Controllability of a Model of Treatment Response to Combined Anticancer Therapy

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***Abstract*—The controllability of a combination of antiangiogenic treatment and chemotherapy for cancer is considered in the paper. The treatment is modeled as a two-dimensional control action in the second order dynamical system described by a model belonging to a class proposed so far. Sufficient conditions of local constrained controllability are found and verified for the model and their biological interpretation is presented.**

Keywords-controllability; dynamics; semilinear systems; biomathematical modelling; cancer therapy.

I. INTRODUCTION

Controllability is a qualitative property of dynamical control systems and its meaning, roughly speaking, is the following: a dynamical system is controllable if it is possible to steer it from an arbitrary initial state to an arbitrary final state using the set of admissible controls. In the existing literature there are many different definitions of controllability strongly depending on the class of dynamical control systems (see, e.g., [1], [2] and references therein). In the present paper, we consider constrained local controllability problems for second-order finite-dimensional semilinear stationary dynamical systems described by a set of two ordinary differential state equations. More precisely, we discuss the control properties of a model belonging to a class proposed in [3] to which two control variables describing two treatment modalities have been introduced. The line of reasoning is similar to our previous study [4] in which however only antiangiogenic therapy was considered, in other words only one control variable was used. The results are based on theorems proved in [2]. The idea of the theorems is that under suitable assumptions the constrained global relative controllability of a linear first-order associated approximated dynamical system implies constrained local relative controllability near the origin of the original semilinear second-order dynamical system. The Hahnfeldt *et al.* model [3] is based on the assumption that tumor growth with an incorporated vascularization mechanism can be described by a Gompertz-type or logistic-type equation with variable carrying capacity which defines the dynamics of the vascular network. The main idea of this class of models is to incorporate the spatial aspects of the diffusion of factors that stimulate and inhibit angiogenesis into a non-spatial two-compartmental model for cancer cells and vascular endothelial cells. The control properties of such models in the context of combined therapy were discussed among others in [5], [6] and [7]. In [5], following the line of reasoning proposed by d'Onofrio and Gandolfi in [8], conditions for asymptotic tumor eradication by constant and periodic therapy were given. Moreover, in [5] and [6], the necessary conditions for optimal treatment protocols in a given finite time were considered. The interesting finding is that for the d'Onofrio-Gandolfi version of the model [8] the optimal trajectory does not contain singular arcs. This property has been found previously for a sub-class of the models of this class for antiangiogenic therapy [9], but for the remaining models from this class the existence of intervals of singular optimal control has been proved rigorously by Ledzewicz and Schattler [6], [10], [11]. All the considerations related to finite time control are however conditioned on the concept of controllability of the dynamical systems discussed which, to our knowledge, has not been analyzed by other authors except in our previous paper [4]. This is a major motivation for the present study.

In the second section we present the most important biological information related to the topic of our study. The mathematical model and its properties are presented and discussed in the third section. In section 4 we define a class of semilinear systems and we present some results related to controllability of such systems. Section 5 contains the most important results of our study dealing with controllability of the models of the combined anticancer therapy. Final remarks and conclusions are given in the section 6.

II. BIOLOGICAL BACKGROUND

Tumors, like normal tissues, have physiological constraints on growth, such as access to oxygen and nutrients for metabolism. The diffusion of oxygen in tissues is limited to a distance of about 150 μm, thus tissue growth is restricted to a few cubic millimeters if no new vasculature is formed. For vascularization to occur, the nearest vessel or capillary needs to become destabilized so that the endothelial cells lining the vessel can loosen from their neighbors and migrate through the extracellular matrix towards the tumor. Only after a tumor has recruited its own blood supply it can expand in size. Tumors do this via the production of angiogenic factors secreted into local tissues and stroma, a process termed the angiogenic switch. The

