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Optimal bacterial resource allocation

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Joint work with

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Dynamic Control and Optimization

Aveiro, February 2021

Honouring Andrey V. Sarychev's 65

Encounter first with the Portuguese team



Geometric control summer school, Bedlewo (2003)

"Even if he falls asleep during a talk, he will ask THE good question!"

Then Trieste, Dijon, Moscow, Paris... (often with Bernard)

Two seminal papers (among many others)

Second order optimality conditions (smooth case)

*Moscow University
Tom 113(155) (1986), Issue 3*

*Math. USSR Sbornik
Vol 41 (1982), No. 3*

THE INDEX OF THE SECOND VARIATION OF A CONTROL SYSTEM

UDC 518.3

A. V. SARVČEV

ABSTRACT. The constancy of sign of the second variation of a nonlinear control system is investigated. Sufficient conditions for controllability of second order and also sufficient conditions for optimality with respect to fast action of the extremals of this system analogous to the Legendre-Jacobi conditions of the classical calculus of variations are obtained.

Bibliography: 6 titles.

The paper is devoted to an investigation of controllability and optimality of nonlinear systems. The investigation of the second variation of the system gives essential information on the behavior of a control system in a neighborhood of a given extremal. The Morse index is the most important invariant of the second variation. The second variation of a control system has previously been studied by many authors; we note, in particular, the papers [1] and [2]. In the present paper a modification of the concept of a conjugate point of an extremal is considered. The structure of the set of conjugate points is investigated depending on whether or not the given extremal satisfies a strong regularity condition. In both cases a constructive method of finding the set of conjugate points and a method for computing the Morse index of the second variation are given.

We consider the problem of fast action

$$\dot{x} = f(x, u), \quad (1)$$

$$x(0) = 0, \quad x(T) = x_1, \quad (2)$$

$$T \rightarrow \min. \quad (3)$$

Here the phase vector $x \in \mathbb{R}^n$, f is a vector field which is smooth (of class C^∞) in x and twice continuously differentiable with respect to the parameter $u \in \mathbb{R}^m$, and the control $u(\cdot)$ is a measurable, essentially bounded function, $u(\cdot) \in L_\infty^m$. We call the control $u(\cdot)$ *admissible* for the system (1)–(2) on the interval $[0, T]$ if the solution of the equation

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

with initial condition $x(0) = 0$ assumes the value x_1 at time T . Let $\bar{u}(\cdot)$ be an admissible control on $[0, T]$ to be checked for optimality in problem (1)–(3). We rewrite the differential equation (1) in the form

$$\dot{x} = f(x, \bar{u}(t)) + (f(x, u) - f(x, \bar{u}(t))) = \bar{f}(x) + \delta f(x, v),$$

Leads to numerically computable conjugacy conditions

Two seminal papers (among many others)

Second order optimality conditions (bang-bang case)

FIRST- AND SECOND-ORDER SUFFICIENT OPTIMALITY CONDITIONS FOR BANG-BANG CONTROLS*

ANDREI V. SAHVICHEV†

Abstract. We study L_1 -local optimality of a given control $\bar{u}(\cdot)$ in the time-optimal control problem for an affine control system. We start with the necessary optimality condition – the Pontryagin maximum principle, which selects the candidates for minimizers, the extremal controls. Generally the corresponding Pontryagin extremals consist of bang-bang and singular subarcs, separated by switching points. In the present paper we treat only pure bang-bang extremals. We introduce extended first and second variations along a bang-bang extremal and establish first- and second-order sufficient optimality conditions for the bang-bang extremal controls.

Key words. optimal control problem, Pontryagin maximum principle, bang-bang extremals, sufficient optimality conditions

AMS subject classifications. 49J20, 49L30

PII. S0895475806283831

1. Introduction. We consider a nonlinear time-optimal control problem:

$$(1.1) \quad t \rightarrow \min,$$

$$(1.2) \quad \dot{q} = f(q) + G(q)u(\tau), \quad q(0) = q_0, \quad q \in M, \quad u \in U,$$

$$(1.3) \quad q(T) = q_1,$$

for an affine control system (1.2) with end-point condition (1.3) on a C^m -smooth n -dimensional manifold M . Here $G(q) = (g^1(q), \dots, g^l(q))$ and $f(q), g^1(q), \dots, g^l(q)$ are C^m -smooth vector fields on M ; admissible controls $u(\tau) = (u_1(\tau), \dots, u_l(\tau))$ are measurable and take their values in a convex compact polyhedron $U \subset \mathbb{R}^l$.

