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Name, title and organisation of the scientific representative of the project’s coordinator:

Enrico Tronci
Sapienza University of Rome
Tel: +39 06 4991 8361
Fax: +39 06 8541 842
E-mail: tronci@di.uniroma1.it

Project website address: http://paeon.di.uniroma1.it
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4.2 Relevant Contact Details  

4.2.1 Project Coordinator  

4.2.2 Sapienza University of Rome (URM1)  

4.2.3 Lucerne University of Applied Sciences and Arts (HSLU)  

4.2.4 Hannover Medical School (MHH)  

4.2.5 University Hospital Zurich (UZH)  

4.2.6 Zuse Institute Berlin (ZIB)  

#### 5 List of Acronyms  

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Executive Summary

PAEON objective is to investigate methods and tools to support development of improved personalised Assisted Reproduction Techniques (ART). PAEON attains its goal by developing mathematical models (Virtual Physiological Human (VPH)) of the human menstrual cycle along with software tools enabling quantitative predictions about time-dependent hormone concentrations as well as follicle dynamics under normal conditions as well as during treatments.

PAEON benefits provided to clinicians, researchers, hospitals and educational institutions are delivered through the cloud based PAEON Platform offering the following software services. (1) Virtual Hospital (VH), providing: a secure repository for clinical data, VPH models (a pool of virtual patients) and treatment models (a pool of virtual doctors) defined using the same standard open language Modelica for which many open source and commercial simulators are available. (2) Treatment Decision Support System (TDSS), taking as input a treatment model and supporting treatment administration by suggesting timing and dosage for drugs on the basis of acquired patient clinical data. (3) Estradiol Estimation (E2E), allowing, during a treatment, estimation of estradiol levels from follicles sizes. E2E can be used to support decisions about drug dosages as well as for remote monitoring by acquiring TV-US via Internet. (4) VPH Model Simulation (VPH-MS), allowing users to run simulation of virtual patients in order to understand dynamics of hormones and follicles. (5) VPH Model Validation (VPH-MV), supporting validation of PAEON models by comparing their predictions with the clinical data gathered within PAEON clinical trials. (6) Clinical Training Service (CTS), a suite of serious games allowing users to practice with hormone dynamics and knowledge of treatments. (7) Model-Based Verification of Treatment Protocols (MBV-TP), taking a virtual patient and a virtual doctor and verifying in-silico (that is through simulation) that treatment goals are met. (8) Model-Based Design of Individualised Treatment Protocols (MBD-ITP), taking as input a class of virtual patients, (e.g., those with Antral Follicle Count in a given range), a treatment model and Key Performance Indicators (KPIs), and returning a Pareto-optimal personalised (for the patient class) treatment.

PAEON clinical trials have validated PAEON models through retrospective and prospective data from University Hospital Zurich (UZH), Hannover Medical School (MHH), University Hospital of Basel (UHB), University Hospital of Lausanne (UHL). PAEON clinical data include: 146 cycles from 90 healthy women, 53 cycles from 30 women with endocrine diseases, 2238 ART from 543 healthy women and 6360 ART from 2684 patients with endocrine diseases. TDSS validation with treatments in use at UZH has shown that TDSS suggestions agree with those from expert clinicians in more than 95%, as for timing, and in more than 80% as for dosing, with negligible discrepancies (37.5 IU), i.e., well below one single dose (usually at least 150 IU). E2E validation showed that after acquiring just 2 measurements personalised estradiol predictions from E2E have a relative percentage error typically below 15%.

Using our 89-core cluster, we validated MBV-TP and MBD-ITP services. As for MBV-TP, we were able to verify effectiveness of two real treatment protocols currently in use at UZH on a pool of 3815 virtual patients in just 30 min. As for MBD-ITP, we computed 48 Pareto-optimal variations of UZH real treatment protocols, which improve the reference treatment on at least one KPI. Such a computation evaluated the performance of 243 treatment variations on a pool of 3815 virtual patients in just 35 hours.
Chapter 1

Project Context and Objectives

In this section we outline the motivations behind the PAEON project (Section 1.1) along with PAEON objectives (Section 1.2)

1.1 Context

Infertility affects 12% to 15% of couples of reproductive age in Europe, and these figures are expected to double in a decade.

Investigation and treatment of infertility is directly and indirectly (by time consuming high frequency medical consultations, expensive medical techniques, limited success rates leading to repetitive treatment attempts, time-off from work, etc.) associated with high expenses for the individual as well as for society. Costs for individual couples in Europe are around 10% of annual household expenditures and overall, infertility in Europe costs approximately 1 billion Euros per year.

Most European countries already show birth rates strongly below the replacement rate for their populations. The global trend of declining fertility rates is most pronounced in industrialised countries, especially in Western Europe, where populations are projected to decline dramatically over the next 50 years, with major economical and social consequences, e.g., lacking of manpower and resulting massive migration.

In about 50% of the cases, infertility is caused by female health problems, more than 40% of which are related to endocrinological diseases. Human fertility is based on physiological events like adequate follicle maturation, ovulation, ovum fertilisation, corpus luteum formation as well as endometrial implantation. Hormones such as Luteinizing hormone (LH), Follicle-stimulating hormone (FSH), Estradiol (E2), Progesterone (P4), Testosterone (T), and Androstendione (A) are the key players controlling these fundamental events. Their secretion follows a strict balanced chronological regime enabling successful pregnancy.

Diseases such as endometriosis, Prolactin (PRL) associated disorders or Polycystic Ovary Syndrome (PCOS) seriously disturb menstrual cycle patterns, oocyte maturation and consequently fertility: pelvic endometriosis, occurring in up to 40% of infertile women, is a hormone dependent disease characterised by ectopic proliferation of endometrial cells, which occurs nearly exclusively during reproductive life. Though considered a benign disorder, it may not only cause infertility, but also debilitating pelvic pain and fatigue. While hyperprolactinemia is present in 20% of women with reproductive disorders, a prevalence of 6-10% makes PCOS the most frequent endocrine disorder in women of
reproductive age. In addition to infertility, PCOS is associated with hyperandrogen- as well as hyperinsulinemia with a strongly increased risk for cardiovascular disease.

Beside endocrine diseases, several environmental and lifestyle factors have a negative impact on fertility: up to 13% of female infertility may relate to smoking. Obesity, which increases in most European countries, is associated with menstrual dysfunction, decreased fertility, as well as increased risks of miscarriage. The prevalence of PRL-associated diseases and PCOS is directly, the prevalence of endometriosis is inversely, related to body mass index. Clinical observations as well as intervention studies show that different hormones influence sexual activity and vice versa, with a serious impact on human fertility.

Modern Assisted Reproduction Techniques (ART), i.e., In Vitro Fertilisation (IVF) or Intracytoplasmatic Sperm Injection (ICSI) have dramatically changed the chances for successful reproduction. Still, current success rates reach only 35% even in top leading centres. Many of the pathophysiological effects of endocrine diseases and environmental/lifestyle factors on fertility as well as dynamics in fertility treatment still remain unclear.

Scientists are in great need of a computerised model of the menstrual cycle under normal and the various pathological conditions, which will allow them to get further insight in fertility dynamics. A better understanding of the endocrinological concert orchestrating the physiology of fertility would open new opportunities for therapeutic options for improved natural fertility as well as success rates in ART. In fact, although the relevant components and feedback mechanisms have been identified from experiments and have been described qualitatively for many years, dynamic (time-dependent) mathematical models, i.e., models that permit medically sound quantitative predictions for the periodic changes in hormone levels and follicular function have just started to be developed.

1.2 Objectives

Within the framework of the Virtual Physiological Human (VPH) vision, PAEON project main objective is to develop mathematical models and software tools enabling quantitative predictions about the changes in hormone levels and follicular function under normal and pathological conditions. Such a better quantitative understanding of the endocrine physiology of fertility will open new opportunities for therapeutic options for improved natural fertility as well as improve success rates in Assisted Reproduction Techniques (ART).