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angiogenic switch is a discrete step in tumor development that can occur at different stages in the tumor-progression pathway, depending on the nature of the tumor and its microenvironment. Since in normal healthy adults the process of angiogenesis is very limited, it should, at least in theory, be possible to inhibit tumor angiogenesis without affecting normal tissues. Antiangiogenic therapies proposed by Folkman in the early seventies of the previous century [12] have become one of the most promising approaches in anti-cancer drug development. Successful preclinical research data lead to clinical trials based on different strategies. Approaches currently under evaluation for inhibiting angiogenesis may either be direct (targeting cell surface bound proteins/receptors) or indirect (targeting growth factor molecules) [13]. The genetic instability and high mutation rate of tumor cells is responsible, in part, for the frequent emergence of acquired drug resistance to conventional cytotoxic anticancer therapy. In contrast, vascular endothelial cells, like bone marrow cells, are genetically stable and have a low mutation rate. Therefore Kerbel [14] proposed the hypothesis that antiangiogenic therapy would be a strategy to bypass drug resistance. In [15] the gap between preclinical (mouse models – localized primary tumor) and clinical testing (late-stage metastatic tumor) is noted; anti-angiogenic agents are not efficient at the level suggested by preclinical trials and different results have been observed depending on the disease stage. Biologists suggest that anti-angiogenic therapy might become an essential component of multidrug cancer therapy [16], [17], especially when combined with chemotherapy. One possible strategy is using angiogenesis inhibitors to normalize the abnormal vasculature and thereby to facilitate drug delivery [18], [19]. Some results from clinical studies of such combination therapy are shown in [16]; a dose of antiangiogenic agent (Bevacizumab 5 mg/kg) showed a significantly different (higher) median survival than chemotherapy alone, and a larger dose (10 mg/kg) even increased survival compared to chemotherapy alone. Several clinical trials of combined therapy have been discussed recently, and some examples are presented in [20]. Continuous treatment with angiogenic inhibitors ultimately leads to a decrease in tumor blood flow and a decreased tumor uptake of co-administrated cytotoxic drugs. In periodic therapy the main goal of anti-angiogenic agents is to normalize tumor vasculature which might facilitate recovery of tumor cells from cytostatic agents [16].

This is why when formulating objectives of the combined therapy mathematically, one should take into account final states which could be reached by the admissible control actions. The problem of the reachability could be solved by the respective conditions of controllability of the model.

III. MODEL OF COMBINED THERAPY AND ITS PROPERTIES

Hahnfeldt *et al.* [3] proposed a model of vascularized tumor development described by a self limiting growth mechanism (e.g. a Gompertz- or logistic-type equation) with a variable carrying capacity defining the dynamics of the vascular network. They proposed to treat the carrying capacity constraining the tumor growth as a varying tumor volume sustainable by the vessels and roughly proportional to the vessel volume. The complete model requires an additional equation describing changes of the volume of the vessels, and the equation below expresses Gompertz-type growth:

$$\frac{dN(t)}{dt} = -\beta N(t) \ln \frac{N(t)}{K(t)} \quad (1)$$

where N represents tumor volume as the size of the cancerous cell population, K describes the maximum tumor volume sustainable by the supporting vascular network, and β is a growth parameter.

The models considered in the present study are based on that proposed by Hahnfeldt *et al* who have developed and biologically validated a two-dimensional model of ordinary differential equations for interactions between primary tumor volume and the carrying capacity of the vasculature network which in turn is proportional to the square of the tumor diameter. For simplification, it was necessary to assume spherical symmetry of the tumor mass. Therefore the expression for K has the following form:

$$\frac{dK(t)}{dt} = \gamma N(t) - \lambda N(t)^{\frac{2}{3}} K(t) - \mu K(t) \quad (2)$$

where γ represents the effect of the stimulation, λ the effect of the inhibition, and μ the natural cell death. Taking into account that tumor growth is relatively slow compared to the rate of release of pro- and anti- angiogenic factors, it is possible to assume that parameters γ, λ, μ are constant. The model (1), (2) may be modified by introducing a logistic-type growth equation instead of the Gompertz-type one and by changing the ratio between stimulating and blocking angiogenic factors [8]. This leads to a set of models which although behaving similarly when uncontrolled, may have different control properties [9]. For example, all the models have the same equilibrium point which is both locally and globally asymptotically stable:

$$N^* = K^* = \left((\gamma - \mu)/\lambda \right)^{3/2} \quad (3)$$

On the other hand, conditions of tumor eradication under periodic therapy are both sufficient and necessary for all the models, except for the original Hanhfeldt model for which they are only necessary. Similar differences are observed when optimal antiangiogenic treatment protocols are considered. The original Hahnfeldt model contains singular arcs in optimal trajectories which are absent in other models [9], [10], [11]. To focus attention we consider the modification of the Hahnfeldt model proposed in [8]:

