Analysis of Models of Chronic Myelogenous Leukemia with Treatment Options using Structural Methods and Computation: Sensitivity to Nonlinearity and Delay

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***Abstract*— This paper focuses on the analysis of delay-differential models of Leukemia and T-cell dynamics during Gleevec treatment for chronic myelogenous leukemia. The analysis shows that this models yields the presence of three fixed points. The second fixed point corresponds to some equilibrium solution in which the leukemia population is kept below the cytogenetic remission level. In this presentation, we consider the robustness of the model with respect to nonlinearity and delay. In the first part of the analysis, we consider a delayed linearization of the model about the second equilibrium. By using geometric structure in the frequency domain representation, we give an estimate of the range of delays for which the models remains stable. In the second part of the analysis, we use recently introduced computational methods based on Lyapunov analysis to verify the frequency domain results. We then use a related computational approach to give estimates of the domain of attraction of the nonlinear model. Our results indicate that the Gleevec treatment model is significantly robust with respect to delay and nonlinearity.**

I. Computational Methodology

In this section, we describe a computational method for determining the stability of systems of differential equations with nonlinearity and delay. We will give only a brief overview. For a detailed explanation, we refer the reader to the [5] and [3].

Consider an ordinary differential equations of the form

$$\dot{x}(t) = f(x(t))$$

where $f : \mathbb{R}^n \to \mathbb{R}^n$ is continuous. This system is exponentially stable if there exists a differentiable function $V : \mathbb{R}^n \to \mathbb{R}$ such that there exist $\alpha, \beta, \gamma > 0$ such that

$$\alpha\|x\|^2 \leq V(x) \leq \beta\|x\|^2$$
$$\dot{V}(x) = \nabla V(x)^T f(x) \leq -\gamma\|x\|^2$$

for any x along trajectories of the system. If the conditions only hold on a subset $\Omega \subset \mathbb{R}^n$, then the region of attraction of the trivial equilibrium can be estimated as $Y_\delta := \{x : v(x) \leq \delta\} \subset \Omega$ for any $\delta > 0$.

The search for a Lyapunov function, V which proves stability of a nonlinear ordinary differential equation has been the topic of research for some time. Recently, It has been shown one can assume that the function V is polynomial. This is important because there exist algorithms for optimization over the cone of positive polynomials. See, e.g., [1] or [4]. Thus the search for a Lyapunov function for stability on nonlinear ordinary differential equations has become significantly more algorithmic in recent years.

Now consider a system with time-delay of the general form.

$$\dot{x}(t) = f(x(t), x(t-\tau))$$

where $f : \mathbb{R}^n \times \mathbb{R}^n \to \mathbb{R}^n$ is continuous and $\tau \geq 0$. For these types of system, Lyapunov theory has been been generalized. In this case, the system is stable if one can find a Lyapunov function $V : \mathcal{C}[-\tau, 0] \to \mathbb{R}$ and positive constants α, β, γ such that

$$\|\phi(0)\|^2 \leq V(\phi) \leq \beta\|\phi\|_\infty^2$$

and

$$\dot{V}(\phi) \leq -\gamma\|\phi(0)\|^2$$

holds for any segment of trajectory, ϕ, and $\dot{V}(\phi)$ is the derivative of V along ϕ. Because for time-delay systems, V acts on the infinite-dimensional space $\mathcal{C}[-\tau, 0]$, the search for a Lyapunov function in this case is significantly more difficult. For linear systems, we can refine our search without loss of generality by only considered quadratic functions of the following form.

$$V(\phi) = \int_{-\tau}^{0} \begin{bmatrix}\phi(0)\\ \phi(s)\end{bmatrix} M(s) \begin{bmatrix}\phi(0)\\ \phi(s)\end{bmatrix} ds + \int_{-\tau}^{0}\int_{-\tau}^{0} \phi(s)N(s,t)\phi(t)\, ds\, dt$$

The parametrization of functions M and N which define a positive function of this form is the subject of the work in [**?**].

In the case when the dynamics of the system depend on some uncertain parameter, one can search for a Lyapunov function which also depends on this parameter. The search for such Lyapunov functions over semialgebraic regions of uncertainty is accomplished using the polynomial optimization techniques in combination with Postivstellensatz results. These are described briefly below.