The PAEON project pursues the above overall objective through three pillars focusing on Modelling, Computation, and Clinical Trials. PAEON pillar objectives are summarised below in Sections 1.2.1, 1.2.2 and 1.2.3.

1.2.1 Modelling Pillar Objectives

PAEON modelling pillar aims at developing quantitative models of the dynamic of the human menstrual cycle focusing on hormone concentrations and follicular development under healthy as well as pathological conditions. This is done by pursuing the following goals.

1. Develop a mathematical model (VPH model) of the human menstrual cycle able to simulate hormone concentrations and follicular development for healthy as well as
pathological conditions (e.g., endocrine disorders like Polycystic Ovary Syndrome (PCOS), endometriosis, etc.) and that can take into account external (e.g., drugs) as well as environmental factors (e.g., obesity, smoke, alcohol).

2. Develop effective algorithms for the computation of model parameters from clinical data. This provides individualised, patient-specific VPH models.

3. Identify inter-individual variations in model parameters and analyse their distributions. This, in turn, enables an a-priori partitioning of individuals into different groups (e.g., women with PCOS versus healthy women) to predict response to given drugs.

4. In order to evaluate in-silico (i.e., through simulation) treatments we need to model treatments in use at specialised centres. Accordingly, the same (open standard) language (to be identified within PAEON) must be used to define treatment and patient models.

1.2.2 Computation Pillar Objectives

PAEON Computation pillar has the goal of exploiting the quantitative models for patients and medical treatments developed in PAEON Modelling pillar (Section 1.2.1) to support in-silico verification and design of personalised treatments.

To this end, we regard the system composed by the treatment and the patient as a feedback-loop control system (see Figure 1.1), where the (physician following the) protocol acts as a feedback-loop controller for the patient by sensing patient clinical data (e.g., hormone concentrations) and by steering patient clinical parameters through administration of drugs (controllable external factors). This framework enables us to use powerful control engineering and computer science methods to analyse treatments by simulation (in-silico). Objectives of the Computational pillar are described below.

1. Develop a software tool, Model-Based Verification of Treatment Protocols (MBV-TP) that takes as input models for the treatment and the patient as well as treatment properties (e.g., hormone levels to be reached within a certain time) and checks if it is true that indeed the given treatment (model), notwithstanding uncontrollable external factors, satisfies the given properties when administered to the given patient (model).

2. Develop a software tool Model-Based Design of Individualised Treatment Protocols that takes as input a parametric model of a treatment protocol (designed by expert clinicians), patient-specific models for the class of target patients, Key Performance Indicators (KPIs) evaluating the treatment performance (e.g., probability of success on the patient class, amount of drugs used, etc). Model-Based Design of Individualised Treatment Protocols (MBD-ITP) returns Pareto optimal values for the treatment protocol parameters maximising the given KPIs.

3. Develop a cloud based application, the Virtual Hospital (VH), providing storage and secure data access policies for data and models. VH will consist of three main layers: Interface (towards users and other tools), Engine (containing PAEON services), and Repository (Knowledge Base) containing clinical data and models.
1.2.3 Clinical Trials Pillar Objectives

The overall goal of the clinical trial is to gather clinical data in order to validate the models developed during the project. This will be done by using retrospective as well as prospective data. A list of the objectives for PAEON Clinical Trials pillar is described below.

1. Collect data from available databases to permit validation and enlargement of currently available computerised models.

2. Gather high density (say one measurement per day) data from normally cycling women.

3. Gather data to control hormonal secretion patterns as predicted by PAEON models in different endocrine diseases (e.g., endometriosis, prolactin-associated disorders and PCOS).

4. Assemble data to estimate the effect of lifestyle and environmental factors such as obesity, cigarette smoke and sexual contacts on the expected hormonal secretion pattern according to PAEON models.

5. Collect data to understand the interactions between menstrual cycle dynamics and the follicle maturation process as a basis for successful reproduction.

6. Assemble data to understand the dynamics between hormonal and clinical parameters in treatment protocols for In Vitro Fertilisation (IVF) and Intracytoplasmatic Sperm Injection (ICSI) (suprastimulation protocols).

7. Accumulate data to explore the dynamics of follicle maturation in supra-stimulation on the background of endocrine diseases known to have a negative impact on oocyte quality.

8. Collect data to investigate the effect of lifestyle and environmental factors such as obesity, cigarette smoke on the results of suprastimulation protocols.
Chapter 2

Main Scientific and Technical Results

PAEON main goal is to develop methods and software tools to support development of improved personalised ART. This goal is attained by developing (VPH) mathematical models of the human menstrual cycle (virtual patients), under normal as well as pathological conditions, of treatment protocols (virtual doctor) along with software tools enabling quantitative predictions about time-dependent hormone concentrations as well as follicle dynamics under normal conditions as well as during treatments.

PAEON benefits to clinicians, researchers, hospitals and educational institutions are delivered through the cloud based PAEON Platform offering a set of software services enabling in-silico (i.e., through simulation) evaluation of effectiveness of treatment protocols. This vision is summarised in Figure 2.1.

In Section 2.1 we describe PAEON Platform whereas in Section 2.2 we describe PAEON main achievements towards the planned objectives.
2.1 PAEON Platform

In this section we briefly outline the main PAEON services towards hospitals, clinicians, researchers and educational institutions.

2.1.1 Virtual Hospital (VH)

The PAEON VH service (see Figure 2.2) provides access to all other PAEON computational services. It also provides data storage capabilities and data access policies, allowing users (e.g., hospitals and researchers) to collect: anonymised experimental results from clinical trials or from computations, Virtual Physiological Human (VPH) models (*virtual patients*) and treatment models (*virtual doctors*). Furthermore, to enable coupling of patient and treatment models, all VH models are defined using the same standard open language, *Modelica*, for which many open source as well as commercial simulators are available (e.g., see https://www.modelica.org/tools/index_html). This enables easy exchange of VPH and treatment models among researchers.

Availability of anonymised experimental data and the high security levels provided by VH data access policies enable hospitals and researchers to create an economy of scale, taking advantage of experimental data from different institutions, thereby fostering synergies among researchers.

![Figure 2.2: PAEON Virtual Hospital (VH).](image-url)
2.1.2 Treatment Decision Support System (TDSS)

TDSS (see Figure 2.3) is an interactive tool designed to support clinicians during administration of treatment protocols. TDSS, on the basis of the treatment model, the patient VPH model, patient clinical data (namely, external factors and patient clinical measurements), suggests to clinicians actions to be performed (e.g., timing and amount of drugs to be administered as well as the day of the next visit).

![Figure 2.3: PAEON Treatment Decision Support System (TDSS).](image)

2.1.3 Estradiol Estimation (E2E)

The E2E service (see Figure 2.4) estimates Estradiol (E2) blood concentration from number and size of growing follicles. E2E aims at reducing the number of blood samples required, during a fertility treatment to check E2 level. This would have several advantages: treatment costs are reduced (as less blood samples are needed), and logistics is improved as Transvaginal Ultrasound (TV-US) measurements can be taken by the patients themselves at home and transmitted via Internet to the doctor. This can be done with small measurement devices now available on the market (see for example Fertihome http://fertihome.com).