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$$\frac{dK(t)}{dt} = \gamma K(t) - \lambda N(t)^{\frac{2}{3}} K(t) - \mu K(t) \quad (4)$$

This model is strongly nonlinear, but by a logarithmic change of variables and some scaling transformation we are able to transform it into the semilinear form. More precisely, by the transformation:

$$\begin{aligned} &x = \ln N / N^*, y = \ln K / K^* \\ &x^* = y^* = 0, \tau = \beta t, \vartheta = (\gamma - \mu)/\beta \\ &x' = dx/d\tau, y' = dy/d\tau \end{aligned} \quad (5)$$

we are led from model (1), (4) to the following semilinear system:

$$\begin{aligned} x'(t) &= y(t) - x(t), \\ y'(t) &= \vartheta(e^{(2/3)x(t)} - 1) \end{aligned} \quad (6)$$

Application of antiangiogenic therapy can be incorporated in the model by a factor increasing multiplicatively the rate of loss of the vessels, which leads to the following equation:

$$\frac{dK(t)}{dt} = \gamma K(t) - \lambda N(t)^{\frac{2}{3}} K(t) - \mu K(t) - \eta K(t) u(t) \quad (7)$$

where $u(t)$ denotes the dose of the agent scaled to its effect on the vascular network, and η is a constant parameter and plays the role of a control variable. For the constant dose U, the equilibrium points take the form:

$$N^* = K^* = \left((\gamma - \mu - \eta U) / \lambda \right)^{3/2} \quad (8)$$

which, according to the conditions of stability given in [8], leads to the conclusion that:

$$U = (\gamma - \mu)/\eta \Rightarrow K^*, N^* = 0 \quad (9)$$

In other words, the vascular network and in turn the tumor can be eradicated, a conclusion which is crucial for the philosophy of the entire analysis. It is enough to ensure that the population of endothelial cells responsible for angiogenesis behaves in the required way because the size of the tumor population in some sense tracks the same transients. A similar line of reasoning could be applied in the case of combined antiangiogenic and chemotherapy when two control variables are present. The main difference is that chemotoxic agents kill both cancer and critical normal tissues including endothelial cells:

$$\frac{dN(t)}{dt} = -\beta N(t) \ln \frac{N(t)}{K(t)} - \psi v(t) \quad (10)$$

$$\frac{dK(t)}{dt} = \gamma K(t) - \lambda N(t)^{\frac{2}{3}} K(t) - (\mu + \eta u(t) + \xi v(t)) K(t) \quad (11)$$

where $v(t)$, the second control variable, denotes the dose of the chemotherapy scaled to its effect on tumor and normal tissues, and ξ and ψ are constant scaling parameters. Of course, the additional chemotherapy supports the effect of antiangiogenic therapy. Moreover the effect of tumor eradication may be achieved more easily and faster, although the theoretical results based on the theory of stability still have an asymptotic form. For constant doses of antiangiogenic and chemotoxic agents (denoted by U and V respectively), the equilibrium point is given by :

$$\begin{aligned} N^* &= ((\gamma - \mu - \eta U - \xi V)/\lambda)^{3/2} \\ K^* &= N^* e^{\xi V/\beta} \end{aligned} \quad (12)$$

In this case the equilibrium point is not the same for both populations, but it is related very closely, and it can be easily seen that the conditions for both its local and global asymptotic stability are similar to those given above. The main difference is that now both control actions "collaborate" in conditions for convergence of solutions of the model equations to 0. More precisely, the condition (9) should be substituted by:

$$U + \xi V/\eta = (\gamma - \mu)/\eta \Rightarrow K^*, N^* = 0 \quad (13)$$

The use of the previously considered transformation of variables leads to the following semilinear model of the combined anticancer therapy:

$$\begin{aligned} x'(t) &= y(t) - x(t) - \varepsilon v(t), \\ y'(t) &= \vartheta(1 - e^{(2/3)x(t)}) + \sigma u(t) + \varsigma v(t), \\ \sigma &= -\eta/\beta, \varepsilon = \psi/\beta, \varsigma = -\xi/\beta \end{aligned} \quad (14)$$

which will be used in further analysis. The main problem with these results is, however, their asymptotic character. In practice only a finite therapy horizon could be considered, which leads to the problem of the system's controllability.

