PAEON: Model-driven Computation of Treatments for Infertility Related Diseases

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Individualised Medicine: Improving Success Rate of Treatment

Treatment of infertility is expensive and time consuming and has limited success rates.

Computation of *patient-specific* predictions from a sufficiently flexible *inter-patient* model, comprising 33 species with 114 parameters, could lead to improved success rates of treatment.

Definition of *biologically admissible* (BA) parameters reduces substantially the search space of individualised parameters, however, a two-phase HPC approach of the computional task is still needed.

Goal: Patient-specific prediction of time evolution of reproductive hormones during treatment.

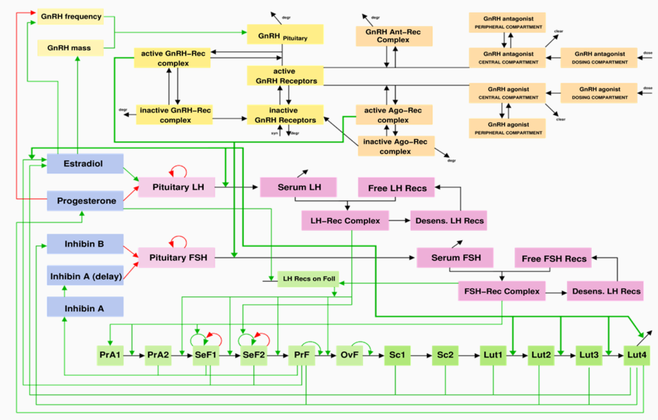
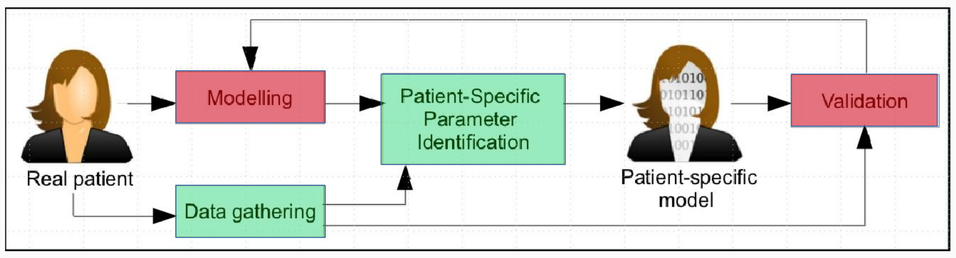


Figure 1: Feedback mechanisms regulating reproductive hormones

Methods

Splitting the search for patient-specific parameters into two phases: an off-line phase, and an on-line phase.



Off-line Phase: **Statistical Hypothesis Testing (model-driven)**

» Sampling, with prescribed high statistical confidence, all BA parameters.

Time consuming, but independent of *any* measurement data.
Significant acceleration possible by massively parallel processing (MPP), i.e. using Open MPI: one master and multiple slaves of a HPC cluster.
Drawback: heavily model-dependent.

On-line Phase: **Fitting in Reduced Parameter Space (patient-specific)**

» Using a standard parameter identification routine (e.g. NLSCON).

Very fast (due to off-line computation: results within minutes!).
Drawback: needs, of course, the results of off-line phase.

Conclusion / Outlook

Building blocks of a **Virtual Hospital** improving treatment.

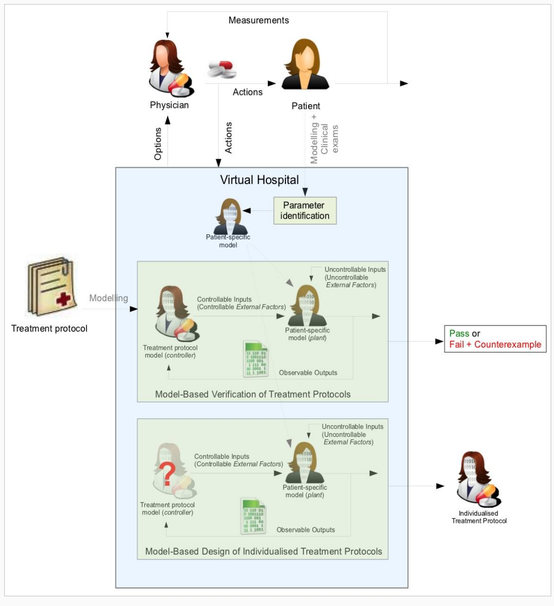


Figure 3: Design and functionality of Virtual Hospital

Development of a web platform that meets essential requirements:

» User Acceptibility (easy-to-use)

» Data Security (crypto-enabled)

» Functionality (stable & relible)

Overall software architecture on representation state transfer (ReST) paradigm and behaviour-driven development (BDD).

Results

All experiments have been carried out on a cluster of Linux machines [Intel(R) Xeon(R) CPU @ 2.27GHz, and 24GB of RAM, each].

Off-line phase determines set of BA parameters $S \subseteq \Lambda$ such that the probability of selecting a BA parameter outside S is less than $\varepsilon = 0.001$, i.e. null hypothesis $H_0(S)$ holds.

Average run time: $O(N \cdot |\Lambda|)$ with $N := \log \delta / \log (1 - \varepsilon)$, rejecting $H_0(S)$ with confidence $1 - \delta$ upon termination.

Parameters θ_1, θ_2, θ_3 in Table 1 are upper limits for *cross-correlation*, *normalised average difference*, and *normalised auto-correlation difference*, respectively, that define the overall range of BA parameters.

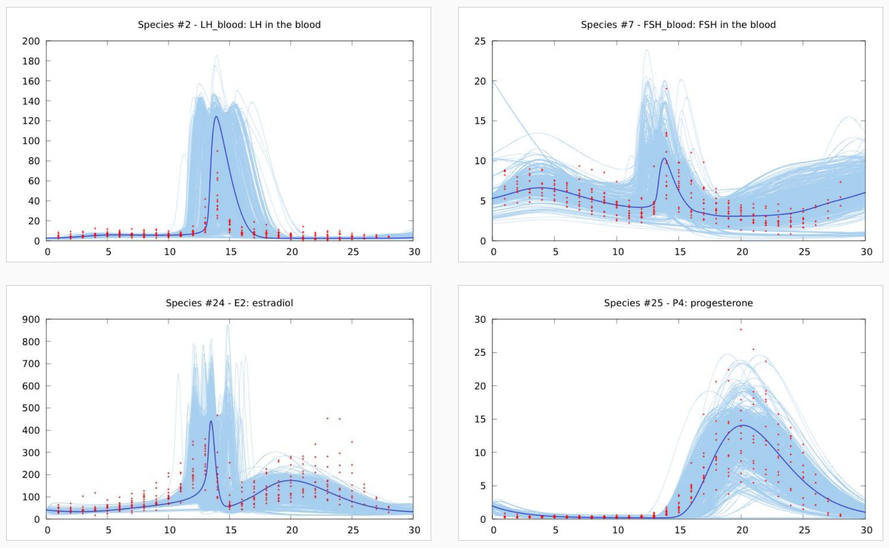


Figure 2: Biologically meaningful time evolution of observable hormone concentrations

run id	θ_1	θ_2	θ_3	discr. steps	|S|	CPU time
r1	0.6	0.5	0.5	10	3940	∼ 31 days
r2	0.6	0.4	0.4	10	3504	∼ 29 days
r3	0.5	0.7	0.7	10	6989	∼ 147 days
r4	0.5	0.5	0.5	10	6406	∼ 167 day
r5	0.7	0.3	0.3	3	126	∼ 6 days

Table 1: Extrapolated sequential CPU run times
[e.g. r3: actually computed on 80 nodes in Open MPI within 3 days]

Publications

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- S. Röblitz, C. Stötzel, P. Deuflhard, H.M. Jones, D.-O. Azulay, P. van der Graaf, S.W. Martin: A mathematical model of the human menstrual cycle for the administration of GnRH analogues, Journal of Theoretical Biology 321, pp. 8-27, 2013.