A. The Positivstellensatz and Sum-of-Squares

A polynomial, p, is said to be *positive* on $G \subset \mathbb{R}^n$ if

$$p(x) \geq 0 \quad \text{for all } x \in G.$$

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If G is not mentioned, then it is assumed $G = \mathbb{R}^n$. A *semialgebraic set* is a subset of $\mathbb{R}^n$ defined by polynomials p_i, as

$$G := \{x \in \mathbb{R}^n \,:\, p_i(x) \geq 0,\, i = 1, \ldots, k\}.$$

A polynomial, p, is said to be sum-of-squares (SOS) in variables x, denoted $p \in \Sigma_s$ if there exist a finite number of other polynomials, g_i such that

$$p(x) = \sum_{i=1}^{k} g_i(x)^2.$$

A necessary and sufficient condition for the existence of a sum-of-squares representation for a polynomial, p, of degree $2d$ is the existence of a positive semidefinite matrix, Q, such that

$$p(x) = Z(x)^T Q Z(x),$$

where Z is any vector whose elements form a basis for the polynomials of degree d. Positivstellensatz results are "theorems of the alternative" which say that either a semialgebraic set is feasible or there exists a sum-of-squares refutation of feasibility. The Positivstellensatz that we use in this paper is that given by Stengle [6].

Theorem 1 (Stengle): The following are equivalent

1)

$$\left\{ x : \begin{matrix} p_i(x) \geq 0 & i = 1, \ldots, k \\ q_j(x) = 0 & j = 1, \ldots, m \end{matrix} \right\} = \emptyset$$

2) There exist $t_i \in \mathbb{R}[x]$, $s_i, r_{ij}, \ldots \in \Sigma_s[x]$ such that

$$-1 = \sum_i q_i t_i + s_0 + \sum_i s_i p_i + \sum_{i \neq j} r_{ij} p_i p_j + \cdots$$

We use $\mathbb{R}[x]$ to denote the real-valued polynomials in variables x. For a given degree bound, the conditions associated with Stengle's Positivstellensatz can be represented as a semidefinite program. Note that, in general, no such upper bound on the degree bound will be known a-priori. One can use Positivstellensatz results to prove stability over regions in the following way.

Proposition 2: Suppose there exists a polynomial $V : \mathbb{R}^n \to \mathbb{R}$, a constant $\epsilon > 0$, and sum-of-squares polynomials $s_i, t_i : \mathbb{R}^n \to \mathbb{R}$ such that

$$V(x,p) - \sum_i s_i(x,p) q_i(p) \geq \epsilon\, x^T x$$

and

$$\nabla V(x,p)^T f(x,p) + \sum_i t_i(x,p) q_i(p) \leq -\epsilon\, x^T x$$

Then there exist constants $\mu, \delta, r > 0$ such that

$$\|x(t)\|_2 \leq \mu \|x_0\|_2 e^{-\delta t}$$

for all $t \geq 0$ and initial conditions x_0 and all p such that $q_i(p) \geq 0$.

II. Computational Analysis: Delay

Consider the the linearized model presented in Section **??**. We note that this model is linear and contains delay. In general, the specific values of the equilibrium and the linearization will be dependent on patient data. Additionally, the estimate of the delay inherent in the model will also depend on patient data.

In this section, we consider patient data taken from clinical trials. A discussion of the collection of the data and estimation of the parameters is given in the thesis work of P. Kim []. In particular, we considered 3 patients for which the linearized model was stable in the absence of delay. We then used the computational methodology in [5] to test stability for a range of values of the delay. Given the patient parameters, as described in Table II, we used a bisection method to determine the maximum stable value of the delay. The results of this analysis are listed in Table I.

