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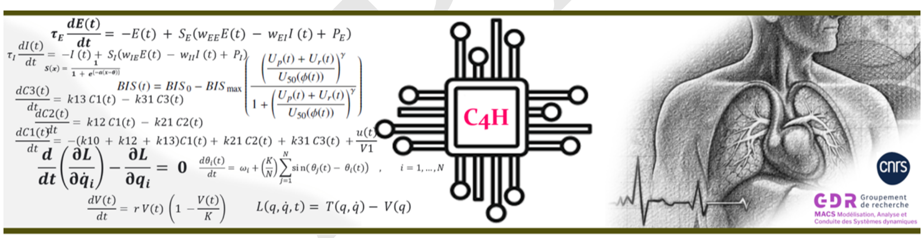
Control4Health

The emerging French community bridging control sciences and medical researches



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GdR MACS

Modélisation, Analyse et Conduite de Systèmes Dynamiques

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Contents

Chapter 1
Introduction

Jérôme Cieslak[1] Antoine Chaillet[2] and Jean-Julien Aucouturier[3]

The aim of this volume is to take stock of initiatives that have been (or are being) carried out in the French academic community of *control engineering* in direction of the healthcare sector, and to demonstrate that the sciences of control (French: *automatique*) are at the heart of various high-potential contributions. By focusing on six areas of application (anesthesia, oncology, cardio-respiratory system, diabetes, medical robotics, and neuroscience), the chapters included in this book do not claim to be exhaustive, but aim to provide a useful overview to facilitate the positioning of control in future national and international research initiatives, in order to respond to the needs expressed by the medical sciences and innovation community.

In this introductory chapter, we provide a short introduction to the Control for Health ("Control4Health") ecosystem, and detail the methodology that lead to the elaboration of this volume, which originated from the "Action: *l'Automatique au service de la Santé*" workgroup of the *Groupe de recherche "Modélisation, analyse et conduite des systèmes dynamiques"* (GdR MACS).

1.1 The field of control sciences

Control sciences, also described as control engineering and/or control theory (French: *automatique*), provides the scientific and technological basis for the design of decision-making systems (e.g. control laws, decision support systems, trajectory planning, etc.), which aim at interacting with processes. The wording 'interaction' means that actions of decision-making systems can take into account the measurements, perception and the environment of such processes to reach full autonomy. This positioning opens the way to initiatives in which processes are studied as dynamical systems.

In this context, control sciences develop methods and tools of different natures: *i*) *modeling* of dynamical systems – may they be physical, chemical, electronic, biological, mechanical, etc. –, *ii*) *identification* to estimate the parameters of this model based on experimental data, *iii*) *analysis* to predict and guarantee safety and performance properties of the coupling between the process and the decision-making system, *iv*)

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observation to estimate process variables that are not directly accessible to measurements, and *v*) *control design* in order for the decision-making system to steer the process towards the targeted behavior.

One of the key strength of control science is its common formalism to tackle these challenges, regardless of the considered application. It therefore proved successful (and even instrumental) in various disciplinary fields, including for instance transport, space, robotics, energy, and bioreactors. This book focuses in control science advances in the healthcare sector to highlight the emerging French community bridging Control4Health.

1.2 The emergence of Control4Health community

In 2011, Françoise Lamnabhi-Lagarrigue (CNRS, *Laboratoire des Signaux et Systèmes*) published the report (Lamnabhi-Lagarrigue, 2011) to highlight the contributions of control sciences in a number of societal challenges. This report, which was the result of a collective work within the HYCON2 network of excellence, also aimed at demonstrating that control sciences have high potential for tomorrow's challenges, and that this scientific topic was to be a priority in future regional and national work programs. In that report, three of the ten identified "crucial needs" for society were in the field of healthcare: neuroscience, blood glucose regulation, and cellular/biomolecular research. In these domains, the report identified several avenues of control research, including the design of automated methods for anesthesia, the control of blood glucose concentration for patients with diabetes using an assessment on "virtual" patients, and tumor growth inhibition to better predict and optimize the outcome of anti-tumor drugs combinations.

Fifteen years after this report, it is clear that the Control community has largely taken up issues related to the field of healthcare, with some results that have already crossed the threshold of translational research. This rise in prominence of health applications in the community of control sciences is now regularly highlighted in review papers. For instance, a 2017 *Annual Review in Control* article (Lamnabhi-Lagarrigue et al., 2017) discusses several of such healthcare applications (sections 3.4, 5.9, 5.10, 5.11 and 5.12 in that reference). More recently, the IEEE control system society published its *Control for societal-scale challenges* roadmap (Annaswamy et al., 2024) in which, once again, the healthcare sector was identified as one of the five 'societal drivers' for the 2030 horizon. In this context, the emergence of the Control4Health community is evident, and requires an inventory of the initiatives undertaken by the French control community.