E2E takes as input: patient data (patient external factors) such as Antral Follicle Count (AFC), presence of infertility related endocrine diseases such as Polycystic Ovary Syndrome (PCOS), endometriosis, etc; drugs used during the treatment; the radius of the follicles (e.g., as measured via TV-US). E2E returns as output the E2 concentration in the blood. Effectiveness of our E2E service rests on the fact that, during the stimulation phase of a fertility treatment, most of the E2 present in the blood stems from follicle production.
Estradiol Estimation Service

<table>
<thead>
<tr>
<th>patient group</th>
<th>follicle measurements</th>
<th>drug used</th>
<th>estimation of E2 blood concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>POF LR FSH</td>
<td>h r d α,β</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCOS HR FSH/LH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>healthy MR FSH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Figure 2.4: PAEON Estradiol Estimation (E2E).

2.1.4 Clinical Training Service (CTS)

CTS (see Figure 2.5) is a suite of simulation-based serious games that, resting on the PAEON VPH models (virtual patients) and treatment models (virtual doctors), support e-learning and training for medical students and clinicians. A distinguishing features of CTS is the availability (thanks to CTS simulation engine and state storage) of an undo command. This enables users to easily explore many therapeutic choices without having to restart the simulation from the very beginning. Through CTS users can practice:

- Their knowledge of the physiology of the human menstrual cycle (in particular hormone blood concentrations and folliculogenesis), by simulating the time evolution of hormones and follicles in healthy patients, with and without drug administrations;
- Their knowledge of a specific treatment protocol, by simulating protocol administration on a virtual (i.e., simulated) patient.
2.1.5 **VPH Model Simulation (VPH-MS)**

VPH-MS (see Figure 2.6) is a generic simulation engine that allows interactive simulation of the Modelica VPH model given as input as well as analysis of the time evolution of the model biological species (e.g., blood concentrations of hormones). This tool is designed for:

- **VPH model designers**, who can simulate their new VPH models written in Modelica with or without drug administrations, and evaluate whether they behave as intended;

- **Treatment designers**, who can apply drug administrations to a trusted VPH model, and evaluate the VPH model behaviour under such administrations.

Much as with CTS (that indeed uses VPH-MS as simulation engine) at each step, users can undo the effects of their last actions (e.g., drug administrations) and try alternative options.

Figure 2.5: PAEON Clinical Training Service (CTS).
2.1.6 VPH Model Validation (VPH-MV)

VPH-MV is a service to assist research in the model validation activity.

VPH-MV takes as input: a set of clinical data about patients, a VPH model along with a set of values for its parameters which yield biologically meaningful model behaviours (Biologically Admissible (BA) parameters), an error function evaluating the mismatch between model predictions (and thus BA parameters) and patient data.

VPH-MV returns as output a statistics about the distribution of the error among model predictions (under all different BA parameters) and patients data.

Using such a statistics we can validate our model by checking that for each patient data there exists a close enough BA parameter.

Each BA parameter represents a virtual patient, representing a class of real patients having similar behaviour.
2.1.7 Model-Based Verification of Treatment Protocols (MBV-TP)

MBV-TP (see Figure 2.8) takes as input a VPH model (with its set of BA parameter values), a model for a clinical treatment protocol (formalising the physician decision strategy, which depends on patient measurements), and a set of treatment goals, formalised as Key Performance Indicators (KPIs). A KPI provides a measure of the effectiveness of a treatment protocol. This allows us to evaluate treatment protocols from different points of view, each of which is formalised as a KPI.

MBV-TP verifies the input treatment protocol by executing it against the given VPH model simulator under all input BA VPH model parameter values. For each such model parameter, values for all the KPIs are collected, and suitable statistics are computed.

Figure 2.8: PAEON Model-Based Verification of Treatment Protocols (MBV-TP).

2.1.8 Model-Based Design of Individualised Treatment Protocols (MBD-ITP)

MBD-ITP (see Figure 2.9) takes as input Modelica models for VPH (namely: time behaviour of hormones and follicles), a clinical treatment protocol, and a set of KPIs. MBD-ITP searches for variations of the input treatment in order to optimise the values of the given KPIs. Variations are defined in terms of changes in parameters in treatment model, which account for e.g., dosages and timing.

As a result, MBD-ITP computes the set of Pareto-optimal (with respect to the given KPIs) values for the treatment model parameters.

For example, if the treatment model parameters are drug amounts, the service would use the input VPH model to compute drug doses that optimise the treatment outcome (i.e., KPIs values).
2.2 Main Achievements

2.2.1 Clinical Data Collection

During the project lifetime we collected prospective clinical data (both on untreated and treated patients) as a result of PAEON activities by partner hospitals (University Hospital Zurich (UZH) and Hannover Medical School (MHH)). We also collected a substantial amount of retrospective clinical data from project partner UZH as well as a result of networking activity with University Hospital of Lausanne (UHL) and University Hospital of Basel (UHB).

Collected data is summarised in Table 2.1. All gathered data has been used to validate the PAEON models, namely Virtual Physiological Human (VPH) patient models and treatment models, as well as PAEON software services.
### Table 2.1: Summary of all clinical data collected within PAEON, both prospective (by PAEON hospitals UZH and MHH) and retrospective (by PAEON hospitals and by UHB and UHL through networking).

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>UZH</th>
<th>MHH</th>
<th>UZH</th>
<th>MHH</th>
<th>UZH</th>
<th>MHH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>W</td>
<td>C</td>
<td>W</td>
<td>C</td>
<td>W</td>
<td>C</td>
</tr>
<tr>
<td>Healthy</td>
<td>40</td>
<td>40</td>
<td>20</td>
<td>10</td>
<td>58</td>
<td>75</td>
</tr>
<tr>
<td>Healthy +/- sex. activ.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Obesity (BMI &gt; 30)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>POF</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Nicotine (&gt; 20 cigar./day)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>0</td>
<td>0</td>
<td>16</td>
<td>33</td>
<td>16</td>
<td>33</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>0</td>
<td>0</td>
<td>12</td>
<td>17</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>No Endocr. pathol., short prot.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No Endocr. pathol., long prot.</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>40</td>
<td>42</td>
<td>91</td>
<td>37</td>
<td>67</td>
</tr>
</tbody>
</table>

(a) Untreated women and cycles

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>UZH</th>
<th>UHB</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>W</td>
<td>C</td>
<td>W</td>
</tr>
<tr>
<td>Healthy</td>
<td>92</td>
<td>141</td>
<td>451</td>
</tr>
<tr>
<td>Healthy +/- sex. activ.</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Obesity (BMI &gt; 30)</td>
<td>11</td>
<td>14</td>
<td>473</td>
</tr>
<tr>
<td>POF</td>
<td>0</td>
<td>0</td>
<td>560</td>
</tr>
<tr>
<td>Nicotine (&gt; 20 cigar./day)</td>
<td>46</td>
<td>63</td>
<td>973</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>18</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>29</td>
<td>41</td>
<td>236</td>
</tr>
<tr>
<td>No Endocr. pathol., short prot.</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>No Endocr. pathol., long prot.</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>382</td>
<td>630</td>
<td>2845</td>
</tr>
</tbody>
</table>

(b) Treated women and cycles

Final Publishable Summary
Chapter 2. Main Scientific and Technical Results
2.2.2 **VPH Model Validation**

The goal of the PAEON VPH model validation activity is to verify that model predictions are in agreement with clinical data and medical knowledge. This has been done for both untreated women (natural menstrual cycle) as well as for women under fertility treatments.

In particular, as for untreated women, Figure 2.10 shows the time evolution of E2, FSH, LH, P4 and size of the single growing follicle in our model under nominal behaviour (dark curves). In our validation activity we computed the set of all BA parameters (i.e., model parameters yielding model evolutions which are consistent with clinical data and knowledge about the physiology of the natural menstrual cycle). Light curves in Figure 2.10 show the time evolution of E2, FSH, LH, P4 and size of the single growing follicle as predicted by our VPH model, under all such parameters.