IV. SEMILINEAR SYSTEMS AND THEIR CONTROLLABILITY

In this section, we study the general form of the semilinear stationary finite-dimensional control system described by the following ordinary differential state equation:

$$\underline{x}'(t) = A\underline{x}(t) + F(\underline{x}(t), \underline{u}(t)) + B\underline{u}(t) \quad (15)$$

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with zero initial conditions: $\underline{x}(0) = 0$, where the state $\underline{x}(t) \in R^n$ and the control $\underline{u}(t) \in R^m$, A is $n \times n$ dimensional constant matrix, B is $n \times m$ dimensional constant matrix. Moreover, let us assume that the nonlinear mapping $F: X \times U \to X$ is continuously differentiable near the origin and such that $F(0,0)=0$, and X and U denote state and control spaces, respectively.

In practice, admissible controls are always required to satisfy certain additional constraints. Generally, for arbitrary control constraints it is very difficult to give easily computable criteria for constrained controllability. However, for some special cases of the constraints it is possible to formulate and prove simple algebraic constrained controllability conditions. Therefore, we assume that the set of values of controls $U_c \subset U$ is a given closed and convex cone with nonempty interior and vertex at zero. Then the set of admissible controls for the dynamical control system (15) has the following form:

$$U_{ad} = L_\infty([0,T],U_c). \qquad (16)$$

For the semilinear dynamical system (15), it is possible to define many different concepts of controllability. In the sequel we shall focus our attention on the so-called constrained controllability in the time interval $[0,T]$. In order to do this, first of all let us introduce the notion of the attainable set at time $T>0$ from zero initial conditions, denoted shortly by $K_T(U_c)$ and defined as follows:

$$K_T(U_c) = \{\underline{x} \in X : \underline{x} = \underline{x}(T,\underline{u}),\ \underline{u}(t) \in U_c\} \qquad (17)$$

where $\underline{x}(t,u)$, $t > 0$ is the unique solution of the differential state equation (15) with zero initial conditions and a given admissible control $\underline{u} \in U_{ad} = L_\infty([0,T],U_c)$. Under the assumptions stated for the nonlinear term F, such a solution always exists. Now, using the concept of the attainable set, we recall the well-known definitions of constrained controllability in $[0,T]$ for a semilinear dynamical system.

Definition 1: The dynamical system (15) is said to be U_c-locally controllable in $[0,T]$ if the attainable set $K_T(U_c)$ contains a neighborhood of zero in the space X.

Definition 2: The dynamical system (15) is said to be U_c-globally controllable in $[0,T]$ if $K_T(U_c) = X$.

Now, we shall introduce certain notations and present some important facts from the general theory of nonlinear operators. Let U and X be given spaces and $g(\underline{u}): U \to X$ be a mapping continuously differentiable near the origin 0 of U. Let us suppose for convenience that $g(0)=0$. It is well known from the implicit-function theorem that if the derivative $Dg(0): U \to X$ maps the space U onto the whole space X, then the nonlinear map g transforms a neighborhood of zero in the space U onto some neighborhood of zero in the space X. In the more general case when the domain of the nonlinear operator g is Ω, U_c denotes a closed and convex cone in U with vertex at 0. In the sequel, we shall use for controllability investigations a property of the nonlinear mapping g, which is a consequence of a generalized open-mapping theorem. This result seems to be widely known, but for the sake of completeness we shall present it here, though without proof and in a slightly less general form sufficient for our purpose.

