	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
	Acytoplas. ring	No	No	No	No	No	No	No	No	No
Results	Expert Eval.	A	C	A	A	A	B	B	B	A
	ASEBIR	A	C	A	A	A	B	B	B	A
	Algorithm	4,00	4,00	2,83	4,00	4,00	4,00	3,83	3,83	3,83

Process		2515	2554	2554	2587	2587	2588	2596	2596	2598
Embryo Nª		2	1	2	1	2	1	1	1	1
Embryo D2	# of cells	4	4	4	4	4	4	4	4	4
	Symmetry	0%	<10%	<10%	0%	<10%	0%	<10%	0%	<10%
	Fragmentation	Even	Even	Uneven	Uneven	Uneven	Even	Even	Even	Even
	Multinucleation	No	No	No	No	No	No	No	No	No
	Vacuoles	No	No	No	No	No	No	No	No	No
	Zona Pellucida	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
	Acytoplas. ring	No	No	No	No	No	No	No	No	No
Embryo D3	# of cells	8	9	8	9	8	8	7	8	8
	Symmetry	<10%	<10%	11% - 25%	<10%	11% - 25%	0%	<10%	0%	<10%
	Fragmentation	Even	Even	Uneven	Even	Uneven	Even	Uneven	Even	Even
	Multinucleation	No	No	No	No	Yes	No	No	No	No
	Vacuoles	No	No	No	No	No	No	Few	No	No
	Zona Pellucida	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
	Acytoplas. ring	No	No	No	No	No	No	No	No	No
Results	Expert Eval.	A	B	C	C	D	A	C	A	A
	ASEBIR	A	B	C	C	D	A	C	A	A
	Algorithm	4,00	4,00	3,83	2,75	2,83	1,67	4,00	2,83	4,00

Process		2598	2670	2670	2688
Embryo Nª		1	1	2	1
Embryo D2	# of cells	4	4	4	5
	Symmetry	<10%	0%	11% - 25%	11% - 25%
	Fragmentation	Even	Even	Even	Uneven
	Multinucleation	No	No	No	No
	Vacuoles	No	No	No	No
	Zona Pellucida	Normal	Normal	Normal	Normal
	Acytoplas. ring	No	No	No	No
Embryo D3	# of cells	10	8	8	8
	Symmetry	<10%	<10%	11% - 25%	11% - 25%
	Fragmentation	Even	Even	Even	Even
	Multinucleatio n	No	No	No	No
	Vacuoles	No	No	No	No
	Zona Pellucida	Normal	Normal	Normal	Normal
	Acytoplas. ring	No	No	No	No
Results	Expert Eval.	B	A	B	B
	ASEBIR	B	A	B	B
	Algorithm	4,00	3,83	4,00	3,83

Appendix 5

Json file for ASEBIR criteria testing


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 "AppIName":"Vacuoles",
                              "ValuesList":[
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        "ApplValue":"Few"
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        "ApplValue":"Many"
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                               ]
    },
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                               "ValuesList":[
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        "ApplValue":"Normal"
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        "ApplValue":"Hatching"
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                      ]
},
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},
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 "ApplName":"Zona Pellucida",
                      "ValuesList":[
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    "JsonValue":"Normal",
    "ApplValue":"Normal"
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                        {
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    "ApplValue":"Hatching"
                        },
                        {
    "JsonValue":"Abnormal",
    "ApplValue":"Abnormal"
                        }
                      ]
},
{
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 "ApplName":"Acytoplasmic Ring",
                      "ValuesList":[
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                      ]
  }
 ]
},
"OrderedResults":[
 "D",
 "C",
 "B",
 "A"
]
}
```

Appendix 6

Traceability Matrices

Administration Module

Following the System requirements chapter the following are defined as requirements for the administration module:

I. Manage laboratory

II. Manage laboratory addresses

III. Manage laboratory contacts

IV. Manage personnel

V. Manage personnel addresses

VI. Manage personnel contacts

The following are the tests that were defined for the given module:

a. Create a Laboratory

b. Update the created laboratory

c. Add and address to the created laboratory

d. Update the address

e. Add a contact to the laboratory

f. Update the contact

g. Create a staff member

h. Update the staff member

i. Set the staff member as a user

j. Create an address for the staff member

k. Update the staff member address

l. Remove the staff member address

m. Create a contact to the staff member

n. Update the staff member contact

o. Remove the staff member contact

p. Remove the staff member

q. Remove the laboratory contact

r. Remove the laboratory address

s. Remove the laboratory

Considering these requirements, placed on the left column; and tests, placed on the top row, the traceability matrix for this module would be:

Traceability matrix for Administration Module

	a	b	c	d	e	f	g	h	i	j	k	l	m	n	o	p	q	r	s
I	X	X																	X
II			X	X														X	