We set the problem of L_1 -local optimality according to the following definition.

DEFINITION 1.1. A pair $(\bar{u}(\cdot), \bar{q}(\cdot))$ meeting (1.2)–(1.3) for $t = T$ is called L_1 locally optimal if there exist $\Delta > 0$ and a ball $B_\Delta > \bar{u}(\cdot)$ in $L_1^l[0, T]$ such that no admissible control from B_Δ can steer the system (1.2) from q_0 to q_1 in time $T \in [T - \Delta, T]$.

A first-order optimality condition for the problem (1.1)–(1.3) is provided by the Pontryagin maximum principle (see [7]). If a pair $(\bar{u}(\cdot), \bar{q}(\cdot))$ inserts this principle for some concave function (Hamiltonian multiplier) $\bar{\lambda}(\cdot)$, then the triple $(\bar{u}(\cdot), \bar{q}(\cdot), \bar{\lambda}(\cdot))$ is called a Pontryagin extremal and $\bar{u}(\cdot)$ is called the extremal control. There can exist different Pontryagin extremals with different $\bar{\lambda}(\cdot)$ corresponding to the same extremal control $\bar{u}(\cdot)$.

In what follows we assume that the extremal control $\bar{u}(\cdot)$ is a piecewise C^1 -smooth function of τ . Then due to the Pontryagin maximum principle the domain $[0, T]$ of $\bar{u}(\cdot)$ can be subdivided into subintervals $0 = \tau_0 < \tau_1 < \dots < \tau_m < \tau_{m+1} = T$ in such way that for each $\tau \in [\tau_i, \tau_{i+1})$ the maximality condition of the Pontryagin maximum principle is fulfilled on a k_i -dimensional ($k_i \geq 0$) face W_i of the polyhedron U . The

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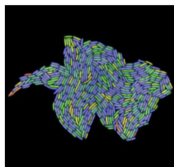
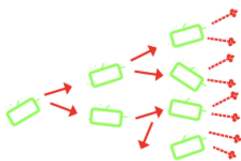
†http://www.siam.org/journals/sicon/45-1/28619.html

‡Department of Mathematics, University of Aveiro, 8010, Aveiro, Portugal (asah@ua.pt).

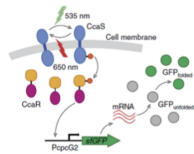
Paved the way for further analysis (Poggiolini, Stefanni et al)

Model definition

Optimal control of microbial cells (ANR Maximic, PI H. de Jong)



Stewart et al. (2005), *PLoS Biol.*, 3(2): e45



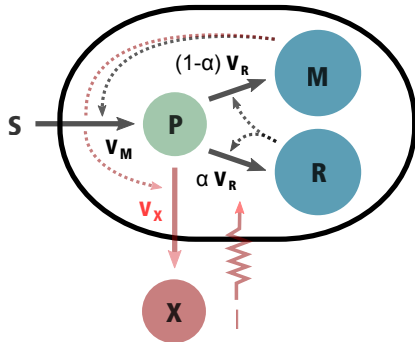
Miliás-Argeitis et al. (2019), *Nat Commun.*, 7:12546

- ▶ Self-replicator model: biomass maximisation (Giordano *et al*'16)
- ▶ Genetic engineering of a strain of bacteria: light-induced control of growth
- ▶ New pathway to produce a metabolite of interest (Egorov *et al*'18)
- ▶ Competition between biomass maximisation and metabolite production

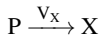
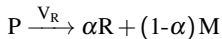
Yabo, A.; Caillaud, J.-B.; Gouzé, J.-L. Optimal bacterial resource allocation: metabolite production in continuous bioreactors. *Math. Biosci. Eng.* **17** (2020), no. 6, 7074–7100

Model definition

Self-replicator model



The model represents three chemical macroreactions between substrate (S), precursors (P), genetic machinery/ribosomes (R), metabolic machinery (M) and produced metabolite (X):