1.3 Control4Health community in France

As part of the GdR MACS, a work group on health and control sciences has been created in 2022 (see *L'automatique au service de la santé: de la modélisation aux thérapies en boucle fermée*) to establish a situational analysis of research carried out by members of the French control community in the field of health.

An online questionnaire was distributed to the entire community of GdR MACS and SAGIP (*Société d'Automatique, de Génie Industriel et de Productique*), with an opening window to complete the questionnaire covering May to November 2022. We give here a short analysis of the 82 responses obtained to this questionnaire, which in our view gives a useful overview of the state of the community as of 2022.

Respondent profiles

Researchers who took part in the survey (see Figure 1.1.A) were mainly permanent staff (87%), with a majority of junior-rank positions (*maitre.ss.e de conférences / chargé.e de recherche*) (49%) and senior-rank positions (*Professeur.e des universités / directeur.rice.s de recherche*) (35%). Only two research engineers (*ingénieur.e d'étude ou de recherche*) replied to this questionnaire. Non-permanent respondents included only two Post-Doctoral researchers and nine PhD students. This number was probably much lower than the number of young colleagues actually involved on Control4Health, given the number of responses from permanent staff who are all potential supervisors.

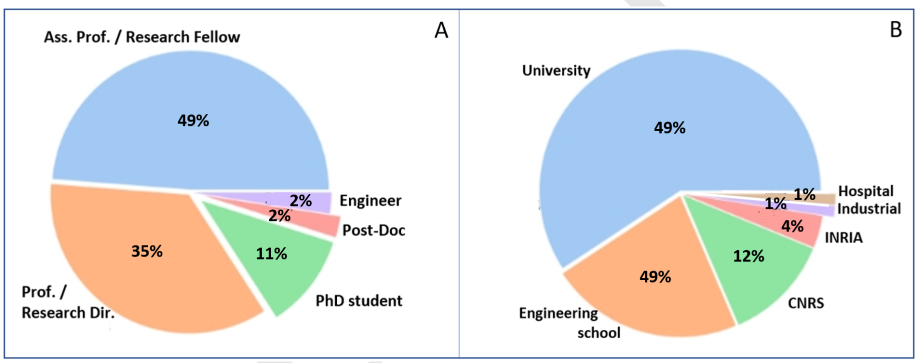

Fig. 1.1 **A**. Distribution of responses in terms of researcher position. **B**. Distribution of responses in terms of employer.

For the surveyed population, the employers were mainly universities (59%), engineering schools (22%) and non-teaching research institutions (CNRS: 12%; INRIA: 4%), see Figure 1.1.B. There was only one response from the industry and one from a PhD student co-financed by an hospital, which underlines that an effort is necessary to reach these groups in future campaigns.

Responses covered a wide range of 33 laboratories (with an average of 2.3 responses per laboratory), including 17 CNRS UMRs, spread relatively evenly across the country, see Figure 1.2. Thirteen laboratories contributed more than two responses, including most of the major laboratories in control and system engineering sciences: L2S (Gif/Yvette: 12 answers), FEMTO-ST (Besançon: 7 answers), LAMIH (Valenciennes: 7 answers), IMS (Talence: 6 answers), GIPSA-Lab (Grenoble: 5 answers), LS2N

(Nantes: 5 answers), CRAN (Nancy: 3 answers), Ampère (Ecully: 3 answers) and LAAS (Toulouse: 2 answers). The 17 CNRS UMRs among these were affiliated in majority to the CNRS *Sciences Informatique* institute (10) but 4 laboratories have a principal affiliation to the CNRS *Ingénierie* institute and no, or only secondary, affiliation to CNRS *Sciences Informatiques*. It should be noted that the 3 laboratories of the organizers accounted for 30% of the responses, which may reflect a bias (easier dissemination to colleagues) that needs to be monitored in future actions.

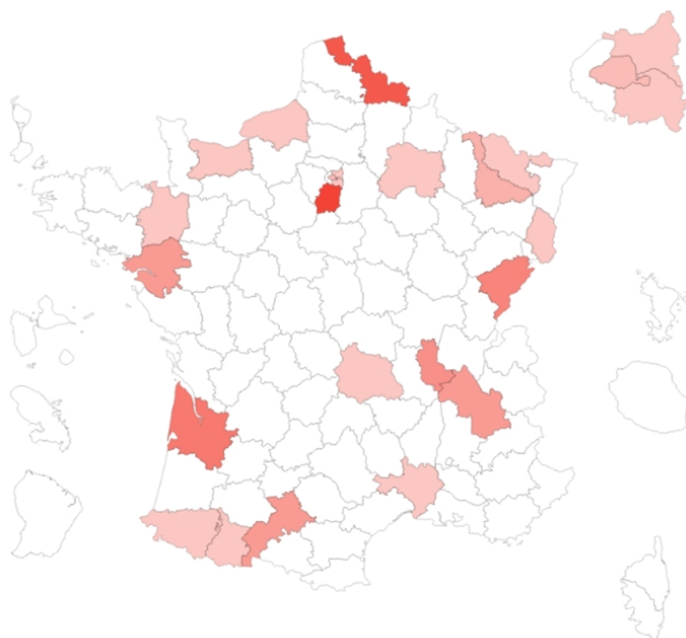

Fig. 1.2 Breakdown by department of origin of laboratories in France working on Control4Health, colour-coded by number of respondents.