We validated our VPH model (with the above defined virtual patient classes) also during fertility treatments. Figure 2.11 shows the time evolution of E2, FSH and size of the multiple growing follicles of our VPH model (under nominal behaviour, i.e., default virtual patient) during simulation, when different doses of a stimulation drug (namely: Merional) are administered (stimulated cycle). It can be observed that our VPH model shows an evolution which is consistent with medical knowledge and expectations, in that to higher drug doses correspond higher blood concentration of FSH and a higher number of growing follicles.
Figure 2.10: Behaviour of the final PAEON VPH model under default (dark curves) and all (light curves) BA parameters, when no drug is administered.
Figure 2.11: Predictions of the generic VPH model under treatment (under different doses of a stimulation drug).
2.2.3 Treatment Decision Support System (TDSS)

In this section we present results of validation of the TDSS software service. The engine of TDSS is a Modelica model that implements a given Executable Treatment Strategy (ETS).

Our validation procedure verifies that our treatment model reproduces doctor decisions during treatments. To do this, we run our Modelica models on retrospective treatment data collected at UZH and we compare doctor actions with those suggested by the model at each decision point.

We have modelled (using Modelica) three different treatment protocols currently in use at UZH, namely: long, short and antagonist protocols.

Results of TDSS validation for the long protocol are summarised in Figure 2.12. The charts report, for each decision point, and for each possible error value, how many times TDSS computes an action that made such an error with respect to the real treatment. Errors are expressed in dose quanta. An error of 1 dose quantum represents a mismatch between the amount of drug administered by the doctor and the dose suggested by TDSS of only 37.5 IU. As typical doses for such drugs are multiples of 150 IU, an error of 1 dose quantum has to be considered very small. As we can see, about half of TDSS decisions are identical to those made by the doctor. For most of the other decisions, the mismatch (error) is of at most 1 dose quantum.

As for timing errors, shown in Figure 2.12, we have even better results. TDSS decisions are almost always perfectly aligned with doctor decisions. When they differ, the mismatch is almost always below one day.

Results of validation for the short protocol are shown in Figure 2.13. They are along the same lines of the long protocol. There are a few cases showing larger errors (12 dose quanta=450 IU). These are caused by the fact that, while our treatment stopped as soon as it recognised that the success condition was achieved, the real doctor decided to wait one more day in order to retrieve a higher number of mature follicles. Also timing decisions are in agreement with the physicians most of the time.

Finally, Figure 2.14 summarises results of our validation activity on UZH antagonist protocol. Results are in line with those for the long and short protocols.

All in all, we consider our results very promising, in particular taking into account that clinician decisions may also consider factors (e.g., logistic needs) currently outside TDSS.
Figure 2.12: **Long protocol**: Error distribution of TDSS results with respect to clinical decisions in the five decision points and distribution of timing errors
Chapter 2. Main Scientific and Technical Results

Figure 2.13: **Short protocol**: Error distribution of TDSS results with respect to clinical decisions in the four decision points and distribution of timing errors.
Figure 2.14: **Anta protocol**: Error distribution of TDSS results with respect to clinical decisions in the five decision points and distribution of timing errors.
2.2.4 Estradiol Estimation (E2E)

In this section we evaluate the PAEON E2E service, which estimates E2 blood concentration from number and size of follicles.

The E2 estimation algorithm depends on parameters (α and β) whose value is computed from:

- The patient group. Patients are classified in groups on the basis of the value of some external factors, namely: health conditions (healthy, Polycystic Ovary Syndrome (PCOS), endometriosis, Premature Ovarian Failure (POF), idiopathic conditions) and value of Antral Follicle Count (AFC) (Low, Medium, Elevated and High Response: LR, MR, ER, HR).
- The drugs used in the treatment (FSH/LH or FSH only).
- The number and size of the growing follicles, along with the methodology used for their measurement (currently those used in UZH and UHB).

Estimation can also take advantage from any previous E2 measurements.

In the following we show the average relative error between E2E estimations and clinical data.

Figure 2.15 shows that, in most patient groups, even if just 2 E2 measurements of a patient are available, the E2E estimation average error for that patient is close to 0. In particular, from 3 measurements onwards, results stabilise to the same results that we obtain if we take into account all available E2 measurements (see Figure 2.16). For some groups like those consisting in patients suffering from PCOS and having high value of AFC (High Response, HR), standard deviation is higher. Figure 2.17 shows the average E2 estimation error when no measurements are available. In this case, the average relative error is course larger (often around 20%), but still useful in clinical practice, e.g., to prevent risk of overstimulation syndrome.
Figure 2.15: Avg errors, std dev, individualized parameters, considering 2, 3, and 4 meas.

Figure 2.16: Average errors, standard deviation, individualised parameters
2.2.5 Model-Based Verification of Treatment Protocols (MBV-TP)

In this section we evaluate our MBV-TP service on the models of the long and short treatment protocols in use at UZH.

For each BA VPH model parameter value, execution of each treatment protocol has one of the following outcomes:


As result, MBV-TP evaluates the robustness and adaptiveness of the input treatment model. In other words it evaluates to which extent the treatment supports personalised health-care by adapting its strategy to the patient.

Treatment verification took about 30 min for the long protocol and 20 min for the short protocol on our 89-core cluster.

Figure 2.20 shows the outcome of the MBV-TP on the long and short treatment protocols in use at UZH, over the 16800 BA parameters (virtual patients) of the final PAEON VPH model. From Figure 2.20, it follows that the long treatment protocol succeeds on 73.7% of the 3815 BA parameters (virtual patients) for which it is applicable, while the short treatment protocol succeeds on 72.6% of the 2230 of the applicable BA parameters.

We stress again that such percentages are not to be intended as estimations of the probability that the treatment would succeed on a random real patient, as each BA parameter in our pool represents an entire class of real patients.

For each treatment in Figure 2.20 and for each treatment outcome, Figures 2.21, 2.22, 2.23 and 2.24 show the evolution of E2, P4 and the follicle profile, as computed by the VPH model simulator run on a witness BA parameter value for which the treatment has that
Figure 2.18: Long protocol

Figure 2.19: Short protocol

Figure 2.20: Treatment verification via MBV-TP: statistics of the different treatment outcomes over the set of BA VPH model parameter values (virtual patients).

outcome, as well as the sequence of stimulation drug dose administrations as computed by the treatment (treatment decisions).

Each column of Figures 2.21, 2.22, 2.23 and 2.24 refers to one of the treatment outcomes (minimum success, full success and failure), and shows the VPH model prediction (under the administered treatment) for a sample BA model parameter (virtual patient) for which the treatment has that outcome. In particular, each column shows (from top to bottom):

- The evolution of E2 and P4 during downregulation/preparation and stimulation (respectively, on the left and on the right of the dashed red vertical line).

- The follicle profile evolution as a sequence of histograms (with time flowing from top to bottom). Each histogram shows the percentage of available follicles of each diameter class (from left to right: \(<10\) mm, 11–12 mm, 13–14 mm, 15–16 mm, 17–18 mm, 19–20 mm, \(>20\) mm).

- The sequence of FSH/LH (stimulation drug) administrations during the stimulation phase (with time flowing from left to right).

As an example, Figure 2.21 shows the VPH model evolution under a sample BA model parameter (virtual patient) for which the treatment outcome is ‘full success’. It can be
observed that the E2 and P4 levels are always below their safety thresholds, and that the follicles gradually grow during stimulation (letting the treatment succeed).

