Domain of Attraction Estimation and Optimization-Based Control: Application to Tumor Growth Models

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PhD subject: The problem of characterizing the regions of stability and convergence, i.e. the domains of attraction, underlies most of the results in control theory, as stability and convergence are usually essential properties of a control law. Notice that the Lyapunov theory for stability is implicitly concerned with the characterization of the regions of the state space where stability and convergence are assured. A feature that makes these methods particularly interesting is the relation with computation-oriented tools and results, as convex analysis and optimization. Moreover, the domains of attraction and invariant sets computation is inherently related to optimization-based control techniques, like predictive control, whose stability and recursive feasibility are often guaranteed by the existence of an invariant set and a local stabilizing control law. Finally, the domain of attraction and invariant computation are tightly related to the problem of control subject to constraints as they characterize the control laws and the trajectories which prevent the constraints violations.

Such classical issues, whose solutions are well assessed in the linear context [3] and based on convex analysis and optimization [4, 18], become nontrivial when more complex systems are dealt with. This is mainly due to the numerical complexity introduced by nonlinearities in the dynamics that often yield to nonconvex conditions and then nonconvex optimization problems to be solved. Nevertheless, recently developed nonconvex optimization techniques, [11, 12], have been established that permit to deal with nonconvex problems and constrained nonlinear optimal control. Those methods have also been applied to the problem of domain of attraction and invariant estimation for nonlinear systems [6, 9, 10], providing theoretical proofs of convergence of the numerical estimations to the exact domain of attraction, under mild assumptions. Moreover, being based on the manipulation of measures in the state and input space, they are suitable also to characterize the evolution of distributions in the state space under stochastically defined control actions. The main drawback of those nonconvex optimization-based approaches is the limitation on the dimension of the nonconvex problems that can be numerically treated.

Among the dynamical systems that recently attracted the interest of automatic control researchers there are those modelling biological phenomena. In particular, the dynamics underlying the tumor growth and the related mechanisms such as the tumor-induced vascular development, i.e. the angiogenesis, is a key step towards rational optimization of cancer therapy, [8]. The combination of cytotoxic drugs that kill the tumor cells, as in chemotherapy, and the drugs affecting its vascularization appears the most promising approach to cancer therapy and dynamical models that take into account both dynamics have appeared recently, [7, 15, 2]. Based on those models, research efforts have been directed to the issue of using control theory techniques for guiding the therapy, [14, 13, 1]. One objective is the design of the profile of the drug administration which provides the desired evolution of the cancer, for instance ensuring the regression of the tumor mass while monitoring health indicators and minimizing the negative side-effects of the therapy, see [5]. In terms of control, an aim is to characterize the domains of attraction of any equilibrium and the reachable sets from every particular initial condition as functions of the control input. This would permit to characterize the set of tumor initial conditions from which a healthy equilibrium can be reached as well as to design the therapy which maximizes the effectiveness while minimizing the negative side-effects, see [16, 17].

Objectives and scheduling: The main objective of the PhD thesis is to apply the methods based on non-convex optimization for computing the domain of attraction for nonlinear systems to validate or design a cancer therapy. As for many biological models, cancer models are to be considered as affected by important uncertainties, since the parameters of the models are often unknown and strongly patient-dependent and the system state is usually not known exactly. On the other hand, the low dimension of the models often employed makes the nonconvex optimization techniques rather suitable for analyzing the dynamical behavior of tumor growth models and the effects of cytotoxic and anti-angionesis drugs. This might lead to an analytical numerical tool for the practitioners that would allow them to verify the effectiveness of a given therapeutic profile or to design an appropriate therapy, by explicitly taking into account the uncertainties and the nonlinearities of the models.

The following 3 years-long scheduling should allow to gradually reach the objectives:

1. Bibliographic research to review set-theoretic methods for control, convex and nonconvex optimization and mathematical models of cancer present in the literature.
2. Modelling the problem in terms of optimization problem on measures and application of the methods for computing the domain of attraction for different models of the tumor growth dynamics.
3. Development of a numerical tool the allow to analyse and to infer the therapeutic efficiency of a given drug delivery profile or to design a therapy in order to optimize its effectiveness, by considering the uncertainties on the model and on the system state.

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