Research activities

Figure 1.3 provides an overview of clinical domains addressed by the French Control4Health community. The research activities listed by respondents covered a wide range of clinical themes, including neurosciences (27% of the collected responses), movement and motor control sciences (21%), diabetes (20%), the cardio-respiratory system (18%), cancerology (16%), and epidemiology (15%). It should be noted that a lot of researchers declared working on several clinical areas. In addition to these purely medical fields, medical robotics was also mentioned in 17% of the responses, for activities which probably included a control part specific to these devices (e.g. control of flexible robotics), but was perhaps also confounded by more specifically robotic research (e.g. robotic architecture design, video sensing, etc.) suggesting it would also be useful to explore interdisciplinary interfaces with other research communities (e.g. GdR Robotics).

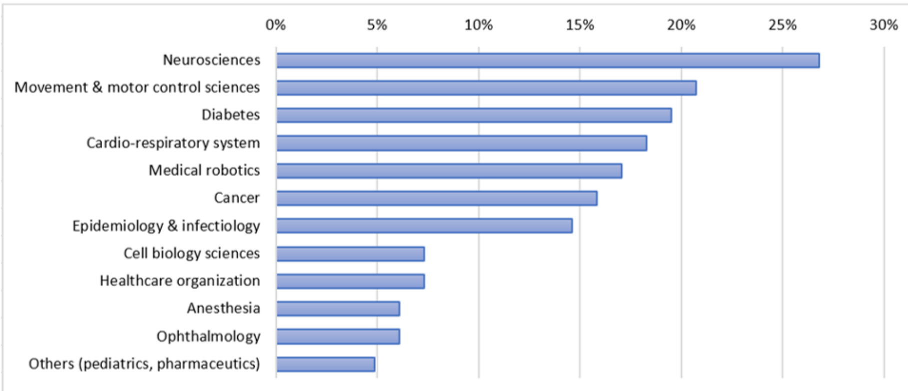

Fig. 1.3 Clinical domains addressed by control researchers who responded to the GdR MACS questionnaire, expressed in % of total number of respondents ($N = 82$).

From a Control perspective, these research activities covered most of the field's methodological subdomains, including modeling (mentioned by 72% of respondents), control design (65%), observers (41%), identification (37%) and analysis (33%). It should be noted that only 14 responses (17%) mentioned so-called "other" methodologies, describing them as AI/machine learning (9%), optimization (3%) and sensors (1%) to name a few. The small number of responses concerning these other domains, which are not typically considered as part of Control, reinforces our diagnosis of the existence of a genuine community specifically dedicated to Control4Health.

Publications

The questionnaire was also useful to compile an impressive bibliography of more than 260 references, including 66% of journal articles and 31% of conference papers. Publications involved more than 540 co-authors. This included both references in journals from the control engineering community (69%) and bioengineering one, but also a wide variety of biological/medical journals (27%). Figure 1.4 shows the word cloud extracted from the 268 collected publications.

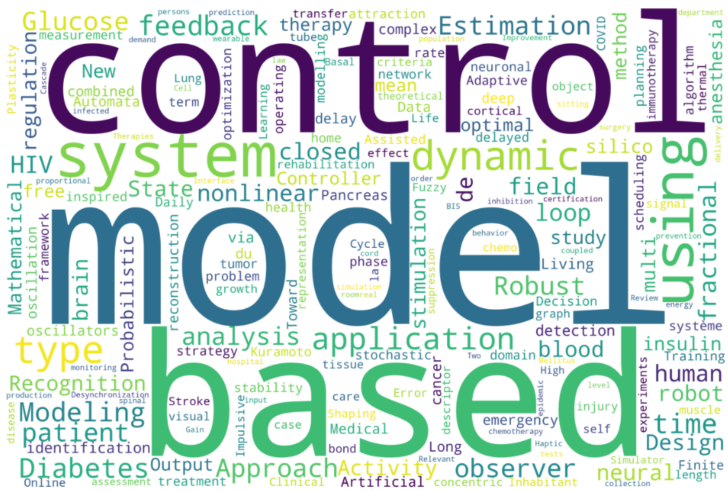

Fig. 1.4 Word cloud based on the titles of the 268 collected articles collected.

