Model Driven Computation of Treatments for Infertility Related Endocrinological Diseases

Stefano Sinisi, Computer Science Department, Sapienza University of Rome, Italy – sinisi.1391213@studenti.uniroma1.it

Motivation

- Infertility affects about 15% of couples in Europe, bearing an increased risk for negative psycho-social functioning.
- Treatment of infertility is expensive and time consuming and has limited success rates.
- In more than 50% of the cases infertility is caused by female health problems, in most cases related to endocrinological diseases.
- Endometriosis, prolactin associated disorders, polycystic ovary syndrome etc. disturb menstrual cycle patterns.

Objectives

Modelling
- Definition of a mathematical model of the human menstrual cycle to simulate infertility-related endocrine disorders.
- Development of algorithms for the design of individualised, patient-specific models, and for the understanding of intra- and inter-individual variability.

Computation
- Model-based verification of treatment protocols and design of individualised protocols.
- Development of the PAEON Virtual Hospital, a web-based software consisting of a knowledge base as a repository for physiological models and patient data, an engine layer for model simulation and validation, a web interface, and web services for external access to the system.

Clinical data collection
- Collect data from normally cycling women to estimate the knowledge base as a repository for physiological models and patient data, an
- Model Driven Computation of Treatments for infertility related endocrinological diseases.

Patient Specific Model Computation

Biologically Admissibility

Param vector $\lambda$ is biologically admissible (BA) iff: model prediction under $\lambda$ and model prediction under default param $\lambda_0$ are qualitatively similar for all species, modulo bounded time shift and stretch. This means that:
- normalised zero-lag cross-correlation is above given threshold
- normalised average difference is below given threshold
- normalised squared norm difference is below given threshold

Offline Phase

Computes set $S$ of Biologically Admissible (BA) parameters which is complete with arbitrarily high statistical confidence

High-level algorithm:

1. $S = \{ \lambda_0 \}$
2. repeat
   - make hyp. $H_0 = \"\text{Pr\{generate BA } \lambda \text{ outside } S} \gg \varepsilon\"$
   - for a “sufficiently high number” $N$ of times do
     1. generate random param $\lambda$
     2. if $\lambda \not\in S$ and $\lambda$ is BA then add $\lambda$ to $S$ and break
     3. until $S$ remains unchanged after $N$ attempts
   - $H_0$ rejected
3. return $S$

Theorem:
For all $\varepsilon, \delta \in (0, 1)$, if $N \geq \ln(\delta) / \ln(1-\varepsilon)$, then $\text{Pr}[H_0 \text{ rejected } | H_0 \text{ holds}] < \delta$

Online Phase

Given patient measurements, find $\lambda$ in $S$ which minimises mismatch between model predictions & available measurements.

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