New control: $u(t) := \alpha(t)I(t)$

Model definition

Continuous stirred-tank reactor dynamics

In terms of concentrations s , p , r , x (and using $m+r=1$) in the CSTR,

$$S_1 : \begin{cases} \dot{s} = D(s_{in} - s) - v_M(s, 1-r)\mathcal{V}, \\ \dot{p} = v_M(s, 1-r) - v_X(p, 1-r) - \mu(p, r)(p+1), \\ \dot{r} = (u-r)\mu(p, r), \\ \dot{x} = v_X(p, 1-r)\mathcal{V} - Dx, \\ \dot{\mathcal{V}} = (\mu(p, r) - D)\mathcal{V}, \end{cases}$$

where \mathcal{V} is the volume of the cell population, D is the dilution rate, s_{in} is the substrate inflow, and

$$\mu(p, r) := \beta v_R(p, r)$$

(β = inverse of cytoplasmic density) is the growth rate of the bacterial population.

Assumption. The synthesis rates v_M , v_R and v_X are *monotone increasing kinetics* (e.g. Michaelis-Menten, $v_R(p, r) := k_R r p / (K_R + p)$) and

$$v_X(p, 1-r) = c(r) v_R(p, r).$$

Asymptotic behaviour

Mass conservation

Proposition. The set

$$\Gamma = \left\{ (s, p, r, x, \mathcal{V}) \in \mathbf{R}^5 : s_{in} \geq s \geq 0, p \geq 0, x \geq 0, 1 \geq r \geq 0, \mathcal{V} \geq 0 \right\}$$

is positively invariant for the initial value problem.

We assume $\mathcal{V}(0) > 0$ and $r(0) > 0$ (no growth otherwise).

Proposition. The ω -limit set of any solution of system S_1 with constant input $u(t) = \bar{u}$ lies in the set

$$\Omega := \left\{ (s, p, r, x, \mathcal{V}) \in \mathbf{R}^5 : s + \left(p + \frac{r}{\bar{u}} \right) \mathcal{V} + x = s_{in} \right\}.$$

This result is used to define a limit system and reduce the dimension by two.

Asymptotic behaviour

Limiting system

As $r(t) \rightarrow \bar{u}$ when $t \rightarrow \infty$ and since x can be eliminated (Ω), we define

$$S_1' : \begin{cases} \dot{s} = D(s_{in} - s) - \bar{v}_M(s)\mathcal{V}, \\ \dot{p} = \bar{v}_M(s) - \bar{\mu}(p)(p + \bar{c} + 1), \\ \dot{\mathcal{V}} = (\bar{\mu}(p) - D)\mathcal{V}, \end{cases}$$

where

$$\bar{v}_M(s) := v_M(s, 1 - \bar{u}), \quad \bar{v}_R(p) := v_R(p, \bar{u}), \quad \bar{v}_X(p) := v_X(p, 1 - \bar{u}), \\ \bar{\mu}(p) := \mu(p, \bar{u}), \quad \bar{c} := c(\bar{u}).$$

We study the local and global stability properties of this reduced system.

Asymptotic behaviour

Local stability

Theorem. Define

$$\bar{f}(p) := \bar{v}_R(p) + \bar{v}_X(p) + \bar{\mu}(p)p = \bar{\mu}(p)(p + \bar{c} + 1),$$

and let p_w be the solution of $\bar{f}(p) = \bar{v}_M(s_{in})$. Then,

- ▶ If $\bar{\mu}(p_w) \geq D$:
 - ▶ The interior equilibrium E_i exists, is unique and locally stable.
 - ▶ The washout equilibrium E_w exists, is unique and locally unstable.
- ▶ If $\bar{\mu}(p_w) < D$:
 - ▶ The interior equilibrium E_i does not exist.
 - ▶ The washout equilibrium E_w exists, is unique and locally stable.
- ▶ The interior equilibrium $E_i := (s_i, p_i, \mathcal{V}_i)$ with

$$\bar{\mu}(p_i) = D, \quad \bar{v}_M(s_i) = \bar{f}(p_i), \quad \mathcal{V}_i := \frac{D(s_{in} - s_i)}{\bar{v}_M(s_i)}.$$

- ▶ The washout equilibrium is $E_w := (s_{in}, p_w, 0)$.