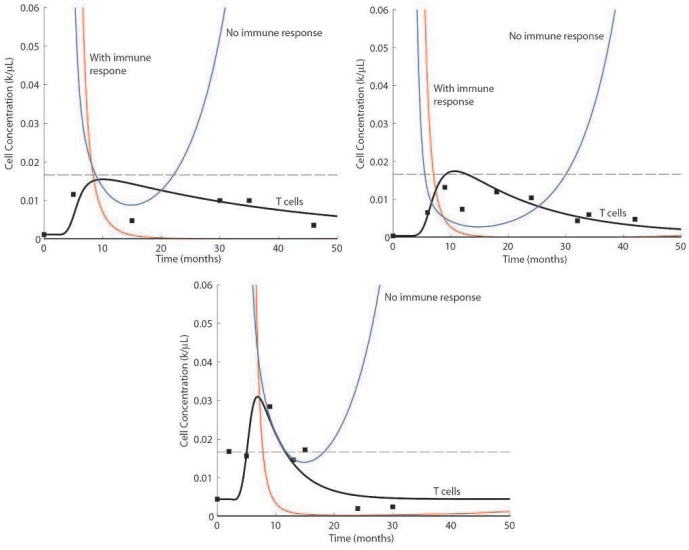

Fig. 1. Data from (reading from upper left) patients 1, 4, and 12 compared to modeled response.

Parameter	Estimates (P1, P4, P12)		
n	2.2	1.2	1.17
d_T	0.001	0.0022	0.007
s_T	2×10^{-6}	9×10^{-7}	3.08×10^{-5}
γ	1	7	0.8
$\tau_{\max}$	222	190	334

TABLE I

Stability Results for patients P1, P4, and P12.

An analysis of the linear stability of this model with respect to the delay was also considered in [**?**]. These results are consistent with the values obtained in that paper.

III. Computational Analysis: Parametric Dependence on Patient Data

Consider the model of Section **??** as developed in the thesis work of [2]. In this section we look at the problem of

Param	Description (units)	Nominal Value
n	Average # of T cell divisions	2.2
d_T	T cell death rate	$5 \cdot 10^{-3}$
s_T	T cell supply rate	$4 \cdot 10^{-6}$
γ	Decay rate of immune responsitivity	1.5
τ	Immune response delay (days)	1 day

TABLE II

DEFINITION OF PATIENT PARAMETERS

estimation of the patient parameters as defined in Table II. We first note that these parameters cannot, at present, be measured directly in an efficient manner. Rather, the values of these parameters, for example as listed in Table I, are inferred in an a-posteriori manner from the clinical data by tuning the values so that observed behavior will match the predicted patient response.

In our work, we consider the realistic problem wherein the values of the patient data are poorly known. In particular, we take a nominal, stable value of the parameters, including a realistic value of the delay. We then develop a linear parameter-dependent model of the patient response using a least-squares type procedure. Finally, we use the methodology described in Section I to given stable regions of the parameter values by constructing parameter-dependent Lyapunov-Krasovskii functionals.

A. Constructing a Parameter-Dependent Model

In order to construct a parameter-dependent model in a single parameter, we fix all other parameters about their nominal values. For the work considered here, we use the nominal values listed in Table II. Recall now the equations in which we are interested.

$$\begin{aligned}
\dot{y}_0(t) &= [r_y - d_0]y_0(t) - q_C p(C(t), T(t))y_0(t),\\
\dot{y}_1(t) &= a_y y_0(t) - d_1 y_1(t) - q_C p(C(t), T(t))y_1(t),\\
\dot{y}_2(t) &= b_y y_1(t) - d_2 y_2(t) - q_C p(C(t), T(t))y_2(t),\\
\dot{y}_3(t) &= c_y y_2(t) - d_3 y_3(t) - q_C p(C(t), T(t))y_3(t),
\end{aligned}$$

$$\begin{aligned}
\dot{T}(t) =& s_T - d_T T(t) - p(C(t), T(t))C(t)\\
&+ 2^n p(C(t-n\tau), T(t-n\tau))q_T C(t-n\tau),
\end{aligned}$$

where

$$p(C, T) = p_0 e^{-\gamma C} kT,$$

and

$$C = y_0 + y_1 + y_2 + y_3.$$

We would like to create a linear model of the equations which retains the dependence on the parameters n, dT, sT, and γ. In order to linearize the equations, we should first determine the values of the equilibrium points in terms of the parameters. Then, by finding the Jacobian at the equilibrium point of interest, we should obtain a parameter-dependent model. Unfortunately, for the equations under consideration, no closed-form solution exists for the equilibrium point in terms of any of the parameters of interest. Therefore, we propose the following slightly less rigorous methodology.

