Singular Controls in Systems Describing Tumor Anti-Angiogenesis

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Abstract: Anti-angiogenic therapy is a novel treatment approach for cancer that aims at preventing a tumor from developing its own blood supply system that it needs for growth. Since it does not target cancer cells, but healthy cells instead, it is not prone to developing drug resistance, the main obstacle to successful cancer chemotherapy. In this paper a class of systems for anti-angiogenic treatments is considered as optimal control problems and the optimality of singular controls is analyzed.

Key–Words: Optimal control, singular controls, high-order conditions for optimality, cancer treatments

1 Introduction

The reason for the failure of most cancer chemotherapy treatments lies in both intrinsic and acquired drug resistance. Malignant cancer cell populations are highly heterogeneous and fast duplications combined with genetic instabilities provide just one of several mechanisms which allow for quickly developing acquired resistance to anti-cancer drugs. In addition, intrinsic resistance makes some cancer cells not susceptible to many cytotoxic agents. Healthy cells, on the other hand, are genetically very stable and do not develop similar features. So, while the cancer population becomes increasingly more resistant to the drugs, these keep on killing the healthy cells eventually leading to a failure of the therapy.

One approach to cancer treatments that tries to circumvent the problem of drug resistance is tumor anti-angiogenesis. A growing tumor, after it reaches just a few millimeters in size, no longer can rely on blood vessels of the host for its supply of nutrients, but it needs to develop its own vascular system for blood supply. In this process, called *angiogenesis*, endothelial cells produce growth factors that stimulate the proliferation of the tumor cell population. Angiogenic inhibitors target the endothelial cells aiming to prevent the tumor from developing its own blood vessel system and thus blocking its growth. Ideally, the tumor, deprived of necessary nutrition, regresses. Since the treatment targets normal cells, no occurrence of drug resistance has been reported in lab studies.

In this paper we consider the question of how to schedule a given amount of angiogenic inhibitors to achieve a maximum tumor reduction as an optimal control problem. The underlying model is a two-dimensional system with the volume of primary tumor cells, p, and the volume of the vascular endothelial cells, q, as variables. The basic structure of the dynamical model follows the mathematical model for the evolution of tumor anti-angiogenesis as it was formulated and clinically validated by Hahnfeldt, Panigrahy, Folkman and Hlatky in [5] and we use this model and two of its modifications, one considered by d'Onofrio and Gandolfi in [3], the other by Ergun, Camphausen and Wein [4], to illustrate our computations. However, much of the analysis can be carried out for models with general inhibition terms $I = I(p, q)$ and stimulations terms $S = S(p, q)$ that define the dynamics of the endothelial cells. A Gompertzian growth model with a variable carrying capacity defined by the endothelial cells is used for the primary tumor volume.

2 Mathematical Models for Dynamic Anti-Angiogenic Monotherapy

The mathematical model we consider is based on the underlying medical research performed by Hahnfeldt, Panigrahy, Folkman and Hlatky [5], but for mathematical reasons we slightly modify their notation. Let p denote the volume of primary tumor cells and let q denote the volume of the vascular endothelial cells. A growth function describes the size of the tumor and here is chosen as Gompertzian with a variable carrying capacity defined by the volume of endothelial cells, q. Thus the rate of change in the volume of pri-

mary tumor cells is given by

$$\dot{p} = -\xi p \ln\left(\frac{p}{q}\right) \tag{1}$$

where ξ denotes a tumor growth parameter. The models we consider differ in the equation modelling the rate of change in the volume of vascular endothelial cells. Endothelial cells produce growth factors that stimulate the proliferation of the tumor cell population, but also have receptors which make them sensitive to inhibitors of inducers of angiogenesis like, for example, endostatin. Thus the overall dynamics is a balance between stimulation and inhibition and its basic structure is of the form

$$\dot{q} = -\mu q + S(p,q) - I(p,q) - Guq \tag{2}$$

where I and S denote inhibition and stimulation terms and the terms μq and Guq that have been separated from the general terms, describe, respectively, loss to the endothelial cells through natural causes (death etc.), and loss of endothelial cells due to additional outside inhibition. The variable u represents the control in the system and corresponds to the angiogenic dose rate while G is a constant that represents the anti-angiogenic killing parameter. Generally μ is small and often this term is negligible compared to the other factors and thus in the literature often μ is set to 0 in this equation.