Asymptotic behaviour

Sketch of proof. If $\bar{\mu}(\rho_w) \geq D$,

$$J_i = \begin{bmatrix} -D - \bar{v}'_M(s)\psi_i & 0 & -\bar{v}_M(s) \\ \bar{v}'_M(s) & \bar{f}'(\rho) & 0 \\ 0 & \bar{\mu}'(\rho)\psi_i & 0 \end{bmatrix},$$

and the characteristic polynomial is

$$P_i(\lambda) = (\lambda + D)(\lambda^2 + \lambda \underbrace{(D + \bar{v}'_M(s)\psi_i + (\rho + \bar{c} + 1)\bar{\mu}'(\rho))}_{>0} + \underbrace{\bar{v}'_M(s)\psi_i(\rho + \bar{c} + 1)\bar{\mu}'(\rho)}_{>0})$$

which, by Routh-Hurwitz criterion, implies that all eigenvalues have negative real part. If $\bar{\mu}(\rho_w) < D$,

$$J_w = \begin{bmatrix} -D & 0 & -\bar{c} \\ \bar{v}'_M(s) & -\bar{f}'(\rho) & 0 \\ 0 & 0 & \bar{\mu}(\rho_w) - D \end{bmatrix}$$

with characteristic polynomial

$$P_w(\lambda) = (\lambda + D)(\lambda + \bar{f}'(\rho))(\lambda - \bar{\mu}(\rho_w) + D). \quad \square$$

Asymptotic behaviour

Global analysis

Proposition. The ω -limit set of any solution of the limiting system S_1' lies in the set

$$\Omega' := \left\{ (s, p, \mathcal{V}) \in \mathbf{R}^3 : s + (p + \bar{c} + 1)\mathcal{V} = s_{in} \right\}$$

As $s = s_{in} - \mathcal{V}(p + \bar{c} + 1)$, one can further reduce S_1' to

$$S_1'' : \begin{cases} \dot{p} = \bar{v}_M(s(\cdot)) - \bar{\mu}(p)(p + \bar{c} + 1), \\ \dot{\mathcal{V}} = (\bar{\mu}(p) - D)\mathcal{V}. \end{cases}$$

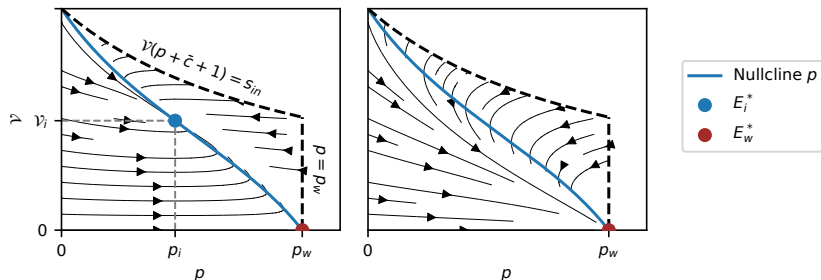
Proposition. Every solution of the limiting system S_1'' converges to

- ▶ $E_i^* := (p_i, \mathcal{V}_i)$ if $\bar{\mu}(p_w) \geq D$,
- ▶ $E_w^* := (p_w, 0)$ if $\bar{\mu}(p_w) < D$.

Sketch of proof. Bendixson-Dulac criterion allows to discard periodic orbits and cycles of equilibria as

$$\begin{aligned} \frac{\partial}{\partial p} \dot{p} + \frac{\partial}{\partial \mathcal{V}} \dot{\mathcal{V}} &= \frac{\partial}{\partial p} \bar{v}_M(s(\cdot)) - \bar{\mu}(p) - \bar{\mu}'(p)(p + \bar{c} + 1) + \bar{\mu}(p) - D \\ &= \bar{v}'_M(s(\cdot)) \frac{\partial s(\cdot)}{\partial p} - \bar{\mu}'(p)(p + \bar{c} + 1) - D < 0. \quad \square \end{aligned}$$

Asymptotic behaviour



Results on asymptotically autonomous systems (Thieme'92) eventually allow to relate the asymptotic behaviour of the 2-dimensional limiting system S_1'' to the behaviour of the full 5-dimensional system S_1 .

Theorem. Every solution of system S_1 converges to

- ▶ the extended interior equilibrium $\hat{E}_i := (s_i, p_i, \bar{u}, x_i, \gamma_i)$, $x_i := \bar{c}\gamma_i$, if $\bar{\mu}(p_w) \geq D$,
- ▶ the extended washout equilibrium $\hat{E}_w := (s_{in}, p_w, \bar{u}, 0, 0)$ otherwise.