Lemma 1: Let X, U, U_c, and Ω be as described above. Let $g: \Omega \to X$ be a nonlinear mapping and suppose that on Ω nonlinear mapping g has derivative Dg, which is continuous at 0. Moreover, suppose that $g(0) = 0$ and assume that linear map $Dg(0)$ maps U_c onto the whole space X. Then there exist neighborhoods $N_0 \subset X$ about $0 \in X$ and $M_0 \subset \Omega$ about $0 \in U$ such that the nonlinear equation $\underline{x} = g(\underline{u})$ has, for each $\underline{x} \in N_0$, at least one solution $\underline{u} \in M_0 \cap U_c$, where $M_0 \cap U_c$ is a so-called conical neighborhood of zero in the space U. Using lemma 1 we study constrained local controllability in $[0,T]$ for a semilinear dynamical system (15) using the associated linear dynamical system.

$$\underline{z}'(t) = C\underline{z}(t) + D\underline{u}(t) \quad \text{for} \quad t \in [0,T] \qquad (18)$$

with zero initial condition $z(0)=0$, where

$$C = A + F_x(0,0) \qquad D = B + F_u(0,0) \qquad (19)$$

are n×n-dimensional and n×m-dimensional constant matrices, respectively. The main result is the following sufficient condition for constrained local controllability of the semilinear dynamical system (15) which will be used to study controllability of the model of combined anticancer therapy:

Theorem 1 [2]. Suppose that (i) $F(0,0) = 0$, (ii) $U_c \subset U$ is a closed and convex cone with vertex at zero, (iii) the associated linear control system (17) is U_c-globally controllable in $[0,T]$.
Then the semilinear stationary dynamical control system (17) is U_c-locally controllable in $[0,T]$.

In practical applications of Theorem 1, the most difficult problem is to verify the assumption (iii) about constrained global controllability of the linear time-invariant dynamical system. In order to overcome this difficulty, we may use the following Theorem.

Theorem 2 [2]: Suppose the set U_c is a cone with vertex at zero and nonempty interior in the space R^m. Then the associated linear dynamical control system (17) is U_c-globally controllable in $[0,T]$ if and only if:

(1) it is controllable without any constraints, i.e.

$$\text{rank}[D,CD,C^2D,...,C^{n-1}D] = n \qquad (20)$$

(2) there is no real eigenvector $w \in R^n$ of the matrix C^{tr} satisfying inequalities

$$w^{tr}D\underline{u} \le 0, \text{ for all } \underline{u} \in U_c. \qquad (21)$$

These theorems could be proved using the generalized open mapping theorem.

V. CONTROLLABILITY OF THE MODEL OF THERAPY

Now, let us consider the constrained local controllability of the model of combined anticancer therapy described by the semilinear differential state equations (14) defined in a given time interval $[0,T]$.
In this case the state vector $\underline{x} = [x, y]^T$, the control vector $\underline{u} = [u, v]^T$, and $\underline{z}$ is the state of the associated linear system. Taking into account the general form of the semi-linear dynamic system we have:

$$A = \begin{bmatrix} -1 & 1 \\ 0 & 0 \end{bmatrix}$$

$$F(x,y,u,v) = \begin{bmatrix} 0 \\ -\vartheta(e^{(2/3)x} - 1) \end{bmatrix}$$

$$B = \begin{bmatrix} 0 & -\varepsilon \\ \sigma & \zeta \end{bmatrix} \qquad (22)$$

Hence, we have:

$$F(0,0,0,0) = \begin{bmatrix} 0 \\ 0 \end{bmatrix}$$

$$F_x(0,0,0,0) = \begin{bmatrix} 0 & 0 \\ -\vartheta\frac{2}{3} & 0 \end{bmatrix}$$

$$C = A + F_x(0,0,0,0) = \begin{bmatrix} -1 & 1 \\ -\vartheta\frac{2}{3} & 0 \end{bmatrix} \qquad (23)$$

In order to consider the controllability of dynamical system (14) we use the Theorems presented in the previous section. The admissible controls are assumed to be positive, hence the set of admissible controls is a positive cone U_c in the space R^2.

The characteristic polynomial for matrix C^{tr} has the form:

$$P(s) = \det(sI - C^{tr}) = \det\begin{bmatrix} s+1 & \frac{2}{3}\vartheta \\ -1 & s \end{bmatrix} = \qquad (24)$$

$$= s^2 + s + \tfrac{2}{3}\vartheta$$

Therefore the discriminate of the characteristic polynomial is : $\Delta = 1 - \frac{8}{3}\vartheta$

and the characteristic equation $P(s) = 0$ has two roots.