Identification of needs

The questionnaire also explored the perceived needs of researchers. The majority of researchers were in favour of organising internal communication (newsletter about project news: 88%; a dedicated website/portal on that topic: 87%) and collective scientific activities (organising scientific days: 83%; publishing a collective volume: 79%).

In addition, this work has made it possible to list some of the identified barriers to a more intensive use of control sciences for health-related research questions. The barriers most frequently reported included the difficulty of collecting and accessing medical data for researchers in control sciences (16%). Reasons listed by respondents were complex and obscure administrative procedure for the control theory community, but also ethical authorizations and confidentiality constraints. The difficulty of accessing clinical collaborators was also highlighted (11%), as well as difficulties identifying the right contacts willing to collaborate (7%), or the lack of time they have to devote to collaboration (6%). Finally, the lack of a dedicated funding for applied control sciences for health applications was also mentioned (11%).

1.4 About this volume

The present volume takes stock of the results of this survey, which we think reveals a genuine community interest for control-science approaches to health research questions. In the following pages, we have invited key French researchers in six of the most active medical application domains (anesthesia, cancerology, cardio-respiratory system, diabetes, medical robotics and neurosciences) to review what they think is the state of art of their field. Each chapter, in its own manner, endeavors to give a short introduction to the key physiological or clinical properties of its system of interest; to review the key advances, past and present, obtained in the French research community; to position these results on a wider international research scene; and to identify the outstanding questions that the field will be addressing in the next 5-10 years. We sincerely thank each of the contributors to this volume for the time and energy they devoted to this project.

What these six chapters show, in our view, is that Control4Health is an important, but largely unrecognized emerging theme in the French research ecosystem. As will be evident in the following pages, the field engages with clearly articulated research questions that lie at the sharpest-possible interdisciplinary edge between information science and biology; it boasts an already steady stream of solid results, with several world-first applications in e.g. diabetes, neurology or cardiology; it is grounded on a well-connected network of small but active research teams spanning the country, many of which established in the past 5-10 years; and it has a vast potential for growth, both in terms of fundamental research, clinical and industrial applications, and international collaboration.

Perhaps most importantly, while the six chapters of this volume make it evident that applying control science approaches to medical or physiological questions necessarily means grappling with domain specificities (the brain, heart or the glucose metabolism in diabetes do *not* have the same properties as dynamical systems, and the scientific and clinical needs for modeling, identifying or controlling these systems also differ), they also paint a clear picture that French Control4Health researchers exhibit much common ground as a community. The ties they share are manifold: scientific (e.g. accounting for individual variability in patient data, differentiating physiological vs pathological states in the same system, modeling slow dynamics in system parameters linked to biological or pathological rhythms, etc.), practical (e.g. access to data, access to clinical collaborators, etc.), and structural (teams working on different systems may be co-located in the same laboratories, and young researchers from one team may move on to subsequent research positions in another). It is our hope that this volume will further consolidate these links, and bring some well-deserved awareness to the community and its achievements.

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Chapter 2
Control sciences for Anesthesia

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2.1 Context and challenges

In the world of clinical healthcare, the practice of anesthesia is a critical part of the surgical process. Local, regional, or general anesthesia plays a fundamental role in providing surgeons with adequate operating conditions, avoiding discomfort or pain for the patient while reducing the adverse postoperative effects of surgery. In medical practice, general anesthesia includes the monitoring and control of the evolution of the areflexia (lack of movement), analgesia (lack of pain), and hypnosis (lack of consciousness) of the patient. Hypnosis is especially necessary to avoid the patient's awareness during surgery and therefore avoid any psychological trauma. In addition, the anesthesiologist is also responsible for the stability of the hemodynamic and respiratory system.

When administering general anesthesia to a patient during a surgical operation using intravenous drugs, the anesthesiologist controls the patient's state of sedation and analgesia (to avoid over- or under-dosing) by adjusting the infusion rate of drug substances according to clinical indicators such as heart rate, blood pressure, and BIS (Bispectral index). The latter, derived from the spectral analysis of the electroencephalogram (EEG) signal, mainly describes the depth of hypnosis of the patient. Although different drugs are used to produce different effects (hypnotic drugs for hypnosis, opioids for analgesia, and curare for areflexia, for instance) physicians must also take into account the interactions between substances. Common drug injection protocols are established a priori, based on statistical studies of patients. However, the considerable variability of patient reactions and sensitivity to drugs implies that the same concentration of an injected drug might have different effects in different patients, making open-loop control strategies ill-suited to control anesthesia.