To see an example where the treatment fails, consider Figure 2.22, showing the VPH model evolution under a sample BA model parameter (virtual patient) for which, at the end of treatment, not enough follicles have grown to maturity. It can be seen that follicles do not grow satisfactorily, and that the treatment correctly reacts to such a slow follicle growth by increasing the daily dose of the stimulation drug, as safety thresholds for E2 and P4 are far from being reached. Notwithstanding treatment adaptations, the treatment fails.
### Time evolution

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<td>E2</td>
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<tr>
<td>P4</td>
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</table>

#### Follicle profile during stimulation

![Graph Follicle profile]

#### FSH/LH administered during stimulation

![Graph FSH/LH]

Figure 2.21: Verification of UZH long protocol: sample VPH model evolutions computed by MBV-TP, showing treatment success.
Figure 2.22: Verification of UZH long protocol: sample VPH model evolutions computed by MBV-TP, showing treatment failure.
### Time evolution

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<td><strong>P4</strong></td>
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#### Follicle profile during stimulation

![Graph](image5)

#### FSH/LH administered during stimulation

![Graph](image6)

Figure 2.23: Verification of UZH short protocol: sample VPH model evolutions computed by MBV-TP, showing treatment success.
### Time evolution vs. Failure

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<td>E2</td>
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<tr>
<td>P4</td>
<td>![P4 Chart]</td>
</tr>
<tr>
<td>Follicle profile during stimulation</td>
<td>![Follicle Profile Chart]</td>
</tr>
<tr>
<td>FSH/LH administered during stimulation</td>
<td>![FSH/LH Chart]</td>
</tr>
</tbody>
</table>

*Figure 2.24: Verification of UZH short protocol: sample VPH model evolutions computed by MBV-TP, showing treatment failure.*
2.2.6 Model-Based Design of Individualised Treatment Protocols (MBD-ITP)

In this section we evaluate our MBD-ITP service, by searching among variations of the long and short fertility treatment protocols currently in use at UZH (our reference treatments).

In particular, the treatments considered by MBD-ITP will have the same structure of the reference treatments, and will differ only in the value of some parameters. Searching among variations of a well established treatment guarantees that the treatments computed by MBD-ITP will have a familiar structure for the clinician, and will ease in vivo clinical trials.

Figure 2.25 shows the outcome of the execution of our MBD-ITP service on the long and short protocols. For each protocol, we evaluated 243 instantiations of the parametric treatment, out of which 48 (respectively, 58) proved to be Pareto-Optimal as for the long (respectively, short) protocol.

For each treatment protocol (long or short), Figure 2.25 shows each Pareto-Optimal treatment found by MBD-ITP as a line connecting the values of all Key Performance Indicators (KPIs) achieved by that treatment.

From the figure, it can be seen that the reference treatments (see the dark blue lines) balance quite well their performance over all KPIs. Anyway, there exist several other candidate treatments who dominate the reference treatments for what concerns at least one KPI.
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(a) Long protocol

(b) Short protocol

Figure 2.25: Pareto-optimal treatments computed by MBD-ITP.
Chapter 3

Potential Impact, Main Dissemination Activities and Exploitation of Results

Below we describe the potential impact (Section 3.1), dissemination activities (Section 3.2) and exploitation plan (Section 3.3) of the PAEON project.

3.1 Potential Impact

In this section we outline the potential impact of the methods and software tools developed within PAEON. We focus on impact towards: hospitals and health system in general, Information and communications technology (ICT) companies providing e-health software and services, educational institutions, clinicians, researchers, the whole society.

3.1.1 Impact Towards VPH Research Activities

PAEON Virtual Hospital (VH) allows sharing of clinical data and models among clinical researchers. Furthermore, models are defined using an open standard modelling language, namely Modelica (http://www.modelica.org), which is powerful enough to define physiology models as well as treatment models. This provides a solid foundation to develop models of other parts of the human physiology, using those developed in PAEON as components, thereby actively contributing to the Virtual Physiological Human (VPH) vision.

Finally, using VH clinical data together with the VPH Model Simulation (VPH-MS) and VPH Model Validation (VPH-MV) allows users to validate their models with respect to PAEON clinical data, thereby providing an effective bridge between in-vivo and in-silico experiments. This, in turn, fosters development of novel, more and more reliable, physiology models.

3.1.2 Impact Towards Clinical Research

PAEON services support clinical researchers during treatment design by providing tools for in-silico verification (Model-Based Verification of Treatment Protocols (MBV-TP)) and design (Model-Based Design of Individualised Treatment Protocols (MBD-ITP)) of individualised treatments. While, of course, in-silico experiments cannot replace in-vivo ones, they provide a very useful pre-screening that will become more and more reliable as evidence of patient model validity accumulates, for example in the VH clinical data.
3.1.3 Impact Towards Educational Institutions

PAEON services will increase quality of medical education and will possibly decrease its cost. This is attained through PAEON Clinical Training Service (CTS) service that, along the lines of tools like JustPhysiology (http://justphysiology.com/pages/learn), enables students to practice with endocrine physiology (not covered by any tool so far) and related drugs.

3.1.4 Impact Towards Hospitals

PAEON Treatment Decision Support System (TDSS) allows clinicians within a team (possibly in different hospitals) to share treatments and monitor their administration. This improves treatment quality and consistency, since treatment strategies are formalised in a (Modelica) model and can be revised and improved over time.

Furthermore, using Estradiol Estimation (E2E), clinicians may reduce the number of Estradiol (E2) measurements thereby enabling usage of remote Transvaginal Ultrasound (TV-US) devices (like the one from FertiHome http://fertihome.com) and also quantitatively compare patient response to drugs with that of other patients with similar external factors. This, in turn, improves Assisted Reproduction Techniques (ART) quality and decreases the probability of having to go through more than one treatment.

3.1.5 Impact Towards the Health System in General

PAEON helps increasing health care quality while decreasing its costs. In fact, by using services like TDSS small hospitals can easily adopt the treatment protocol used in large specialised centres. As a result, TDSS creates new business opportunities for large and small hospitals, while at the same time decreasing health care costs. This of course provides a benefit for the hospitals and, eventually, for the patients and the whole health care system.

3.1.6 Impact Towards ICT Companies

Exploitation of PAEON services will create many new high-tech jobs and, possibly, enterprises that, in turn, will foster the development of new e-health services.

In fact, PAEON Platform consists of cloud based services for hospitals and educational institutions (namely, TDSS, CTS and E2E) as well as for clinical researchers (namely, VPH-MS, VPH-MV, MBV-TP, MBD-ITP). Developing such services requires a highly skilled multidisciplinary team. Accordingly, we anticipate a positive effect of PAEON technology on employment opportunities.

3.1.7 Impact Towards the Whole Society

PAEON benefits for the whole society can be summarised as follows.

First, health care quality will improve while its cost will decrease. In fact, increasing the chances that a treatment will be successful at the first attempt automatically decreases expected health care costs since this reduces the expected number of treatments a patient must undergo.

Second, thanks to services like E2E, logistics for patients may also improve, since remote E2 monitoring and estimation will be possible from home.
Third, employment opportunities will be created by the exploitation of PAEON services.

### 3.1.8 Attainability of the Potential Impact

Of course, as always for technology, the realisation of the potential impact of PAEON rests on the actual uptake of the developed technology.

Our discussions with stakeholders like hospitals and ICT companies providing e-health software clearly show that one of the main driving forces in the health care system focuses on increasing quality while at the same time decreasing costs.

Indeed PAEON technology addresses both such issues. This has triggered interest in PAEON activities even before the project was over. Thanks to such interest we were able to get retrospective data for about 8000 patients from University Hospital of Basel (UHB) and 40 healthy women from University Hospital of Lausanne (UHL), as well as support from ICT companies for a first investigation of integration strategies of PAEON technology within HL7/FHIR compliant Hospital Management System (HMS).

We think that such interest from hospitals and ICT companies (two important stakeholders for us) in PAEON outcomes, as well as, more in general, very positive market forecasting for cloud based e-clinical solutions and Clinical Decision Support System (CDSS), witnesses market readiness for PAEON technology and fosters its uptake.