The problem of how to administer a given amount of inhibitors to achieve the "best possible" effect arises naturally. One possible formulation, considered also in [4], is to solve the following optimal control problem: for a free terminal time T, minimize the value $p(T)$ subject to the dynamics (1) and (2) over all Lebesgue measurable functions $u : [0,T] \to [0,a]$ which satisfy a constraint on the total amount of anti-angiogenic inhibitors given,

$$\int_0^T u(t)dt \leq A. \tag{3}$$

Here a is a maximum dose at which the inhibitors can be given. The solution to this problem gives the maximum tumor reduction achievable with a given amount of inhibitors. Mathematically it is more convenient to adjoin the constraint as third variable and consider the problem in $\mathbb{R}^3$. Hence we consider the following optimal control problem:

[OC] For a free terminal time T, minimize the value $p(T)$ subject to the dynamics (1), (2), and $\dot{y} = u$ with initial conditions p_0, q_0 and $y(0) = 0$, over all measurable functions $u : [0,T] \to [0,a]$ for which the corresponding trajectory satisfies $y(T) \leq A$.

In the paper by Hahnfeldt et al. [5] a spatial analysis of the underlying consumption-diffusion model was carried out that led to the following two principal conclusions about the qualitative relationships between inhibition and stimulation terms:

1. The inhibitor will impact endothelial cells in a way that grows like volume of cancer cells to the power $\frac{2}{3}$. (The exponent $\frac{2}{3}$ arises through the interplay between the surface of the tumor and the volume of endothelial cells.)

Thus in [5] the inhibitor term is taken in the form

$$I(p,q) = dp^{\frac{2}{3}}q \tag{4}$$

with d a constant, the death rate. The second implication of the analysis in [5] is that:

2. The inhibitor term will tend to grow at a rate of $q^\alpha p^\beta$ faster than the stimulator term where

$$\alpha + \beta = \frac{2}{3}. \tag{5}$$

However, the choice of α and β is not imperative in their analysis and in fact is one of the main sources for other models considered in the literature [3, 4]. In their original work [5], Hahnfeldt et al. select $\alpha = 1$ and $\beta = -\frac{1}{3}$ resulting in the simple stimulation term

$$S(p,q) = bp \tag{6}$$

with b a constant, the birth rate. However, other choices are possible and, for example, choosing $\alpha = 0$ and $\beta = \frac{2}{3}$ results in the equally simple form

$$S(p,q) = bq \tag{7}$$

chosen in [3]. In that paper the dynamics for both these models is analyzed and it is shown for the uncontrolled system that there exists a unique globally asymptotically stable equilibrium (which, of course, is not viable medically). Adding a control term, this equilibrium can be shifted to lower values, or, depending on the parameter values, even eliminated altogether. In the latter case all trajectories converge to the origin in infinite time. This, in principle, would be the desired situation.

A characteristic of the dynamic behavior of either system is that, compared with the p-dynamics, the q-dynamics is fast; the system very much has a differential-algebraic flavor. In fact, as is argued in [4], compared to the real situation observed in labs, in the model the system tends to reach its steady state too fast. Since p and q tend to move together in steady

state, there is some freedom in selecting the terms in the dynamics and Ergun, Camphausen and Wein in [4] modify the $\dot{q}$ equation to

$$\dot{q} = -\mu q + bq^{\frac{2}{3}} - dq^{\frac{4}{3}} - Guq. \tag{8}$$

The justification for this change or approximation lies in a better balance in the dynamics for the substitution of stimulation and inhibition, but the inhibitor in this model is now only proportional to the tumor radius. Also, the dynamics itself is a simplification in the sense that it eliminates a direct link between tumor cells p and endothelial cells q. We summarize the functional forms for the inhibition and stimulation terms in these three models in Table 1:

Model	$I(p,q)$	$S(p,q)$	Reference
(A)	$dp^{\frac{2}{3}}q$	bp	[5]
(B)	$dp^{\frac{2}{3}}q$	bq	[3]
(C)	$dq^{\frac{4}{3}}$	$bq^{\frac{2}{3}}$	[4]

Table 1: Models for inhibition and stimulation

Models (A) and (B) have the same globally asymptotically stable equilibrium point $(\bar{p}, \bar{q})$ for the uncontrolled system, $u = 0$, namely $\bar{p} = \bar{q} = \left(\frac{b-\mu}{d}\right)^{\frac{3}{2}}$. For model (C) this value shifts a bit, but agrees for $\mu = 0$. These values naturally are too high to be acceptable and the medically relevant region is contained in the domain $\mathcal{D} = \{(p,q) : 0 < p \leq \bar{p},\ 0 < q \leq \bar{q}\}$.