III					X	X											X		
IV							X	X	X							X			
V										X	X	X							
VI													X	X	X				

Management Module

Following the System requirements chapter the following are defined as requirements for the management module:

I. Manage parameters

II. Manage stage

III. Manage parameters in stage

IV. Manage reading

V. Manage stages in reading

VI. Manage parameters in the reading stage

VII. Manage category

VIII. Manage type of external

The following are the tests that were defined for the given module:

a. Create a parameter

b. Update the parameter

c. Create stage

d. Update stage

e. Associate existing parameter in stage

f. Update parameter in stage

g. Create reading

h. Update reading

i. Associate stage to reading

j. Update stage in reading

k. Define parameter in stage as mandatory in reading

l. Update mandatory status of parameter in stage of reading

m. Disassociate stage from reading

n. Delete Reading

o. Disassociate parameter in stage

p. Delete stage

q. Delete Parameter

r. Create category

s. Update category

t. Delete category

u. Create type of external

v. Update type of external

w. Delete type of external

Considering these requirements, placed on the left column; and tests, placed on the top row, the traceability matrix for the management module would be:

Traceability matrix for the Management Module

	a	b	c	D	e	f	g	h	i	j	k	l	m	n	o	p	q	r	s	t	u	v	w
I	X	X															X						
II			X	X												X							
III					X	X									X								
IV							X	X						X									
V									X	X			X										
VI											X	X											
VII																		X	X	X			
VIII																					X	X	X

Laboratory Management

Following the System requirements chapter the following are defined as requirements for the laboratory module:

I. Manage couples

II. Manage couple addresses

III. Manage couple contacts

IV. Manage couple processes

V. Manage embryos in process

VI. Manage embryo stage

VII. Manage parameters reading in embryo stages

VIII. Calculate embryo evaluation

IX. Manage Medication

X. Manage external

The following are the tests that were defined for the given module:

a. Create couple

b. Update couple

c. Create couple address

d. Update couple address

e. Create couple contact

f. Update couple contact

g. Create process

h. Update process

i. Create embryo in process

j. Update embryo in process

k. Create embryo stage

l. Update embryo stage

m. Record parameters reading for given stage

n. Update parameters reading for given stage

o. Calculate embryo evaluation

p. Delete embryo stage

q. Delete embryo

r. Delete process

s. Delete couple contact

t. Delete couple address

u. Delete couple

v. Create medication

w. Update medication

x. Delete medication

y. Create external

z. Update external

aa. Delete external

For an easier visualisation of this module the axis wil be flipped; so considering these requirements, placed on the top row; and tests placed on the left column, the traceability matrix for the laboratory module would be:

Traceability matrix for the Laboratory Module

	I	II	III	IV	V	VI	VII	VIII	IX	X
a	X									
b	X									
c		X								
d		X								
e			X							
f			X							
g				X						
h				X						
i					X					
j					X					
k						X				
l						X				
m							X			
n							X			
o								X		
p						X				
q					X					
r				X						
s			X							
t		X								
u	X									
V									X	
w									X	
x									X	
y										X
z										X
a a										X

Appendix 7

WorldCist 2014 published paper

ARTE: an Embryo Quality Assessment Tool

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Abstract. This paper proposes an assessment model of putative embryos for in vitro fertilization (IVF) based on a triangular norm. One of the most common difficulties of IVF treatments is multiple pregnancy. Therefore the number of embryos for transfer is of paramount importance considering the need to reduce the incidence of multiple births without compromising overall pregnancy rates in fertility treatments. Consequently the selective embryo transfer is recommended to optimize efficacy and safety outcomes. The embryo evaluation is of enormous relevance, since it directly affects the success of different techniques used in assisted reproductive technologies (ART). The gathering of all the information needed to embryo evaluation, as well as software that can serve as aid in the decision is of great importance. The tool herein presented accomplishes these two objectives. The analysis of the requirements of the assessment process has resulted in a flexible data model, used in the presented prototype, supporting the selective embryo transfer decision-making process.