### 3.2 Main Dissemination Activities

During the project lifetime (February 2013 – January 2016), PAEON project carried out various dissemination activities aimed at promoting its research to the widest and varied audience possible. The Dissemination Plan was released at Month 6 and provided guidelines for dissemination activities by project partners, by presenting information on the dissemination strategy of the project, the aim of the dissemination actions, the communication and dissemination tools to be used, and the activities and mechanisms for information exchange with various stakeholders.

Key dissemination tools and activities conducted by the project are described below.

#### 3.2.1 Project Website

The public website (http://paeon.di.uniroma1.it) was made available in December 2013 (month 11 of the project) and it has been used as an important dissemination channel, describing project activities and outcomes, such as latest news, articles, presentations, internal and external documents. The website will be maintained at least 5 years after the project ends.

The statistics as of January 2016 are as shown in Table 3.1.
Chapter 3. Potential Impact, Main Dissemination Activities and Exploitation of Results

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<td>Visits from Asia</td>
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</tr>
</tbody>
</table>

Table 3.1: Some statistics about the PAEON website.

3.2.2 Logo, Power Point and LATEX Templates

A logo was created to establish an identity for the project. Templates for Power Point and LATEX presentations and deliverables were designed to ensure a visual identity to PAEON material.

3.2.3 Artefacts

Dissemination artefacts produced by the project (and available in the public website) include: 5 posters, the set of PAEON Computational Services, 2 sets of project presentation slides.

3.2.4 Social Media

Twitter and Facebook accounts were activated in January 2014 (Month 12 of the project). LinkedIn account and group were activated in July 2015 (Month 30 of the project). All social media accounts of the project are accessible from the project website.

The statistics as of January 2016 are: 120 followers on Twitter, 103 likes on Facebook, 17 connections on LinkedIn.

3.2.5 Newsletter

A total of 8 Newsletters were published during the project period, highlighting project activities, outputs and upcoming events. The newsletters have been sent to all who subscribed for the newsletter on the website. At the end of the project there were 29 subscribers.

3.2.6 Publications

This section shows the publications produced by PAEON consortium.

3.2.6.1 Scientific Publications

The project produced a total of 14 scientific peer reviewed publications. Furthermore, 6 papers were submitted to peer reviewed journals and 1 paper is currently in preparation.
The list of scientific (peer reviewed) publications is shown in Template A1 of “Use and dissemination of foreground” part of the final report.

3.2.6.2 Online Appearance

PAEON has appeared online on: MATHEON ECMath web portal.

3.2.6.3 Master Theses

On January 2016, one PAEON related Master Thesis in Computer Science has been defended at the Computer Science Department of Sapienza University of Rome. Other two PAEON related Master Theses in Medicine have been supervised at the Clinic for Reproductive Endocrinology of University Hospital Zurich (UZH).

3.2.7 Participation in Events

During the project lifetime, members of the PAEON consortium participated in 19 international and national events: conferences, workshops, fairs, annual meetings, congresses, schools (17 of these events took place in Europe, 1 in Asia and 1 in America). These events have been an opportunity to disseminate the project results as well as to undertake networking and cooperation activities with other projects, to identify and use synergies between research projects, and to figure out the requirements and relevant topics for future research and collaborations. Successful partnerships have been established with the FP7 project VPH-Share (http://www.vph-share.eu) and the company Care-On srl (http://www.careon.it/index-e.html).

The list of dissemination activities is shown in Template A2 of “Use and dissemination of foreground” part of the final report.

3.3 Exploitation of Results

We describe PAEON services to be exploited in the short and medium term (Section 3.3.1), the envisaged users for such services (Section 3.3.2), and, finally, summarise our exploitation plan (Section 3.3.3).

3.3.1 PAEON Computational Services

PAEON computational services suitable for exploitation in a stand-alone way as well as in a synergistic way are those described in Section 2.1: Treatment Decision Support System (TDSS), Estradiol Estimation (E2E), Clinical Training Service (CTS), VPH Model Simulation (VPH-MS), VPH Model Validation (VPH-MV), Model-Based Verification of Treatment Protocols (MBV-TP), Model-Based Design of Individualised Treatment Protocols (MBD-ITP).

3.3.2 Envisaged Users

In this section we describe the envisaged users for the computational services developed within PAEON and summarised in Section 3.3.1. PAEON users can be classified into two main categories: PAEON Customers and PAEON Knowledge Providers.
3.3.2.1 PAEON Customers

PAEON Customers are hospitals and educational institutions: they buy the PAEON computational services devoted to them, and exploit them in clinical practice as well as in educational and training activities.

3.3.2.1.1 Hospitals

In our context, PAEON customer *hospitals* basically denotes any health care institution providing Assisted Reproduction Techniques (ARTs).

Customer hospitals can benefit from the following PAEON computational services: Treatment Decision Support System (TDSS), Estradiol Estimation (E2E), Clinical Training Service (CTS). Figure 3.2 gives an overall view of the services devoted PAEON customer hospitals.

We plan to target European hospitals of any size active in the ART business. From our analysis we know that there are 971 ART hospitals in Europe, performing, in total, around 374,986 cycles/year.

We describe hospital exploitation plan for TDSS, E2E and CTS.

PAEON customer hospitals can use TDSS to monitor the execution of ART treatment protocols, as designed by experts and already verified (both *in silico* and *in vivo*). By using TDSS, clinicians in the hospitals can be sure that the agreed upon treatment protocol is...
Figure 3.2: Overall view of the PAEON computational services devoted to customer hospitals.

applied consistently among different teams. In fact, TDSS will suggest measurements to be taken and actions to be performed in agreement with the selected treatment protocol.

Usage of TDSS within clinical practice in a customer hospital also enables a fast training of new (non-expert) clinicians, as they can quickly start administering treatments via TDSS on their own, under strict remote monitoring by expert colleagues, who can also give recommendations.

TDSS also enables networking activities and commercial agreements among hospitals. For example, large hospitals with outstanding and cutting-edge medical knowledge can make their expertise available to smaller hospitals via TDSS, under suitable alliance and commercial agreements. This would make small hospitals able to increase quality of their service (and, as a consequence, the number of their patients) by having access to the latest clinical protocols and to remote consultancy by experts, while large hospitals providing knowledge could have additional income stemming from, e.g., payback of royalties for the usage of such treatments. To this end, large hospitals also play the role of Knowledge Providers within the PAEON platform (see Figure 3.1).

PAEON customer hospitals can also provide an in vivo clinical trial for new, experimental, treatments, as designed by experts in their commercial network, and already verified and optimised in silico via the other PAEON computational services. This would allow such hospitals to contribute to the development of new clinical practices and to have timely access to cutting-edge medical knowledge.

We envision a business model where customer hospitals pay a fee for using TDSS within their clinical practice. Such a fee will be proportional to the number of treated patients. In case a customer hospital decides to grant the PAEON service provider usage of anonymised clinical data collected through TDSS (such data will be precious to improve the quality of other PAEON services) the usage of TDSS will be granted at highly discounted rates (of even for free).

Customer hospitals can use E2E to estimate the Estradiol (E2) value from knowledge of the radius of the follicles (follicle profile). Since the latter is easily acquired during the patient visit using Transvaginal Ultrasound (TV-US), this saves on the cost of blood
samples to analyse, hence would contribute to lower the overall cost of a treatment cycle, making customer hospitals more competitive.

E2E is also a nice match to the technology developed by Fertihome http://fertihome.com which enables patients to take TV-US by themselves at home and transmit the results (via Internet) to the doctor. In such a context, E2E would also allow to estimate remotely patients blood E2 concentration.

We envision a business model where customer hospitals pay an annual fee for using E2E within their clinical practice. Much as for TDSS, in case a customer hospital decides to grant the PAEON service provider usage of anonymised clinical data, the usage of E2E will be granted at highly discounted rates (of even for free).

