ISSN 1992-6502 (Print)
Vol. 18, no. 5 (66), pp. 96-98, 2014
Вестник УГАТУ
Vestnik UGATU
ISSN 2225-2789 (Online)
http://journal.ugatu.ac.ru

UDC 004.65

FORMAL VERIFICATION OF INDIVIDUALIZED ENDOCRINOLOGICAL TREATMENTS

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Submitted 2014, June 10

Abstract: Female infertility due to endocrinolocal diseas costs over one billion Eur per year when accounting for treatments and life impact. In this paper we propose a model based approach to endocrinological treatment verification and design.

Key words: treatment verification; endocrinolocal diseas.

1. INTRODUCTION

In this section we will outline motivations, main contributions and related work.

Motivations

Nowadays, infertility affects at least 12 % of European reproductive couples (Fig 1.) and costs about 1 billion Euros per year (caused by frequent and costly visits to the specialists, high level equipment). This basically means that infertility takes a lot of money from family's budget – around 10 % of annual income.

According to statistics over 50% childless cases are due to the woman and are almost twice less due to the men. However, large amount frequently accounted for unexplained. Female health problems are generally related to endocrinological diseases. This later may lead to personal suffering and depression.

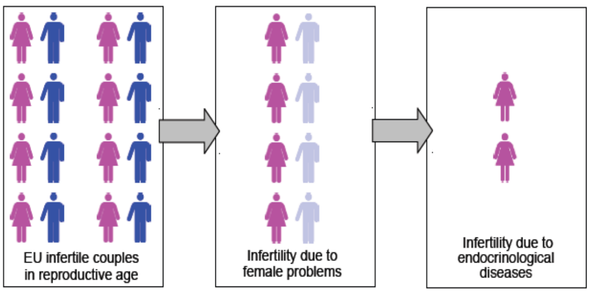


Fig. 1. 12–15 % of EU couples of reproductive age are infertile. For dozens of millions of them, infertility results from female endocrinological diseases

Human fertility is based on several hormones such as Luteinizing hormone (LH), Follicle-stimulating hormone (FSH), Estradiol (E2), Progesterone (P), Testosterone (T), and Androstendione (A) who are responsible in turn for the human cycle. For positive fertility dynamics, scientists all over the world are in great need of the platform simulating menstrual cycle with respect to different conditions such as influence of endocrinological diseases.

Medical treatment protocol basically asks to take some measurements from a patient and depending on the results tells which kind of actions should be applied to the patient. We are taking in consideration that the outcome from taken measurements should be directed to healthy values, by representing a treatment as a computer procedure.

Contributions

In this paper we outline an approach to automatic formal verification of treatments.

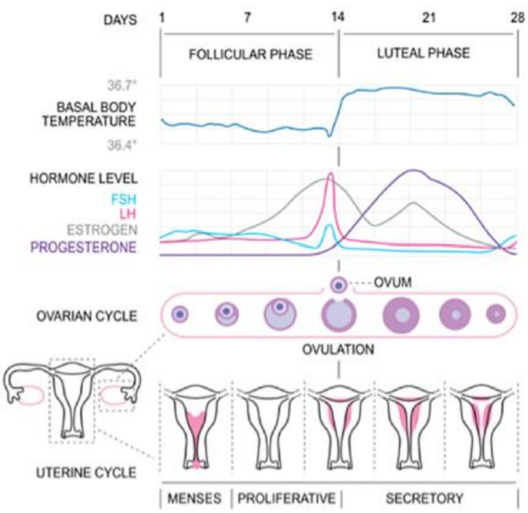
By checking whether species are periodic or not we are creating a set of biologically sound parameters $S = \{\lambda\}$. This will be verified on the second phase. To complete verification we are going to check two functions – the liveness property (that treatment has a healthy impact on values) and the safety property(this guarantees that the patient's health is never at risk if the treatment is applied).

Related work

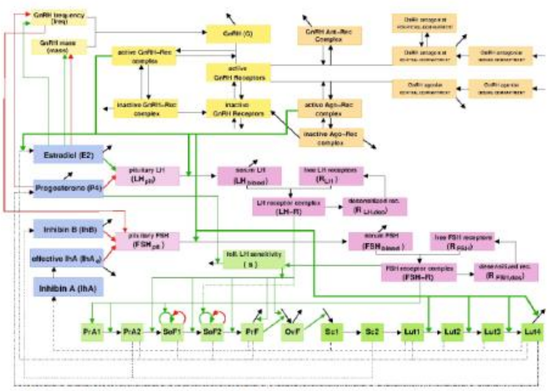
Model-based verification techniques have been applied in healthcare scenarios since three decades. Examples are the verification of clinical guidelines and protocols to detect inconsistencies and ambiguities in their definition (by using different technologies as decision tables [5], logics, semantics and knowledge-based approaches [6]) and verification of health surveillance systems (e. g., [7]).

2. MODELING HUMAN FEMALE MENSTRUAL CYCLE

Unfortunately, existing models of human menstrual cycle (Fig. 2, *a*) have no flexibility and frequently designed for some specific aims, e. g., GynCycle [1] for simulating GnRH analogue treatment, the model in [2] for analyzing prolactin patterns (Fig. 2, *b*). Our goal is to have a system modeling a female menstrual cycle under influence of endocrine disorders and external factors such as drugs. Since we are mainly interested in the answer of a given system (the human menstrual cycle) to external factors such as drugs, this can only be modeled by time-dependent equations such as ordinary differential equations (ODEs).



(a) Schematics (from Wikipedia, the free encyclopedia).