The origin of the idea of controlling a patient's drug injection to maintain a safe and efficient level of anesthesia during surgery dates back to the 1950s (Soltero et al., 1951). Many advances have been proposed since then, especially in the last thirty years, applying several control strategies issued from control theory, and published both in anesthesia journals (Struys et al., 2005; Haddad and Bailey, 2009) and control journals (Beck, 2015; Nogueira et al., 2017), to cite a few. A survey paper from Ghita and co-authors (Ghita et al., 2020) illustrates the many directions investigated to control

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anesthesia. Moreover, several closed-loop infusion control strategies have been applied to real patients to evaluate their feasibility. Meta-analyses (Pasin et al., 2017; Brogi et al., 2017; Spataru et al., 2024) suggest that closed-loop control of anesthesia outperforms manual control in maintaining patient physiological parameters within a target range and may reduce post-anesthetic recovery time. However, further data are required to fully assess these conclusions.

Basically, control of anesthesia mainly concerns the induction and maintenance phases, while the control theory community has paid little attention to the reanimation phase. From a clinical point of view, the *induction phase* of anesthesia consists in the initialization of the sedation, through a given amount of drug (bolus) injected over a short time span. This phase is generally followed by a short time interval without any drug addition, before moving on to the *maintenance phase*, controlled either with an open-loop strategy (where the anesthesiologist actually acts as the controller) or a closed loop using physiological indicators such as the classical Bispectral index (BIS), such as (Absalom and Kenny, 2003) for instance. To dose the drug rate, anesthesiologists usually employ a target-controlled infusion (TCI) pump, which allows targeting a specific drug concentration level inside the patient's body using an open-loop strategy and relies on pharmacokinetic (PK) models that describe the kinetics of how drugs are disseminated, metabolized and eliminated by the body (see Box 1).

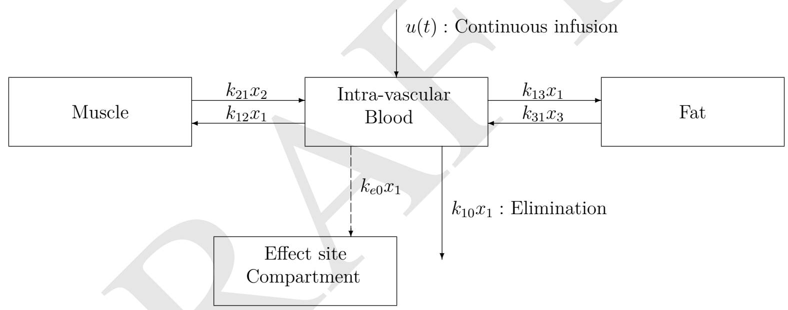
Traditional approaches to automatic control of anesthesia have aimed at designing a single control law that's common to both the induction and maintenance phases, for instance with techniques such as PID-based feedback control (van Heusden et al., 2014), adaptive control (Haddad et al., 2003), nonlinear control (Nogueira et al., 2017) or predictive control (Ionescu et al., 2008). However, this approach is now increasingly considered suboptimal. Indeed, the two phases have rather different control objectives: during induction, the goal is to optimize the trade-off between undesired overshoots of the BIS and long sedation intervals which are either associated with risk of patient recovering consciousness or longer recovery time (Zhang et al., 2011; Zorrilla-Vaca et al., 2017), whereas the aim during the maintenance phase is to maintain the BIS in the range [40,60] despite the exogenous disturbances coming from the surgery. If closed-loop monitoring is started as soon as the initialization phase, without a particular attention given to the induction phase, there is a high risk of BIS overshoot unless the induction phase is slowed down considerably compared to what would be done manually. For all these reasons, control strategies are now increasingly concerned with the maintenance phase, considering that the loop can be closed only after the patient has been initially sedated. A PID control algorithm based on the BIS information is used and clinically evaluated in (Absalom and Kenny, 2003). In (Zabi et al., 2015), a robust control strategy is developed for the maintenance phase of anesthesia, taking into account the saturation of the actuator, the multiple time scales of the drug dynamics, and the patient model uncertainty.

In control-engineering terms, the modeling and control of drug injection has given rise to a great deal of work on the analysis and synthesis of controllers (Bailey and Haddad, 2005; Caruso et al., 2009; Ghita et al., 2020; Coeckelenbergh et al., 2024), generally based on pharmacokinetic models which are now well established (Lemos et al., 2014). Nevertheless, a number of problems remain open:

- Control design is based on classical compartmental models which should be adapted to each patient: which key parameter(s) should be tailored for each patient?
- What measurement(s) can be used before/during surgery?
- Control in windows of non-observability is not really addressed;
- There are still too few clinical trials of closed-loop control;
- Control approaches generally consider continuous action, whereas discretely injected doses (such as pulses) are often applied. The use of hybrid systems with state jumps, for example, has never been considered to represent drug injections by syringes;
- In plus of using models, anesthesiologists consider knowledge about a given patient condition, such as comorbidities and medical history to infer the dosage of induction drug or target concentration. Thus, they may be more accurate than controllers based on models that do not consider this information. It could be interesting to propose controllers that benefit from these knowledge.
- Most of the work focuses on the control of hypnosis without linking it to analgesia, and in particular neglects the interaction between both types of drugs (Milne et al., 2003). Moreover hypnosis control is sometimes achieved through drug inhalation while analgesia is performed intravenously, leading to different delays in the MIMO control system.