Keywords: Embryo Assessment, Decision Making, Software Engineering, Assisted Reproductive Technologies

1. Introduction

Worldwide, it is estimated that one out of every six couples experience some form of infertility problem at least once during their reproductive lifetime [1], and it is also estimated that 11.3% to 26.4% of women, under 50, in more developed countries have a lifetime prevalence of infertility [2]. In 2009 the Portuguese Society for Reproductive Medicine (SPMR), conducted a joint study with Keypoint, aiming to quantify and characterize the type of infertility existent in Portugal. According to this study there where at the time 116.630 couples facing infertility[7] problems, and 7.9% of women from 25 to 44 have problems in conceiving [4].

In recent years the number of couples who resort to Assisted Reproductive Technologies (ART) has increased considerably [5], consequently the amount of in vitro fertilization (IVF) clinics has enlarged worldwide and the need to improve IVF techniques has become a major endeavor.

[7] According to the World Health Organization, Sterility is defined as the "inability to fertilize the ovum with a spermatozoan" while Infertility refers to "the inability to ensure that the fertilized ovum develops sufficiently for the birth of a viable child" [3]. In this paper we will use the word "infertility" to describe both situations since the type of diagnosis associated with reproductive problems will not have an influence on the current work

The Assisted Reproductive Technologies (ART) grew in importance medically, socially and economically. The number of units available keeps increasing both in the public and private sectors, greatly due to the considerable growth of the number of couples who resort to these techniques in recent years. Although this is a field with enormous potential there are gaps in some areas including that of information technology (IT).

The available ART units are multidisciplinary units that cover three different fields: medical, nursing and laboratory. Despite their importance and complementary character, the laboratory component has proven to be of particular importance [6, 7]. After infertile couples are diagnosed most of the process of becoming pregnant is largely dependent on the embryology lab.

Several ART techniques are applied in the embryology lab, namely *In Vitro Fertilization* (IVF) [8] and *Intracytoplasmic Sperm Microinjection* (ICSI) [9], [10]. Daily view of oocytes and embryos under an inverted microscope is required in both techniques for a period ranging between 3 to 5 days. Several morphological parameters are assessed during these observations in order to determine the embryo quality and implantation rate. These parameters are later used to determine which of the embryos are transferred, frozen or destroyed. Evaluation should be continuous, systematic and reducing the variability between observers [11].

Since it directly affects the chances for success, the different techniques used in reproductive medicine embryo assessment are of enormous importance. One of the main problems concerning embryo assessment is the lack of a single evaluation criterion, although several efforts have been made to obtain a consensus [12]. The need to compare results makes it imperative to achieve some sort of standardization.

A software that allows its user both the possibility of collecting and storing all needed information as well as assisting in the process of decision making would prove not only to be a valuable resource, but also it would help to fill a gap in terms of specialized software in the field of human embryology.

This paper is organized as follows. Section 2 presents a brief review of related works. In Sec. 3 it is proposed a model for the embryo quality assessment. Section 4 presents the functional requirements and the data conceptual model of the application. In Sec. 5 are referred some major design choices for the developed prototype and finally Sec. 6 draws the conclusions and discusses future work.

2. Background

The available software consists mainly of small applications usually created from generalist tools, like MS Access, Filemaker, or even MS Excel files, for personal

(laboratory) use. Moreover, the existing commercial programs are “heavy” and best suited for the medical component. These are programs designed for patient management, assisting in the patient diagnose, medical history, gamete bank management, lab data storage and produce several kind of reports. The fact that these are multifaceted programs makes them of little use in the laboratory, being used more often than not as a simple tracker of the results obtained in the several cycles that were performed during a period of time.

Nevertheless there are good integrated equipments commercially available. Arguably the most distinguishable one is the EmbryoScope™ Embryo Monitoring System, developed by Unisense FertiliTech, a built-in gas incubator that is controlled by an embedded PC [13]. This system allows uninterrupted observation of embryo development in a stable controlled environment. It features a camera that collects images of the embryos. The software associated, the EmbryoViewer™, allows the review, annotate and compare the development of selected embryos using data files acquired by the EmbryoScope; it also allows a retrospective analysis of the embryo development, and helps the embryologist to easily assess several parameters for embryo selection [14]. Unfortunately these are costly systems, too expensive for most national laboratories or even considering an Iberian scale.