Dynamic optimisation

Metabolite production

Maximisation of the metabolite X is considered over a finite time horizon:

$$\text{maximize } D\mathcal{V}_{\text{ext}} \int_0^T x(t) dt,$$

resorting to $(q := (s, p, r, x, \mathcal{V}) \in \mathbf{R}^5)$

$$(\text{OCP}) : \begin{cases} \text{maximize} & \int_0^T x(t) dt \\ \text{subject to} & \dot{q}(t) = F(q(t), u(t)), \\ & q(0) = q_0, \quad q(T) \text{ free}, \\ & u(t) \in [0, 1]. \end{cases}$$

Proposition. Existence holds.

Dynamic optimisation

Extremal flow

We write the (normal) Hamiltonian in terms of state $q := (s, p, r, x, \mathcal{V})$ and costate $\lambda := (\lambda_s, \lambda_p, \lambda_r, \lambda_x, \lambda_{\mathcal{V}})$:

$$H(q, \lambda, u) = -\lambda^0 x + \langle \lambda, F(q, u) \rangle,$$

where F is the right-hand side of S_1 . As the dynamics is control-affine, $H = H_0 + uH_1$ with

$$\begin{aligned} H_0 &= \lambda_s (D(s_{in} - s) - v_M(s, 1-r)\mathcal{V}) + \lambda_p (v_M(s, 1-r) - v_X(p, 1-r) - \mu(p, r)(p+1)) \\ &\quad - r\lambda_r \mu(p, r) + \lambda_x (v_X(p, 1-r)\mathcal{V} - Dx) + \lambda_{\mathcal{V}} (\mu(p, r) - D)\mathcal{V} - \lambda^0 x, \\ H_1 &= \lambda_r \mu(p, r). \end{aligned}$$

By virtue of Pontrjagin's maximum principle, a.e. one has

$$u(t) = \begin{cases} 0 & \text{if } H_1(q(t), \lambda(t)) < 0, \\ 1 & \text{if } H_1(q(t), \lambda(t)) > 0, \end{cases}$$

and the control is singular if H_1 vanishes along a whole subarc.

Dynamic optimisation

Singular arcs

Along a singular arc

$$0 = \dot{H}_1 = \frac{\partial H_1}{\partial q} \dot{q} + \frac{\partial H_1}{\partial \lambda} \dot{\lambda} = \sum_{i=1}^n \left(\frac{\partial H}{\partial \lambda_i} \frac{\partial H_1}{\partial q_i} - \frac{\partial H}{\partial q_i} \frac{\partial H_1}{\partial \lambda_i} \right) = \{H, H_1\} = \{H_0, H_1\} := H_{01}$$

and

$$0 = \dot{H}_{01} = H_{001} + uH_{101}.$$

Proposition. Singular arcs are at least of order two.

$$H_{101} = \mu(p, r) \left[\dot{\lambda}_r \mu_r(p, r) + \lambda_r \frac{\partial}{\partial r} \left(\mu_r(p, r) \dot{r} + \mu_p(p, r) \dot{p} \right) \right] \\ - \lambda_r \mu_r(p, r) \frac{\partial H_{01}}{\partial \lambda_r} - \lambda_r \mu_p(p, r) \frac{\partial H_{01}}{\partial \lambda_p}$$

which is also equal to 0 when $H_1 = 0$. \square

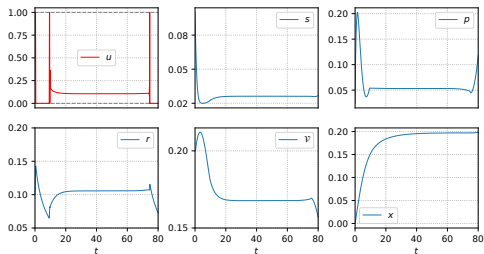
In the case of an order two singular control ($H_{10001} < 0$ along the arc, generalized Legendre-Clebsch condition)

$$u = -\frac{H_{00001}}{H_{10001}}.$$

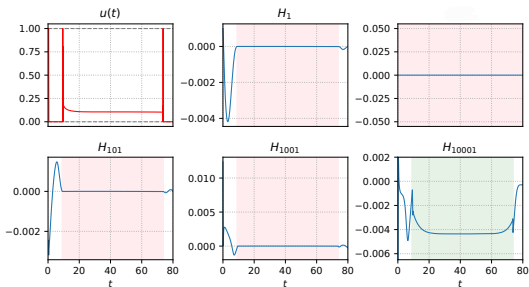
Although the order is *local* (H_{101} is not everywhere zero), one expects connection between bang and singular arcs through Fuller phenomenon.