Box 1: Pharmacokinetic-Pharmacodynamic models of anaesthesia

Drug absorption, circulation, metabolism and elimination from the patient body are complex phenomena. Mathematical models of drug dynamics, also know as pharmacokinetic/pharmacodynamic (PK/PD) models, are classically used to describe the evolution of drugs concentration in the patient's body, and are considered sufficiently expressive to represent the key ingredients of the drug dynamics in view of controller design (Lemos et al., 2014). PK/PD models are based on the classical three-compartment model (muscle/blood/fat) (Derendorf and Meibohm, 1999), associated to a first-order dynamics to links the concentration of drug in the central compartment to its action at the brain level, often denoted as the 'effect-site' compartment (Beck, 2015). This results in a simple four-state linear model, which parameters are the transfer rates of the drug between compartments, the rate of elimination from the central compartment and the blood volume. Challenges come from the fact that these parameters highly depend on each patient, vary during surgery, and are highly drug-dependent.



Several models have been suggested in the literature to account for different drugs and patient characteristis, typically their sex, age, weight and height. The most popular ones are the Schnider model (Schnider et al., 1998) and the Marsh model (Marsh et al., 1991), which consider propofol as hypnotic drug; and the Minto model (Minto et al., 1997) in which remifentanil is used as analgesic drug. Eleveld models for propofol (Eleveld et al., 2018) and remifentanil (Eleveld et al., 2017) are the most recent ones, have been validated on significantly more data and can be currently considered as the-state-of-the-art.

The depth of anesthesia indicator widely used by clinicians is the BIS (the bispectral index), which is a signal derived from the EEG analysis. The BIS quantifies the level of consciousness of a patient from 0 (no cerebral activity) to around 100 (fully awake patient). The relationship between the concentration at the effect site and the BIS is most often empirically described by a decreasing sigmoidal function (Bailey and Haddad, 2005), which introduces nonlinearity in dynamical models that relate drug injection as input to BIS as measured output, as do many control laws proposed in the literature. When considering the additional effect of opioid on the BIS, a sigmoidal surface is often used to describe the interaction between hypnotic and analgesic drugs. Other indicators may also be used (although less frequently for closed-loop control), a particular attention being dedicated to the pupil diffraction which may be used as an indicator of the analgesic state (Guignard, 2006), (Mazerolles, 2009).

2.2 Contribution of the French Control community

The topic of anesthesia has not attracted many researchers in the French control community before the past fifteen years and only a handful of teams are currently working on the subject. One of the first researcher in France who began publishing work concerning the control of anesthesia was Valérie Billard, medical anesthesist at *Institut Gustave Roussy* (Hentgen et al., 2002). Although it was not properly about closed-loop control, the core ideas of using compartmental models to determine the optimal concentrations of drugs given by target-controlled infusions were already present.

From a clinical perspective, the team of Ngai Liu, Marc Fischler and colleagues from *Hospital Foch* in Paris has been working on the subject since 2005, and have conducted multiple clinical trials to evaluate the feasibility of closed-loop control of anesthesia and the possible benefits, see (Liu et al., 2007; Dussaussoy et al., 2014; Liu et al., 2015; Mahr et al., 2021) to cite a few. Those trials have also included *Hospital V.-Dupouy* (Argenteuil), the *Saint-Augustin Clinic* (Bordeaux), the *University Hospitals of Besançon and Angers*. In most of those studies, the control algorithm used was a dual proportional-integral-derivative along with hard-coded rules to compute target propofol and remifentanil concentrations, then fed to the TCI to get the two drugs rates. In the same time, Cedrick Zaouter and colleagues from the *University Hospital of Bordeaux* have been working to test the McSleepy algorithm which allows dosing propofol, remifentanil and rocuronium (a drug for muscle relaxation) simultaneously. This controller, developed at McGill University (Canada), is also a mix of proportional control and hard-coded rules (Hemmerling et al., 2013). It is also worth mentioning the *Doloris Medical Systems* company, created in a public-private collaboration with the *University Hospital of Lille*, which main product is the Analgesia Nociception Index (ANI). This monitor of analgesia is based on the analysis of the effects of the respiratory fluctuations on the heart rate. A recent meta-analysis (Kim et al., 2023) has demonstrated its ability to accurately reflect pain and to reduce drug consumption when used as indicator in the surgery room.