There is also software that, using computer analysis of images of planes at various depths within the sample (z-stacks) allows the observation of the 3-dimensional morphology of an embryo, particularly a 4-cell. This Image Analysis software operates on a series of digital images acquired at different focal planes (acquired either by means of a common microscope equipped with a digital camera or by specialized hardware) and finds the boundaries of blastomeres as closed contours with regular shapes [15].

The Artemis™ from Medialogic, is a software that helps to manage, track and report several reproductive techniques. More turned to the aspect of reporting production and storage of data related to the patients and the embryo cycle itself [16].

Besides these software there are also studies being made, on the prevention of multi-pregnancy, taking in consideration the embryo quality, as the main objective is always the ability to select the best embryo for transfer [17,18], thus avoiding the transfer of more than one embryo, that could lead to an undesirable multi-pregnancy. In some countries the current legislation is very strict on transferring and freezing embryos, for example in Germany no cleavage embryos can be frozen, so all embryos that reach this stage must be transferred, this leads of course to a high rate of twins and triplets [19].

The main objective of our research is to build an application that using parameters previously defined by an administrator, performs an a-priori embryo classification

(predictive value). The purpose will be the elective selection for embryo transfer or cryopreservation. Additionally, it must allow the comparison of different existing classifications, providing insight on which classification produces more accurate results on certain situations. In addiction it should also allow data analytics studies based on actual classifications.

By allowing the parameters to be managed by the administrator a major obstacle is overcome, the constant evolution in the scientific research that brings new parameters to light, and questions the importance of other parameters previously gathered. Also different evaluations can take in consideration different parameters and even with different correlation and/or importance between them.

Another objective is to deploy a tool that will help to uniform the parameters, their more common names, as well as their evaluation.

Summing up we can say that this work empowers the administrator with the tools to tune the evaluation, creating the parameters and defining them, as a programmer creates the set of properties on classes. Then he/she will also be able to "program" the way these parameters will interact to return a result, as a method. Having this liberty the administrator will have no need to ask for an upgrade every time a change happens.

3. **Algorithm to calculate the quality of the embryo**

One of the key concerns of this work is the elicitation of a formula that will allow the evaluation of the embryo and give it a percentage score, this formula must be flexible enough so that it will not be dependent of any parameter in concrete; this is because all the parameters will be inserted by the administrator of the application, allowing this way a flexible use that will not require the intervention of a programmer to rebuild the project just because a new parameter must be inserted.

Another point is that the evaluation on a certain day of a certain embryo must be conditioned by the previous evaluations of that same embryo. In the following it will be presented a plausible mathematical formula that is flexible enough to be used on such vague environment, but on the same time is precise enough to return reliable results.

In order to simplify the explanation let us start by assuming that the ASEBIR recommendations [20] are enforced making one reading per day, recording the parameters that are indicated in the examination of that specific day. The readings are taken on day 1 after 16-19 hours of the insemination; on day 2 after 44-47 hours; on day 3 after 67-71 hours, etc.

All parameters will have an importance, and the different values that the parameter can take are also discriminated, the system administrator defines all these values.

Let's take in consideration all the parameters P, that must be evaluated on a given day d; and that a certain parameter p on that group has an importance i_{pd}, already defined, so we can say that the relative weight of that parameter p in the score for the day is:

$$\omega(\pi,\delta) = (\iota_{\pi\delta} / \bullet \iota_{\varphi}) \phi o \rho \alpha \lambda \lambda \varphi \iota \nu \Pi . \qquad (1)$$

i.e. the relative weight of the parameter is equal to its importance divided by the sum of the importance of all the parameters of that day; this way the relative weight of a parameter will be a value between 0 and 1.

Each parameter p will have a set A_p of associated answers (or range of answers in case of numerical answers) each one of those answers will have a certain grade G_{ap}. The normalized score of each answer, $S(p, d)$, is constrained to the unit interval [0, 1] so that the maximum score possible in any day is lesser or equal to 1.

The score of a parameter p, in a given day d, is obtained through the following formula:

$$\Delta\Sigma(\delta) = \bullet\ \Sigma(\pi, \delta).\ \omega(\pi, \delta)\ \phi\rho\ \alpha\lambda\lambda\ \pi\iota\nu\ \Pi. \qquad (2)$$

The final score must be obtained by considering all the days, but not forgetting that the score of a previous day must always affect the score for the next day.

$$\Phi\Sigma = \prod_{d} DS(d) \qquad (3)$$

Where d is a placeholder for the elements of the set of days passed after the insemination.