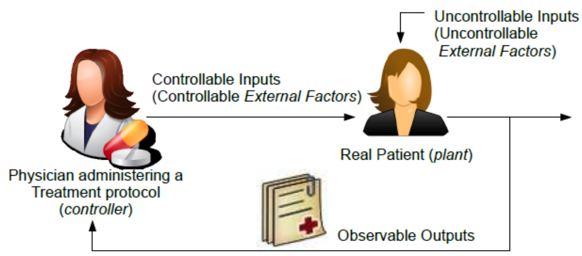
(b) Flowchart of the model for the human menstrual cycle as presented in [1].

Fig. 2. Human reproductive cycle

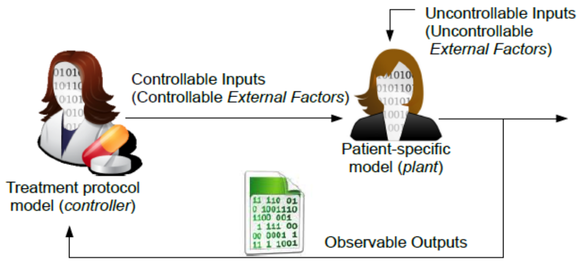
In order to solve large systems of ordinary differential equations (ODEs) was used the extrapolated linearly implicit Euler methods with an adaptive control of time step size and order, the code LIMEX (Linearly IMplicit Euler method with EXtrapolation) [3, 4].

3. MODELING TREATMENTS

By having both mathematical model of each patient and medical treatment give us an opportunity to make an assumption based on system control engineering approach. At this time we see the system combined from the treatment and the patient as a feedback-loop control system (Fig. 3). This gives us a chance to use powerful control engineering and computer science methods for analysis. A medical treatment protocol basically tells which kind of treatment a patient needs and depending on outcome, hand out solution.



(a) Medical level



(b) Computation level

Fig. 3. Medical treatment protocol administration as a feedback-loop control system under a control engineering perspective: the physician administering the treatment acts as a controller and patient acts as a control theory plant

4. VERIFYING TREATMENTS

We need to make sure that given treatment will fulfill its goals despite the possible disturbances between a patient model and actual behavior of the patient. Such differences could be caused by model approximations, unmodelled or unpredictable effects of external factors on some model parameters. By using control engineering terms, we would like to have stable system (consisting of treatment protocol and a patient) to different disturbances and always satisfies some properties (e. g. harmless and liveness). Fig. 4 shows a high-level view of our envisioned tool for Model-Based Verification of Treatment Protocols.

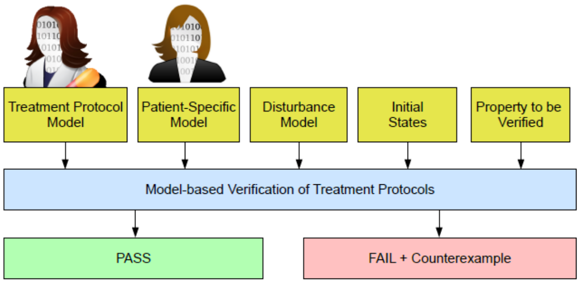


Fig. 4. model-based verification of treatment protocols

As an input for the checker we have: treatment protocol under verification, properties it should satisfy, the patient initial states and disturbance model. The patient-specific model is going as an input for the simulator (in our case – Limex) which sends its state to the checker – for reviewing properties under verification. The idea is summarized in Fig. 5. In order to have successful verification, treatment should do no harm to the patient and be liveness, so it would lead patient to the healthy state.

The basic idea of algorithm is to randomly choose value $\lambda \in \Lambda$, test whether it is periodic and do not already exist in S and in this case we add it to the set S of biologically sound parameter values. The algorithm stops when N attemps fail to find a biologically sound parameter. N is chosen in such a way that with confidence $(1 - \delta)$ the probability of finding other biologically sound parameter values not in S is less than ε(δ and ε are two positive real numbers). Next, for each $\lambda \in S$ we need to verify the functions harmless and liveness.

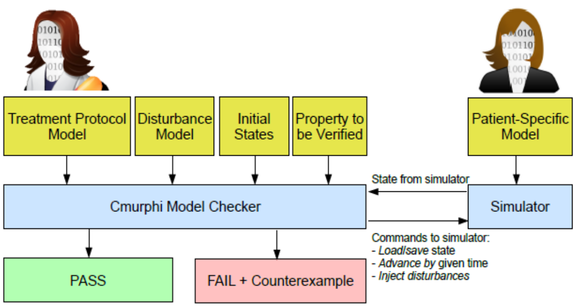


Fig. 5. Formal verification of individualised treatment protocols via model checking driven simulation of patient – specific models

5. CONCLUSIONS

By having formal verification of individualised endocrinological treatments we will decide whether it would lead the patient to a healthy state or it will fail.

ACKNOWLEDGMENTS

This work has been partially supported by the the EC FP7 project PAEON (Model Driven Computation of Treatments for Infertility Related Endocrinolog- ical Diseases, 600773).

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МЕТАДАННЫЕ

Название: Formal Verification of Individualised Endocrinological Treatments
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Организации: [1] ФГБОУ ВПО «Уфимский государственный авиационный технический университет» (УГАТУ), Россия. [2] Университет Рима "La Sapienza", Италия.
Email: mariya.markelova@gmail.com; tronci@di.uniroma1.it
Язык: английский.
Аннотация: Женское бесплодие вследствие эндокринных заболеваний обходится более одного миллиарда евро в год на лечение и условия жизни. В этой статье предлагается основанный на модели подход к эндокринологической проверке лечения и дизайна.
Key words: проверка обращений; эндокринологические болезни.

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