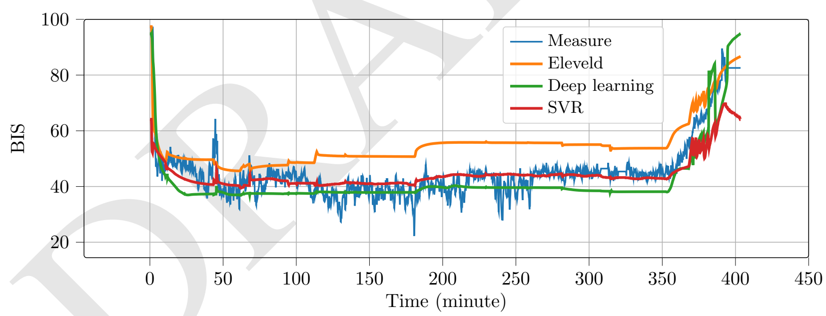
From a more control-theoretic point of view, a team at LAAS-CNRS (Toulouse) began to address the problem of control of anesthesia from 2010, with first publications dating almost 10 years ago. Teams at GIPSA-lab (Grenoble) and LAMIH (Valenciennes) have been also investigating this topic for a few years. The following sections illustrate several directions of research that have attracted their attention in the past ten years.

Although control of anesthesia may appear reasonably simple at first glance, considering the linear dynamic model to describe the evolution of drugs in the patient's body, it involves several modeling and control challenges. Many of them are related to huge model uncertainty, to the absence of direct measurement of anesthesia indicators, to the interaction of drugs, and to the presence of different time scale dynamics. We illustrate these challenges in the next sections.

2.2.1 Modeling

Data-based modeling:

As previously seen, the PK/PD family of models of anesthesia is widely accepted to represent the effects of intravenous drugs on the patient. However, such models are highly patient-dependent and are not able to fully capture the intra-patient variability, despite many attempts in the literature (Schnider et al., 1998; Marsh et al., 1991; Minto et al., 1997; Eleveld et al., 2018, 2017). In particular, the PD part of the model, which describe the interaction between drugs, has been less studied and is responsible for a large part of the uncertainties. In (Aubouin-Pairault et al., 2024b), a mixed data/model-based dynamical system has been proposed, using the classical PK model along with machine-learning regressor to replace the standard 3D-Hill function in the PD model. This model has been tuned and tested on the open-source VitalDB database (Lee et al., 2022), which includes high-resolution data from more than 6,000 surgeries. The results demonstrate that this approach allows to outperform standard models in terms of prediction accuracy for BIS and mean arterial pressure, reaching almost the same performance as deep-learning models (Lee et al., 2018) while keeping a linear dynamics, as only the static output function is a data-based regressor. An illustration of the results obtained with this apporach is given below (SVR in the figure).



Model identification:

In parallel, approaches for online identification have been proposed to adapt the model to each individual patient during surgery. In (Moussa et al., 2023) and (Aubouin-Pairault et al., 2024a), the authors proposed to use Moving Horizon Estimators (MHE) or Multiple Extended Kalman Filters (MEKF) to estimate both the system's states (drug concentrations) and the PD model parameters. Although the system is barely observable, the results show that the estimation is possible during the induction phase of the surgery, when the system is most actuated.

Open-source simulator:

In order to facilitate the development and comparison of control algorithms, two open-source simulators have been proposed to the research community, one for MATLAB (Ionescu et al., 2021) and another one for Python (Aubouin-Pairault et al., 2023). Both simulators allow to choose among different PK/PD model to test the control algorithms. In addition, the Python simulator allows simulating uncertainties in the patient model by sampling model parameters using the log-normal distribution. This allows one to employ the simulator in Monte-Carlo simulations, for instance.

2.2.2 From PID to advanced control strategies

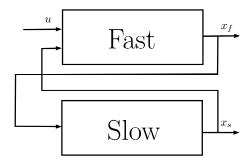
PID and MPC control:

While most of the clinical trials in France and in the rest of the world are using PID, the use of more advanced control strategies has also been investigated. Particularly, the use of Model Predictive Control (MPC) has been proposed in (Aubouin-Pairault et al., 2024c) along with the online identification method mentionned above. This method is based on an individual model of the patient used to compute the optimal drug rates to be delivered in order to reach a given BIS target. On the one hand, comparison with the PID method using Monte-Carlo simulations has demonstrated the superiority of MPC in terms of performance indicators such as time to reach the BIS target or propensity to undershoot. On the other hand, the MPC method requires more complex tuning and bigger computational resources. Clinical trials are still needed to fully assess the benefit of the method.