Notice that in this way it is assured that the score on a given day of a given embryo will never be higher than the score of that same embryo the day before, as is a consensual assumption that an embryo is not likely to evolve to become a better embryo than what was expected based on previous evaluations. Instead of the product norm (the standard semantics for strong conjunction) another triangular norm, such as the minimum norm, could be used to compose a given day-score with the previous ones.

This composite score is returned as a value between 0 and 1 that can be easily converted to any classification table.

4. System Requirements

For a question of organization we divided the project in 3 major modules, these modules are relatively independent, they each are focused on a field of work, although the last module depends on the other two. The first of these modules is an administration module; where it will be possible the management of the users of the application and organize them by laboratories. The second module, model management, here are defined and managed the several parameters, organized them by stages, and organized this stages by readings; also is where it is defined the several types of externals that may be used and interact with the embryo. The last, but not least is the laboratory module, where the real data is managed, the couples, the referred processes and all the information that is related with it, also the medications that will be used and the externals elements.

4.1. Administration management

The administration is composed by the class relative to the Personnel, these can be Embryologists or Physicians; they can also be registered as users or not. The personnel are associated with a Laboratory. Both of them can have addresses and registered contact. There is a class, Entity, which gathers the common data between the Personnel and the Laboratories. Also, there are several degrees of authorization that a User, registered personnel, can have. These authorizations will indicate what operations a User can or cannot perform .

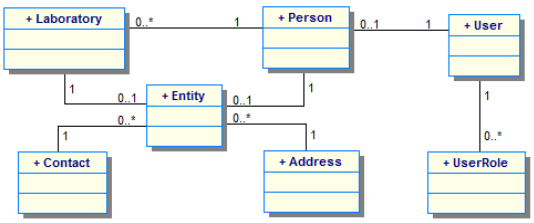

Fig. 1. Administration management class diagram

4.2. Model management

The model encodes the theoretical part of the application. It is composed by the Parameter class the Stages where this parameter can be evaluated, and the several possible results. Also it has the definitions of the readings that can be made – what Stages will be examined, and what parameters in these stages will be taken into consideration. Since the several parameters can be used in several stages, and the several stages can be used in several readings the association between them is a many-to-many relationship.

There is also the external types class, where it is be defined what types of externals interacting with the embryo that will be registered (i.e. incubator, CO2 Gas, etc.)

The Category is used to register different categories that an embryo may assume, these are status that can be used to register the step where the embryo is and/or its destiny.

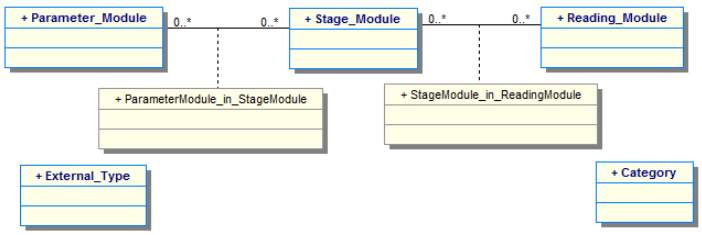

Fig. 2. Model management class diagram

4.3. Laboratory management

This is where the main data is registered. The Couple class has addresses and contacts therefore, likewise the Personnel and Laboratory, the Couple is also associated with the Entity class. These couples are of course registered in a certain laboratory. These couples have processes that have Embryos associated to them, there is also a class to classify and register the sperm that will be used. These processes have a collection of embryos associated to them, which in turn have a collection of stages. These stages also have a collection of resulting parameters.

These are the results that will be taken into consideration to calculate the evaluation of the Embryo. In order to relate the result of the evaluation with the pregnancy there is also a class that processes the data related to the transfer and the evolution of the pregnancy. A process can imply several transfers because there is the possibility of cryopreserved embryos to be transferred later; also a single transfer may imply more than one embryo in it.

The Sperm is in a different class as a possibility to be studied in future. In this section there is also place for an external class that will register the specific externals that exists and, may be used, in each laboratory.

There is also a class to register the several medication that can be used in the process, this will allow an easier way to fill the information and reduce the chance of the same medication be inserted with different nomenclature.