Dynamic optimisation

Fuller phenomenon



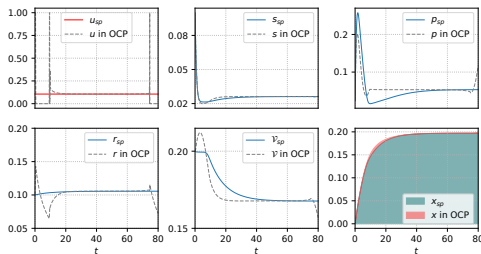
Generalized Legendre-Clebsch condition



Dynamic optimisation

Turnpike property

$$(SP)_X : \begin{cases} \text{maximize} & \bar{x} \\ \text{subject to} & F(\bar{q}, \bar{u}) = 0, \\ & 0 \leq \bar{u} \leq 1. \end{cases}$$



A Lagrange pair $(\bar{q}, \bar{u}, \bar{\lambda})$ of $(SP)_X$ defines a hyperbolic equilibrium of the Hamiltonian singular flow on $\Sigma'' := \{(q, \lambda) \mid H_1 = H_{01} = H_{001} = H_{00001} = 0\}$,

$$H_s(q, \lambda) := H(q, \lambda, u_s(q, \lambda)), \quad u_s(q, \lambda) := -\frac{H_{00001}}{H_{10001}}(q, \lambda).$$

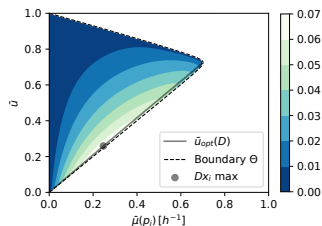
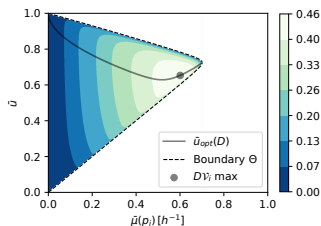
See Trélat-Zuazua'14, Pighin'16 in the regular case, ongoing work with S. Maslovskaya, W. Djema, J.-B. Pomet in the singular case

Static optimisation

Metabolite production vs. biomass maximisation

Maximisation is now performed wrt. the static control \bar{u} plus the dilution rate D of the CSTR:

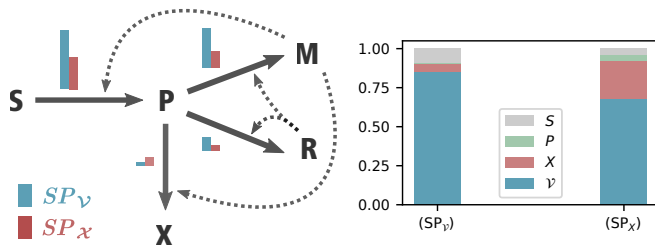
$$(SP_{\gamma}) : \begin{cases} \text{maximize} & D\bar{\gamma} \\ \text{subject to} & F(\bar{q}, \bar{u}) = 0, \\ & 0 \leq \bar{u} \leq 1, \end{cases} \quad (SP_X) : \begin{cases} \text{maximize} & D\bar{x} \\ \text{subject to} & F(\bar{q}, \bar{u}) = 0, \\ & 0 \leq \bar{u} \leq 1. \end{cases}$$



Proposition. Any solution of the two static problems lies in the region of existence of the interior equilibrium, $\bar{\mu}(p_w) > D$.

Static optimisation

Discussion



- ▶ 20% decrease of biomass (ν) but 500% increase of produced metabolite (χ)
- ▶ Difference between static and "gold standard" dynamic optimisation negligible for large fixed final time ($< 1\%$)
- ▶ Richer models: ubiquity of Fuller and (singular) turnpike phenomena
- ▶ Second order conditions in the Fuller case: preliminary approach in Agrachev-Beschastnyi'2020
- ▶ Reproducible research: ct (= control toolbox) initiative ct.gitlabpages.inria.fr/gallery

Standing on the shoulders of giants

Revaz Valerianovich Gamkrelidze
(born February 4, 1927)



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