The following statement about the dynamical behavior of systems (A) and (B) is an easy corollary of the results proven in [3] and is also easily verified for model (C) [7].

Proposition 1 *For each of the models (A), (B) and (C), given any admissible control u and arbitrary positive initial conditions p_0 and q_0, the corresponding solution (p,q) exists for all times $t \geq 0$ and both p and q remain positive.* □

If we denote the region where the variables are positive by $\mathcal{P}$, $\mathcal{P} = \{(p,q) : p > 0, q > 0\}$, then this is the statement that $\mathcal{P}$ is positively invariant for any admissible control. For arbitrary functions I and S such a statement cannot be made a priori, but clearly the state variables need to remain positive for the model to make sense. In the general setting, we therefore assume that

(+-inv) $\mathcal{P}$ is positively invariant for any admissible control u, i.e. given any admissible control u and arbitrary positive initial conditions p_0 and q_0, the solutions (p,q) to (1) and (2) exist for all times $t \geq 0$ and remain positive.

3 General Properties of Optimal Solutions

It follows from classical results that there exists an optimal solution to our problem [2]. However, for some initial conditions this may be $T = 0$, i.e. the minimum value is already attained for the initial condition. This situation arises when the amount of available inhibitors simply is not sufficient to reach a point that would have a lower p-value than p_0. Given the Gompertzian growth dynamics (1) this happens since the tumor volume increases in the region $\mathcal{P}_- = \{(p,q) \in \mathcal{P} : p < q\}$ regardless of the control. In such a case, tumor growth can only be delayed as much as possible by administering inhibitors at full dose until they are exhausted, but mathematically this is not the "optimal" solution for problem [OC].

Definition 1 *We say an initial condition $(p_0, q_0) \in \mathcal{P}_-$ is* ill-posed *if for any admissible control it is not possible to reach a point (p,q) with $p < p_0$. In this case the optimal solution for the problem [OC] is given by $T = 0$. Otherwise (p_0, q_0) is* well-posed *and the optimal time T will be positive.*

It is clear that all initial conditions with $(p_0, q_0) \in \mathcal{P}_+ = \{(p,q) \in \mathcal{P} : p > q\}$ are well-posed (since p decreases in $\mathcal{P}_+$). In this paper we only consider well-posed initial conditions.

First-order necessary conditions for optimality of a control u are given by the *Pontryagin Maximum Principle* [10, 1]: For a row-vector $\lambda = (\lambda_1, \lambda_2, \lambda_3) \in (\mathbb{R}^3)^*$, we define the Hamiltonian $H = H(\lambda, p, q, u)$ as

$$\begin{aligned} H &= -\lambda_1 \xi p \ln\left(\frac{p}{q}\right) + \lambda_3 u \\ &\quad + \lambda_2 \left(-\mu q + S(p,q) - I(p,q) - Guq\right). \end{aligned} \tag{9}$$

Then, if u_* is an optimal control defined over the interval $[0,T]$ with corresponding trajectory (p_*, q_*, y_*), there exist a constant $\lambda_0 \geq 0$ and an absolutely continuous co-vector, $\lambda : [0,T] \to (\mathbb{R}^3)^*$, such that the following conditions hold: (a) $(\lambda_0, \lambda(t)) \neq (0,0)$ for all $t \in [0,T]$, (b) λ_3 is constant and λ_1 and λ_2 satisfy the adjoint equations

$$\dot{\lambda}_1 = -\frac{\partial H}{\partial p}(\lambda(t), p_*(t), q_*(t), u_*(t)), \tag{10}$$

$$\dot{\lambda}_2 = -\frac{\partial H}{\partial q}(\lambda(t), p_*(t), q_*(t), u_*(t)), \tag{11}$$

with transversality conditions $\lambda_1(T) = \lambda_0$ and $\lambda_2(T) = 0$, (c) the optimal control u_* minimizes the Hamiltonian along $(\lambda(t), p_*(t), q_*(t))$ over the control set $[0, a]$ with minimum value given by 0. □

