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WYDZIAŁ AUTOMATYKI, ELEKTRONIKI I INFORMATYKI

Rozprawa doktorska

Struktury sterowania i wrażliwość wybranych modeli układów biomedycznych

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Summary

This dissertation focuses on the analysis of mathematical models of biological and medical systems in the context of the occurrence and application of control structures, which have been successfully employed in industrial solutions. It represents a link between engineering experience in the field of control and the pursuit of understanding mechanisms occurring in living organisms. The emphasis has been placed on models of systems related to medicine—the development of diseases and their treatment—at different scales. The diversity of scales of the investigated phenomena consisted in selecting examples operating at the level of the whole organism (physiological level), cellular populations (population level), and a single cell (intracellular level).

Sensitivity analysis carried out for signaling pathway models in various contexts, including the search for potential drug targets, is highly time-consuming due to the large number of model parameters. This dissertation proposes a solution aimed at reducing this number by employing engineering knowledge of the properties of control systems with feed-forward structures, through verification of whether such structures exist in the model and subsequently focusing primarily on parameters associated with processes involved in these structures. The dissertation also examines other control structures present in biological systems. For a selected physiological model, the study concerned the regulation of blood glucose levels, which, in its basic form, implements classical feedback control. Particular attention was given to reducing the impact of physical exercise through modifications of the control system structure and the reference value. In the case of cancer therapy models, one can speak of open-loop control. As is well known, such a structure is highly sensitive, among others, to disturbances that may affect the system as well as to variations in plant parameters. The focus was therefore placed on the problem of generating sets of parameters representing individual patients from a hete-

rogeneous population, so that the results of numerical experiments—estimating patient survival time or time to metastasis—would be consistent with clinical data.

Three theses were formulated in this dissertation, namely:

1. In the artificial pancreas system, improvement of control quality may be achieved not only through modification of the control algorithm and structure, but also through appropriate changes of the reference value.
2. Incorporating clinical parameter distributions within subpopulations when generating a virtual cohort has a significant impact on the qualitative agreement of model results with real data in survival analysis.
3. Knowledge of the presence of feed-forward structures in biological models allows one to reduce the number of parameters considered in sensitivity analysis.

These theses were verified through the analyses carried out and described in the subsequent chapters of the dissertation.

Keywords: mathematical modeling, control structures, simulation analysis, numerical analysis, artificial pancreas, type 1 diabetes, cancer with metastasis, survival analysis, signaling pathways, feedback control, feedforward control