1) We begin by fixing at their nominal value all parameters other than the one of interest.
2) We then finely grid the parameter space in the region of interest (the regions of interest are the stable regions shown in Figures 3 and 4).
3) At each point in the parameter space, we solve for the equilibrium point using the Matlab command `fzero` and compute the Jacobians with respect to the delay and undelayed values at this point to obtain the linearized system matrices.
4) For each element of each of the system matrices, we minimized the least squares of the error at the grid points to fit the data to a polynomial curve.

For all the models used to generate the results of this paper, the error between the fitted curve and the grid points was less than .01% of the size of the range of values considered. While a number of elements of the system were not sensitive to variation of parameters, others showed variation. Some of this variation can be observed in the examples, as shown in the dependence of a particularly important element of the linear system matrices and plotted in Figure 2. In most cases, we found that a second order polynomial was sufficient to provide the needed accuracy.

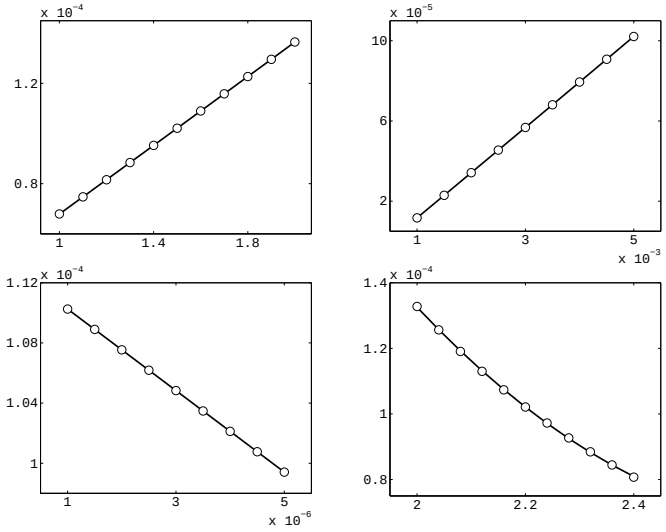

Fig. 2. Variation in the $1,1$ entry of A_0 as a function of, reading from upper left, γ, dT, sT, and n. Both the model and selected data points are shown.

Note: A natural alternative to the proposed approach would be to consider a robust stability proof, wherein the system matrices are assumed to lie in some unit ball. We note that there are a number of algorithms which have been proposed to treat this problem, although the complexity of these algorithms is high and may be inappropriate for a system of 5 dimensions. Additionally, treatment of the effect of parameter variation as a a robustness problem may be overconservative, since one loses knowledge of exactly how the disturbance affects the dynamics. In short, we leave this

topic as a subject of future research.

B. Numerical Results

Using Matlab code to obtain parameter-dependent linear delay-differential models of the dynamics of CML on various regions of the parameter-space, we investigated the effects of the variation of patient values of the parameters on the stability of the dynamics. In some cases where we could only prove marginal stability on the entire interval, the interval was subdivided and stability proven on each of the subintervals. This seems to have improved the numerical performance of the algorithm. The regions of stability over which we were able to prove stability are shown in Figures 3 and 4. We note briefly that we were not able to find a positive result for the patient parameter sT. We are not sure whether this is a result of a lack of computational resources, which restricts the degree of the polynomial, or of some actual sensitivity of the model to this parameter.

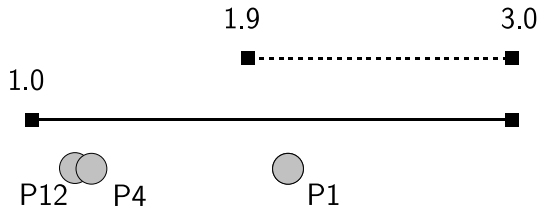

Fig. 3. Stability region (dashed line) with respect to parameter n compared to patient data

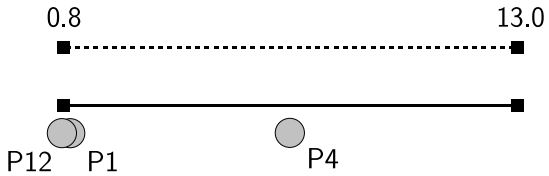

Fig. 4. Stability region (dashed line) with respect to parameter γ compared to patient data

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