Customer hospitals can use CTS to train junior physicians and/or new colleagues in administering the reference treatment in silico, i.e., on virtual patients. This would speed-up their (now very long) training time as training via CTS would take much less time, in that no real patient is involved.

After being trained through CTS, trainees could move into the real clinical practice and still be assisted, by senior expert colleagues possibly via TDSS.

We envision a business model where customer hospitals pay an annual fee for using CTS within their training practice. Much as for TDSS and E2E, in case a customer hospital decides to grant the PAEON service provider usage of anonymised clinical data, the usage of CTS will be granted at highly discounted rates (of even for free).

### 3.3.2.1.2 Educational Institutions

In our context, educational institutions are public and private institutions who are interested in accessing the CTS services within the VH for educational purposes. Educational institutions can use the PAEON Clinical Training Service (CTS). Figure 3.3 gives an overall view of the services devoted to PAEON customer educational institutions.

We plan to target Medical and Biological Sciences faculties in Europe as well as in other countries. In Europe there exist at least 569 medical schools and at least 296
Biological Sciences faculties. Biomedical engineering schools are also interesting potential PAEON customers.

Educational institutions can use PAEON CTS to support the learning process of their students. In fact, CTS will be for student a *virtual* tutor allowing them to exercise their knowledge of human physiology as well their knowledge of specific treatment protocols. In fact, CTS allows student to simulate Virtual Physiological Human (VPH) models, to learn the effects of different clinical actions (e.g., drug administrations), and to verify their understanding of a given treatment protocol. In this way, CTS supports the learning process by providing students with an *in silico* laboratory to carry out their experiments.

Bearing in mind that, in such a context, CTS enables educational institution to increase course quality and decrease their costs (by reducing the human effort for tutoring) we envisage that educational institutions will pay a small fee to get unlimited access to CTS for an entire year.

### 3.3.2.2 PAEON Knowledge Providers

PAEON Knowledge Providers are research institutions, VPH model designers and treatment designers: they can use the PAEON computational services devoted to them for free, in order to create and validate new VPH models and new treatments, which will then be included within the PAEON platform (with suitable mechanisms to protect their Intellectual Property (IP)), hence creating added value to the other PAEON services.

#### 3.3.2.2.1 Treatment Designers

In our context, treatment designers are researchers or expert clinicians, for example working in large cutting-edge ART hospitals, who design new treatments, possibly by modifying those used in current practice. Treatment designers will be mainly interested in using the following PAEON computational services: VPH-MS, MBV-TP, MBD-ITP. Figure 3.4 gives an overall view of the services devoted to PAEON treatment designers.

We plan to target all European hospitals active in the ART business and in particular large hospitals (those performing at least 500 cycles/year) which are more likely to perform...
in-house design and experimentation of cutting-edge clinical protocols and to continuously improve the state-of-the-art.

From the available data on existing ART centres across Europe it follows that in Europe there exist at (the very) least 228 large ART hospitals. Experts can gain confidence with VPH models available in PAEON VH using VPH-MS, provide new treatments to VH and, by using MBV-TP, verify them in silico, using clinical data stored within VH. Furthermore, experts can optimise their treatment by using MBD-ITP.

In case the new treatment passes the in silico verification procedure based on such PAEON services, the expert can choose to upload it into VH (protecting IP) and making it available to hospitals of his choice (e.g., small hospitals with which the institution of the treatment author has started commercial agreements). In this case, the new treatment will be offered to such PAEON customer hospitals within TDSS as an experimental treatment. In this way, PAEON computational services provide the treatment designer with the possibility of carrying out large-scale in vivo clinical trials via other PAEON customer hospitals (e.g., those with which a research and/or a commercial agreement has been signed), in an effective and closely monitored way (via TDSS).

We envision a business model where PAEON customer hospitals can use the computational services devoted to treatment design for free, in order to support the definition of new treatments and carry out their in silico verification.

Upon successful completion of the in vivo clinical trials, the treatment will enter the library of VH treatments accessible to PAEON hospitals chosen by the treatment author.

3.3.2.2.2 Research Institutions and VPH Model Designers In our context, VPH model designers are researchers who design new VPH models, possibly by modifying those used in current practice. Research institutions and VPH model designers will be mainly interested in using the following PAEON computational services: VPH-MS VPH-MV. Figure 3.5 gives an overall view of the services devoted to research institutions and VPH model designers.
We plan to target expert researchers (e.g., in systems biology) working on mathematical models of the human menstrual cycle, both in physiological and pathological cases. Researchers provide new VPH models to VH and, by using the VPH simulation services can analyse and validate them. Validation is performed using anonymised clinical data stored within VH (whose usage was explicitly granted by their providers, e.g., PAEON hospitals). Upon successful completion of model validation (in silico through VPH-MS and in vivo –via retrospective clinical data– through VPH-MV) and approval by the scientific community (e.g., after peer-review), the new model will enter the VH library of VPH models. From this point on, the model will be available to treatment designers.

We envision a business model where model designers use the the above computational services for free for research purposes and earn royalties from the actual usage of their models (namely, through TDSS in clinical practice and through CTS in an educational context).

### 3.3.3 Conclusions

Table 3.2 shows, for each PAEON computational service, the list of users that are likely to be interested in it. Namely, for each user (Hospitals, Treatment Designers, Model Designers, Education Institutions) we show “•” if the service in that row is of interest for the user on the column.

<table>
<thead>
<tr>
<th>PAEON Computational service</th>
<th>H</th>
<th>T</th>
<th>M</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Decision Support System (Section 2.1.2)</td>
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<tr>
<td>Estradiol Estimation (Section 2.1.3)</td>
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<td>CTS (Section 2.1.4)</td>
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<td>VPH Model Simulation (Section 2.1.5)</td>
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<td>VPH Model Validation (Section 2.1.6)</td>
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<tr>
<td>Model-Based Verification of Treatment Protocols (Section 2.1.7)</td>
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<tr>
<td>Model-Based Design of Individualised Treatment Protocols (Section 2.1.8)</td>
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<tr>
<td>Virtual Hospital (Section 2.1.1)</td>
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</tr>
</tbody>
</table>

Table 3.2: Correspondence between PAEON computation services and envisaged customers: Hospitals (H), Treatment Designers (T), Model Designers (M), Education Institutions (E).
Chapter 4

Public Website and Relevant Contact Details

This section contains the address of the project website and relevant contact details.

4.1 Address of the PAEON Project Website

PAEON Project Website is accessible at http://paeon.di.uniroma1.it.

4.2 Relevant Contact Details

The sections below show contact details of the project coordinator as well as of each PAEON partner.

4.2.1 Project Coordinator

Enrico Tronci
Sapienza University of Rome
Computer Science Department
Via Salaria 113, 00198 Rome, Italy
Email: tronci@di.uniroma1.it
URL: http://mclab.di.uniroma1.it
Phone: +39 0649918361
Fax: +39 068541842

4.2.2 Sapienza University of Rome (URM1)

Sapienza University of Rome, one of the largest universities in Europe, has a long standing experience in participation and coordination of European Projects. Its Computer Science Department has about 40 faculties, 15 Ph.D. Students and 5 Post-Docs covering most of subjects in mainstream computer science. The project has been carried out by the Model Checking Research Lab of the department. The lab, led by Prof. Enrico Tronci, focusses on model-checking-based algorithms and tools for the automatic verification and synthesis of mission- or safety-critical systems.
Role in the project: URM1 is the project coordinator. URM1 activities will focus on formal modeling of treatment protocols, formal verification of treatment protocols by model checking driven simulations and model checking based synthesis of individualised treatment protocols.