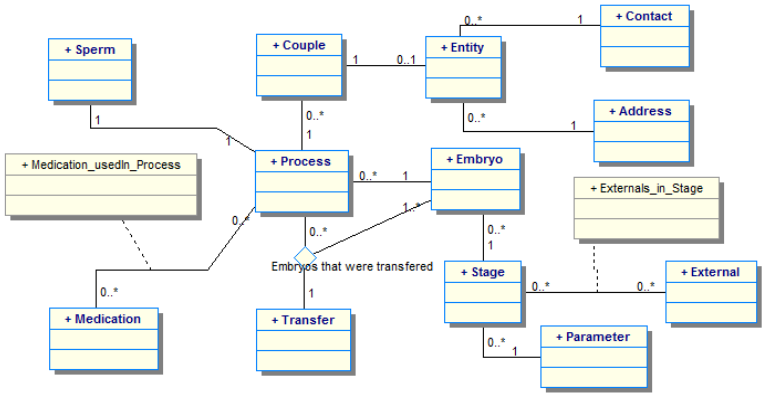

Fig. 3. Laboratory management class diagram

4.4. Evaluation

The evaluation should not be an embedded part of the solution, as one of the objectives is the option to create evaluation rules, and be able to share them easily with other installed versions. So the option was to create a template, for json files, that must be followed by all evaluation files. The files created this way can be deserialized by the application and be used to give the result of a certain reading, or set of readings, of an embryo, or group of embryos.

5. Implementation

The implementation of the application has followed the modulation that was defined on the analysis section. It was decided that, in its current release, it would be a local application, with the possibility of a central database. The main concern during the implementation was always the scalability of the application due to two main reasons: Firstly, as the field of study is very complex and with several sub-fields, each one of them with its own nuances and specifications, and maybe its own application if deemed appropriate. All these sub-fields are determinant for the final result, a successful pregnancy. Secondly, it is expected that individual components of the application may be reused on future works.

5.1. Database

The database has to respect the laws of standardization, and to be constructed in a way that will allow scalability for future implementations on aspects that are not being addressed at the present moment, for example, a more thorough study of the oocyte or the sperm, or recording more information about why a couple should use ART.

The database, of course, must be implemented respecting the rules of normalization trying to reduce the redundancy and dependency as much as possible, isolating the data so that the basic operation of creation, modification and removal of a field can be made on a single table and then, using defined relationships, propagated through the rest of the database.

5.2. Solution

This solution is implemented as an Object-Oriented approach following a basic 3 Tier architecture. Data Access Layer: that should be implemented following the CRUD methods directives (Create, Retrieve, Update, Delete) and that is responsible to communicate with the Database. Business Layer: the heart and soul of the solution, where most of the operations must take place, and where are defined relations between the different classes and how they interact. Presentation Layer: responsible for the communication with the users

These 3 layers must be implemented independently, this way any change or upgrade on a layer will have a minimum impact on any of the others layers, also it will allow that an entire layer can be reused on future developments of the project without need of re-implementing the architecture, or mixing implementations that may not be directly related; for example the implementation of several User Interfaces, or a need of change in the used database engine.

6. Conclusion

The selective embryo transfer is necessary in order to optimize efficacy and safety of the different techniques used in assisted reproductive technologies. The accurate embryo evaluation and the up-to-date laboratory workflow management are essential parts of a successful outcome for this task.

This work produced, so far, a tool that allows the administrator to determine what should be studied during the several observations of the embryo development and record these data. After that, these data are available to be analyzed; also it already returns the grade of the embryo(s) according to the ASEBIR criteria [20], even in the cases where the available information is incomplete (not all the necessary parameter measurements are collected). Additional evaluation criteria are also being studied and their interplay being modeled.

The distinguish factor that is being aimed is to develop a tool that is ready to keep up with the evolution and continuous change on a field of active research and constant innovation. Also independence from a particular criterion will allow the authorized users to choose and tune-up their favorite evaluation criteria.

The suggested evaluation model, based on a triangular norm , is plausible for the accurate assessment of the embryo quality. The implemented algorithm produces evaluation results heavily dependent on the somewhat subjective importance weights provided by the domain specialist. As a future work, based on the initial values, information collected from the different evaluation criteria, and, more important, real life results, we intend to apply machine learning techniques that based on the initial

values, information collected from the different evaluation criteria, and, more important, real life results, it can tune the current algorithm (or a reformulated one) correcting the parameters' importance and its answers' grading system.

Another possible improvement is to extend the embryo assessment process with the inclusion of the data related with the sperm used and the oocyte quality, whenever available. We believe that this information can help to increase the accuracy of the evaluation process.

From the functional side, laboratory management of the external elements can also be integrated on this tool, helping to control the stock of consumables and disposables.

It could also be interesting the implementation of several User interfaces for different levels of access, with different objectives of use of the application (web or mobile devices).

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