It is necessary to consider the following three cases:

I. $\Delta < 0$, for $\vartheta > \frac{3}{8}$

In this case, we have two complex eigenvalues

$$s_1 = 0.5(-1 - j\sqrt{\Delta}) = 0.5(-1 - j\sqrt{1 - \tfrac{8}{3}\vartheta})$$

and when the eigenvalues are complex, then the system is constrained controllable.

II. $\Delta = 0$, for $\vartheta = \frac{3}{8}$

In this case, we have one real eigenvalue

$s_{12} = -0.5$ with multiplicity 2.

Therefore, to verify controllability it is necessary to use Theorem 2. In order to do that we first find the eigenvector w of the matrix C^{tr}. From the spectral equation

$$C^{tr}w = -0.5w \qquad (25)$$

the real eigenvector has the following form:

$$w = \begin{bmatrix} -1 \\ 2 \end{bmatrix}$$

thus

$$w^{tr} B\underline{u} = 2\sigma u + (\varepsilon + 2\xi)v > 0 \qquad (26)$$

for all positive controls. Therefore, there is no real eigenvector satisfying (21). Hence, taking into account Theorem 2 the system is controllable with positive admissible controls.

III. $\Delta > 0$, for $\vartheta < \frac{3}{8}$

In this case, we have two different real eigenvalues. Hence, to verify controllability we use Theorem 2. The real eigenvalues have the following form:

$$s_1 = 0.5(-1 - \sqrt{1 - \tfrac{8}{3}\vartheta}) < 0$$

$$s_2 = 0.5(-1 + \sqrt{1 - \tfrac{8}{3}\vartheta}) < 0$$

Therefore, the corresponding real eigenvectors are

$$w_1 = \begin{bmatrix} -1 \\ -s_1^{-1} \end{bmatrix} \quad \text{and} \quad w_2 = \begin{bmatrix} -1 \\ -s_2^{-1} \end{bmatrix}$$

Thus,

$$w_1^{tr} B\underline{u} = -s_1^{-1}\sigma u + (\varepsilon - s_1^{-1}\xi)v > 0$$

$$w_2^{tr} B\underline{u} = -s_2^{-1}\sigma u + (\varepsilon - s_2^{-1}\xi)v > 0$$

for all positive controls.

Therefore, there is no real eigenvector satisfying inequality (21). Hence, taking into account Theorem 2 the system is controllable with positive admissible controls. Summarizing, the semilinear dynamical system (14) is constrained controllable in a given time interval $[0,T]$ with positive controls. From the biological point of view, this means that if the size of the tumour and its vascular network is not too large then there exists a combination of antiangiogenic therapy and chemotherapy which enables eradication of the tumour. The important finding is that this property does not depend on the parameters of the model, whose estimation may be difficult. In the existing literature, e.g., [3], [8] one can find some estimates for the parameters, but their accuracy is of course very low. This may be not true if only one modality (e.g., antiangiogenic therapy) is used. As proved in [4], local constrained controllability of the model of antiangiogenic therapy is guaranteed only when its parameters satisfy additional conditions related to oscillatory behavior in the untreated case.

VI. CONCLUSION

In this study, we have shown how, by using quite simple models, we can analyze and design therapy protocols of combined antiangiogenic and chemotherapy of tumors. This type of cancer treatment is still in experimental and clinical trials. The results are promising, but knowledge of the processes behind the evolution of cancer vascular networks, the equilibrium between stimulatory and inhibitory factors, different forms of antiangiogenic therapy, its side effects. and the results of combined use of different treatment modalities is still far from being complete. The important finding presented in this paper is that sufficient conditions of local constraint controllability for the simple model of combined therapy are satisfied independent of its parameters, which is not true for the model of antiangiogenic therapy alone [4]. A more realistic model should take into account drug resistance of the cancer cell population caused by cytotoxic agents (see, e.g., [7]). Of course the situation *in vivo* is more complicated than the two-compartment models considered in this paper but, in our opinion, it may be treated similarly and may lead to similar qualitative results. The results will not change if linear pharmacokinetics of antiangiogenic and/or cytotoxic drugs is included in the model. Qualitatively, the controllability problem will change if delays in the dynamics of tumor growth and vascular network development are taken into account, and such a model was proposed in [21] and analyzed without control terms in [22]. We hope that its controllability could be also examined using theorems presented in [23] based on the similar mathematical engine.

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