Contact Person: Enrico Tronci, Email: tronci@di.uniroma1.it

4.2.3 Lucerne University of Applied Sciences and Arts (HSLU)

Lucerne University of Applied Sciences and Arts, is one of seven publicly funded Universities of Applied Sciences in Switzerland that were founded on January 1, 1997. Despite its recent foundation, the Hochschule Luzern can look back on a long history, as it resulted from the merger and further development of several former advanced technical schools. The five schools of Lucerne University of Applied Sciences and Arts are: The School of Engineering and Architecture, The School of Business, The School of Social Work, The School of Art and Design, The School of Music. The Lucerne University of Applied Sciences and Arts is a powerful driver of business and cultural life in Central Switzerland. Innovative curricula and a state-of-the-art infrastructure are geared to the needs of our students and their future employers. Research and close co-operation with industry, business, and cultural institutions at a local, national and international level, are part of our success. The Center of Competence in Aerospace Biomedical Science and Technology (a.k.a. Space Biology Group) is a scientific unit within the Department of Architecture and Technology at the School of Engineering and Architecture of HSLU and was founded in 1977 at the Swiss Federal Institute of Technology (ETH) in Zurich. It moved to HSLU at the end of 2012. The center is engaged in biomedical research projects as well as in the realisation of cell biological experiments in space, in particular under the unique environmental condition of low gravity and in the design of the supporting infrastructure. Ground studies of the Center of Competence in Aerospace Biomedical Science and Technology are focused on physiological aspects of fertility mechanisms and their pathologies as well as of microgravity induced deficiencies and pathological conditions. Furthermore, the Center of Competence in Aerospace Biomedical Science and Technology maintains the User Operations and Support Center (USOC) for the International Space Station (ISS). The members of the Center of Competence in Aerospace Biomedical Science and Technology are generally involved in activities on all the different scientific topics of the group.

Role in the project: The role of the Center of Competence in Aerospace Biomedical Science and Technology at HSLU is to contribute to the model definition by providing a parameterised basic model with the underlying experimental and clinical data. Additionally the Center of Competence in Aerospace Biomedical Science and Technology is going to support Model Validation aspects that require experimental input. Furthermore the group provides the underlying framework and infrastructure that is required to integrate the simulation and validation applications into a user-friendly dynamical Virtual Hospital (VH) compatible application with an ergonomical graphical user interface. Additionally HSLU is going to be involved in the design of the clinical trial as well as conducting certain aspects of the trial together with the clinical partners of PAEON.

Contact Person: Marcel Egli, Email: marcel.egli@hslu.ch
4.2.4 Hannover Medical School (MHH)

Hannover Medical School, founded in 1965, is one of the world’s leading university medical centres. Due to its interdisciplinary research MHH has strong collaborative links with many academic and industrial research organisations worldwide. The activities of this project will be carried out by the Division of Clinical Psychology and Sexual Medicine, part of the Clinics of Psychiatry, Social Psychiatry and Psychotherapy at MHH.

Role in the project: MHH will plan and conduct clinical trials and data collections. MHH will focus mainly on endocrinological experiments such as serial blood samplings in healthy females to assess endocrine alterations. This will contribute to the development of the physiological model.

Contact Person: Tillmann Krüger, Email: Krueger.Tillmann@mh-hannover.de

4.2.5 University Hospital Zurich (UZH)

University Hospital Zurich is one of the largest and most important teaching hospitals in Europe. With its 40 divisions and institutes, the hospital is renowned for its achievements in health care, research and teaching, as well as for compassionate care. It offers state-of-the-art treatment for a broad range of illnesses, provided by a dedicated team of leading consultants of the highest international standing. The Division of Reproductive Endocrinology is one of the leading clinical and research centres for gynaecological and reproductive endocrinology in Europe and is considered to be a pioneering centre in Switzerland. Novel approaches such as microinsemination, pre-implantation diagnostics, and ovarian tissue cryopreservation have been initiated with success. The Centre for Reproductive Medicine has been certified for its high quality. The pregnancy rates are high compared with those from other Swiss centers. The Division of Reproductive Endocrinology focuses on the diagnosis of and therapy for involuntary childlessness and the treatment of menopausal symptoms, hormonal disorders, and contraception. The division performs more than 10,000 consultations each year.

Role in the project: The role of UZH Division of Reproductive Endocrinology is to contribute large amounts clinical data to allow for the modelling of pathological conditions as well as the creation of a knowledge base, supporting validation processes. The main contribution to the project consists in designing and conducting clinical trials to support the validation of the implemented model as well as to utilise the PAEON VH application as a supportive tool for clinical diagnostics and treatment design.

Contact Person: Brigitte Leeners, Email: brigitte.leeners@usz.ch

4.2.6 Zuse Institute Berlin (ZIB)

Zuse Institute Berlin is a research institute for applied mathematics and computer science. It was founded by law as a statutory establishment and as a non-university research institute of the State of Berlin in 1984. In close interdisciplinary cooperation with the Berlin universities and scientific institutions Zuse Institute implements research and development
in the field of information technology with a particular focus on application-oriented algorithmic mathematics and practical computer science. ZIB also provides high-performance computer capacity as an accompanying service. ZIB finances its scientific work mainly out of three sources: the basic financial stock of the Federal State of Berlin, the raised third-party funds of public sponsors as well as funds of industrial cooperations (about 75% third-party funds).

**Role in the project:** ZIB provides expertise in the construction of efficient and reliable algorithms for simulation, parameter identification and optimization (including optimal control) in the human menstrual cycle model. ZIB does research and development work in the field of algorithm oriented numerical mathematics focusing on nonlinear models, in particular differential equation models.

**Contact Person:** Susanna Röblitz, Email: susanna.roeblitz@zib.de
Chapter 5

List of Acronyms

A  Androstendione ................................................................. 3

AFC  Antral Follicle Count .................................................. 23

ART  Assisted Reproduction Techniques ............................ 39

BA  Biologically Admissible .................................................. 12

BMI  Body Mass Index

CDSS  Clinical Decision Support System ............................. 36

CTS  Clinical Training Service .............................................. 38

E2  Estradiol ........................................................................ 40

E2E  Estradiol Estimation .................................................. 38

ETH  Swiss Federal Institute of Technology .......................... 46

ETS  Executable Treatment Strategy .................................... 19

FSH  Follicle-stimulating hormone ..................................... 3

HMS  Hospital Management System .................................. 36

HSLU  Lucerne University of Applied Sciences and Arts ........ 46
ICSI  Intracytoplasmatic Sperm Injection ............................................. 6
ICT  Information and communications technology .......................... 34
IP  Intellectual Property .............................................................. 42
ISS  International Space Station .................................................. 46
IVF  In Vitro Fertilisation ............................................................ 6
KPI  Key Performance Indicator .................................................. 32
LH  Luteinizing hormone ........................................................... 3
MBD-ITP  Model-Based Design of Individualised Treatment Protocols ............ 38
MBV-TP  Model-Based Verification of Treatment Protocols .................. 38
MHH  Hannover Medical School .................................................. 47
P4  Progesterone ....................................................................... 3
PCOS  Polycystic Ovary Syndrome ............................................. 23
POF  Premature Ovarian Failure .................................................. 23
PRL  Prolactin ........................................................................ 3
T  Testosterone ....................................................................... 3
TDSS  Treatment Decision Support System .................................. 39
TV-US  Transvaginal Ultrasound .................................................. 40
UHB  University Hospital of Basel ............................................... 36
UHL  University Hospital of Lausanne ........................................ 36

USOC  User Operations and Support Center .......................... 46

URM1  Sapienza University of Rome ...................................... 45

UZH  University Hospital Zurich .......................................... 47

VH  Virtual Hospital ............................................................ 46

VPH  Virtual Physiological Human ......................................... 42

VPH-MS  VPH Model Simulation ........................................... 38

VPH-MV  VPH Model Validation ............................................ 38

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