We call a pair $((p, q, y), u)$ consisting of an admissible control u with corresponding trajectory (p, q, y) for which there exist multipliers (λ_0, λ) such that the conditions of the Maximum Principle are satisfied an *extremal* (pair) and the triple $((p, q, y), u, (\lambda_0, \lambda))$ is an extremal lift (to the cotangent bundle). Extremals with $\lambda_0 = 0$ are called abnormal while those with a positive multiplier λ_0 are called normal. The following Lemmas summarize some properties of optimal controls and extremals for problem [OC] for well-posed initial conditions that we state without proofs.

Lemma 1 *Extremals are normal. The multipliers λ_1 and λ_2 cannot vanish simultaneously; λ_2 has only simple zeroes. The multiplier λ_3 is constant and non-negative.*

Lemma 2 *If u_* is an optimal control with corresponding trajectory (p_*, q_*, y_*), then at the final time $p_*(T) = q_*(T)$. If the inhibition term at the endpoint is larger than the stimulation term,*

$$S(p_*(T), q_*(T)) < I(p_*(T), q_*(T)) + (\mu + Ga)p_*(T), \tag{12}$$

then $y_*(T) = A$, i.e. all available inhibitors have been used up.

An optimal control u_* minimizes the Hamiltonian H over the interval $[0, a]$. This is equivalent to minimizing the linear function $(\lambda_3 - \lambda_2(t)Gq_*(t))v$ over $v \in [0, a]$. Thus, if we define the so-called *switching function* Φ as

$$\Phi(t) = \lambda_3 - \lambda_2(t)Gq_*(t), \tag{13}$$

then optimal controls satisfy

$$u_*(t) = \begin{cases} 0 & \text{if } \Phi(t) > 0 \\ a & \text{if } \Phi(t) < 0 \end{cases}. \tag{14}$$

A priori the control is not determined by the minimum condition at times when $\Phi(t) = 0$. However, if $\Phi(t) \equiv 0$ on an open interval, then also all derivatives of $\Phi(t)$ must vanish and this may determine the control. Controls of this kind are called *singular* while we refer to the constant controls as *bang* controls. Optimal controls then need to be synthesized from these candidates through an analysis of the switching function. For example, if $\Phi(\tau) = 0$, but $\dot{\Phi}(\tau) \neq 0$, then the control switches between $u = 0$ and $u = a$ depending on the sign of $\dot{\Phi}(\tau)$. In this paper we investigate the local optimality of singular controls.

4 Analysis of Singular Controls

We need to analyze the switching function and its derivatives. These computations can be expressed concisely within the framework of geometric optimal control theory and we therefore now write the state as $z = (p, q, y)^T$ and express the dynamics in the form

$$\dot{z} = f(z) + ug(z) \tag{15}$$

where

$$f(z) = \begin{pmatrix} -\xi p \ln\left(\frac{p}{q}\right) \\ -\mu q + S(p, q) - I(p, q) \\ 0 \end{pmatrix} \tag{16}$$

and

$$g(z) = \begin{pmatrix} 0 \\ -Gq \\ 1 \end{pmatrix}. \tag{17}$$

The derivatives of the switching function can easily be computed using the following well-known result that can be verified by a direct calculation.

Proposition 2 *Let h be a continuously differentiable vector field (written as a column vector), $h \in \mathbb{R}^3$, and define*

$$\Psi(t) = \lambda(t)h(z(t)). \tag{18}$$

Then the derivative of Ψ along a solution to the system equation (15) for control u and a solution λ to the corresponding adjoint equations is given by

$$\dot{\Psi}(t) = \lambda(t)[f + ug, h](z(t)), \tag{19}$$

where $[f, h]$ denotes the Lie bracket of the vector fields f and h. In local coordinates the Lie bracket is expressed as $[f, h](z) = Dh(z)f(z) - Df(z)h(z)$ with Df and Dh denoting the matrices of the partial derivatives of f and h, respectively. □

For the switching function Φ,

$$\Phi(t) = \lambda(t)g(z(t)) \tag{20}$$

we therefore have that

$$\dot{\Phi}(t) = \lambda(t)[f, g](z(t)), \tag{21}$$

$$\ddot{\Phi}(t) = \lambda(t)[f + ug, [f, g]](z(t)). \tag{22}$$

These formulas are crucial in the analysis of singular controls: If u_* is singular on some open interval J, then the switching function and all its derivatives vanish on J. It is a second-order necessary condition for minimality, the so-called Legendre-Clebsch condition [6], that

$$\lambda(t)[g, [f, g]](z(t)) \leq 0 \tag{23}$$

and if this quantity is negative, we say the *strengthened Legendre-Clebsch condition* is satisfied. In this case the singular control indeed is locally optimal and we can formally solve the equation $\ddot{\Phi}(t) = 0$ for the singular control as

$$u_{\sin}(t) = -\frac{\lambda(t)[f,[f,g]](z(t))}{\lambda(t)[g,[f,g]](z(t))}. \tag{24}$$

Because of the special form of the control vector field g, even for the general model these Lie brackets with g can be expressed in a succinct form: Let I denote the interval $(0,\infty)$ and for an infinitely often continuously differentiable function $f \in C^\infty(I)$ denote by $\mathcal{L}$ the linear differential operator

$$\mathcal{L} : C^\infty(I) \to C^\infty(I),\ f \mapsto \mathcal{L}f, \tag{25}$$

defined by

$$(\mathcal{L}f)(t) = tf'(t) - f(t). \tag{26}$$

Note that for any $\alpha \in \mathbb{R}$ the functions $f(t) = t^\alpha$ are eigenfunctions of this operator with eigenvalue $(\alpha - 1)$, i.e.

$$\mathcal{L}(t^\alpha) = (\alpha - 1)t^\alpha. \tag{27}$$

In particular, linear functions lie in the kernel of the operator.

If we set $\Delta = S - I$ and let the operator $\mathcal{L}$ act on the variable q, then a direct computation verifies that the Lie bracket of f with g is given by

$$[f,g](z) = G\begin{pmatrix} \xi p \\ \mathcal{L}(\Delta)(p,q) \\ 0 \end{pmatrix}. \tag{28}$$

For $n \in \mathbb{N}$ inductively define $\mathcal{L}^n$ as $\mathcal{L} \circ \mathcal{L}^{n-1}$. Then another computation verifies that

$$[g,[f,g]](z) = -G^2\begin{pmatrix} 0 \\ \mathcal{L}^2(\Delta)(p,q) \\ 0 \end{pmatrix} \tag{29}$$

and thus

$$\lambda(t)[g,[f,g]](z(t)) = -G^2\lambda_2(t)\mathcal{L}^2(\Delta)(p(t),q(t)). \tag{30}$$

In these equations the operator $\mathcal{L}$ only acts on the variable q with p as a parameter. Based on these computations the following result can be shown:

Theorem 1 *If a control u_* is singular on some open interval (α,β), then $\lambda_3 > 0$ and λ_2 is positive on the closed interval $[\alpha,\beta]$. If $\mathcal{L}^2(\Delta)(p(t),q(t)) > 0$ on (α,β), then the singular control is of order 1 and the strengthened Legendre-Clebsch condition is satisfied. In this case there exists a locally minimizing singular curve $\mathcal{S}$ for problem [OC]. This curve is the locus of the points (p,q) where the vector fields f and $[f,g]$ are linearly dependent, i.e.*

$$\Delta(p,q) + \mathcal{L}(\Delta)(p,q)\ln\left(\frac{p}{q}\right) - \mu q = 0. \tag{31}$$

The singular curve is admissible at points where the singular control defined by (24) takes values in the control interval $[0,a]$.

In the models (A)-(C) introduced above, the inhibition terms I and stimulation terms S are always given as powers of q and thus are all eigenfunctions of this operator $\mathcal{L}$. This allows for quick and simple computations:

(A) For the model by Hahnfeldt et al. [5] we have $S(p,q) = bp$ and $I(p,q) = dp^{\frac{2}{3}}q$ and thus by (27) $\mathcal{L}(S) = -S$ and $\mathcal{L}(I) = 0$. Hence $\mathcal{L}(\Delta) = \mathcal{L}(S) - \mathcal{L}(I) = -S$ and thus

$$\mathcal{L}^2(\Delta) = \mathcal{L}(-S) = S > 0. \tag{32}$$

Hence by Theorem 1 there exists a locally minimizing singular curve for model (A). Fig. 1 depicts the singular curve for the following parameter values from [5], $\xi = \frac{0.192}{\ln 10} = 0.084$ per day (adjusted to the natural logarithm), $b = 5.85$ mm per day, $d = 0.00873$ per mm per day, $G = 0.15$ kg per mg of dose, and $\mu = 0.02$. The solid curve represents the admissible portion of the petal like singular curve $\mathcal{S}$ for $a = 75$; the full singular curve is shown dashed. The qualitative structure shown in Fig. 1 is generally valid with the admissible portion shrinking for smaller values a.

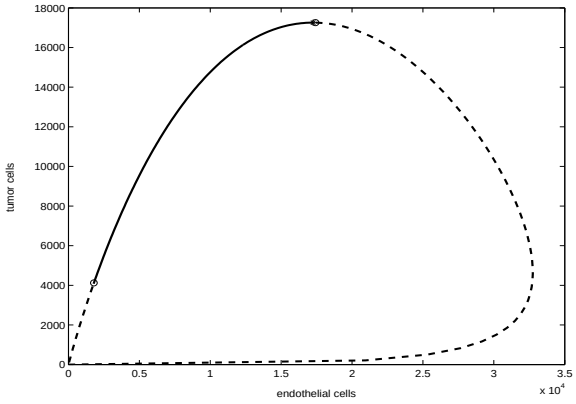

Figure 1: The singular curve for model (A)

(B) In the model considered by d'Onofrio and Gandolfi [3] both stimulation and inhibition are linear in q and therefore

$$\mathcal{L}(\Delta) = \mathcal{L}^2(\Delta) = 0. \tag{33}$$

Thus, while the Legendre-Clebsch condition is satisfied trivially, singular arcs would need to be of higher order. However, it is easily seen that the vector fields f, g and $[f,g]$ are in fact everywhere linearly independent in this case. But then H, Φ and $\dot{\Phi}$ cannot all vanish simultaneously and thus no singular curve exists. As shown in [9], for this system optimal controls are bang-bang.

(C) For the model by Ergun, Camphausen and Wein [4] we have $S(p,q) = bq^{\frac{2}{3}}$ and $I(p,q) = dq^{\frac{4}{3}}$ and thus $\mathcal{L}(S) = -\frac{1}{3}S$ and $\mathcal{L}(I) = \frac{1}{3}I$. In this case we therefore get $\mathcal{L}(\Delta) = -\frac{1}{3}(S+I)$ and thus

$$\mathcal{L}^2(\Delta) = \frac{1}{9}\Delta. \tag{34}$$

This quantity is positive in the relevant region $\mathcal{D}$ and thus, as for model (A), by Theorem 1 there exists a locally minimizing singular curve. Fig. 2 depicts the singular curve for this model with the same values as above, but the variable on the horizontal axis scaled as $x = q^{\frac{1}{3}}$. Again the admissible portion is marked by the solid line.

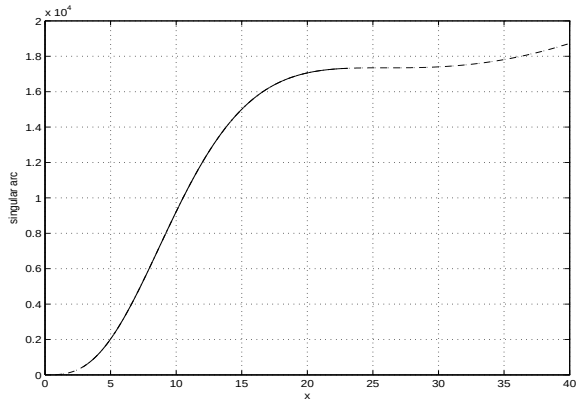

Figure 2: The singular curve for model (C)

5 Conclusion

In this paper we presented a general framework that allows for a quick determination of the local optimality status of singular controls for systems describing tumor anti-angiogenesis. It is much more difficult to establish the global optimality of these singular arcs and this requires the construction of a local synthesis. For both models (A) and (C) these constructions are explained in [8] and [7] and indeed for both models the singular arcs are also globally optimal and form an integral part of the corresponding optimal synthesis indicated in these papers.

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