Multi-time scale dynamics control:

The dynamics of drug metabolism and circulation in the central and the effect-site compartments are ten times faster than in muscles, and a hundred times faster than in fat. A classical way to address this multi-scale problem is to describe the system as a singularly perturbed system, as done in (Tarbouriech et al., 2017). In such a case, the compartmental system describing the anesthesia model is re-expressed through a singularly perturbed system allowing to decouple the fast dynamics (blood, effect site) from the slow ones (muscles, fat). Many studies have addressed the synthesis of controllers for systems with such slow and fast dynamics (see the seminal work of (Kokotovic et al., 1999)). However, in contrast with general approaches for singularly perturbed systems, the main objective in the anesthesia context is to control and accelerate the fast system without interest in modifying the slow dynamics. Furthermore, the control design has to explicitly take into account the positivity of the states and inputs, as well as the upper limitation constraints of the variables during a surgery.

In (Queinnec et al., 2018), an alternative approach is investigated to separate slow and fast dynamics. The approach pursued is to synthesize a controller for the fast dynamics, considering the slow dynamics as a bounded perturbation of the fast system. This is made possible since the input signal (drug injection) directly acts on the fast dynamics, and, at the same time, the output information (typically the BIS) is directly related to the effect site concentration.



This means that the fast dynamics alone could be considered in the control design problem (this has been actually done in (Tarbouriech et al., 2017) for example), by considering the influence of the slow dynamics as a coupled disturbance which makes the problem more realistic. Then, any robust control design strategy can be considered to solve the problem of maintenance of anesthesia.

Probabilistic certification of control:

Obtaining theoretical guarantees in terms of convergence or constraints satisfaction is often unfeasible in the case of systems affected by significant uncertainties, such as the models involved in anesthesia. Alternative approaches exist, though, that permit to ensure some probabilistic properties under mild assumptions on the uncertainty distribution. In this line, the work of (Alamir et al., 2018) proposes a control strategy for propofol injection during anesthesia which is partially independent of the specific pharmacokinetics model, provided that bounds on the effects of the uncertainty are satisfied. The model allows a probabilistic validation of constraints satisfaction for the obtained control. Another approach for designing a PID controller that enforces probabilistic guarantees has been proposed in (Denardi Huff et al., 2024), in which the clinical knowledge on the model parameter distributions is exploited for the control design. The result is a PID law that ensures a predefined bound on the probability of undershooting during induction, while minimizing a performance metric.

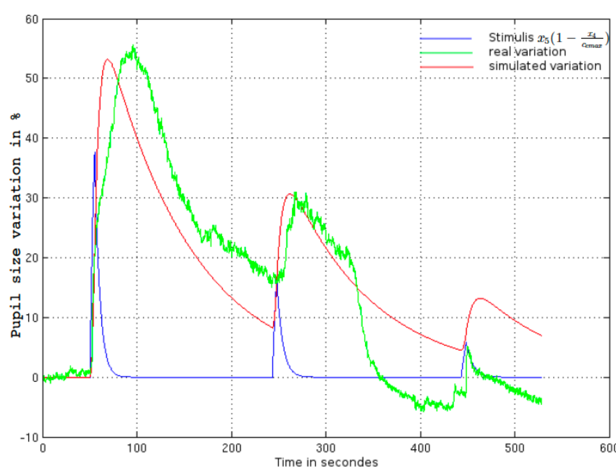
2.2.3 Measurement and control

Dead-zone observer-based control to compensate noisy BIS measurement:

Measurements are essential for closed-loop control and EEG signals may be corrupted by as much as 10% noise (Bailey and Haddad, 2005). Experimental data exhibiting noisy effects on the BIS evolution are, for example, given in (Beck, 2015). Rather than considering a filter, which introduces delay in the control process, the problem can be addressed by employing an adaptive dead-zone mechanism to do high-frequency noise rejection during the observation step. This has been done in (Tarbouriech et al., 2020), which proposes an observer-based control strategy, where a dead-zone observer is designed to mitigate the presence of output noise. The presence of multi-time scale dynamics in the anesthesia model is also considered, and the observer is designed for the fast subsystem. The global exponential stability of the complete closed-loop system in the noise-free case is guaranteed thanks to a linear matrix inequality condition; the paper also proves input-to-state stability in presence of noise.

Control based on pupillometry:

Since the BIS signal is an indicator mainly related to the hypnotic drug, although influenced also by the analgesic drug, it appears useful to also manipulate other indicators that are more specifically linked to analgesia. Pupil dilatation in response to nociceptive electric shocks may be used for this task (Guignard, 2006; Mazerolles, 2009). A control strategy that uses pupil size has been proposed in (Zabi et al., 2016b,a). The information used in the output feedback control is given by the smallest stimulus magnitude that induces a significant variation of pupil size. Actually, pupil size variation in reaction to an electrical pulse of given intensity is related to the effect-site concentration of drug. From a practical point of view, successive pulses of increasing intensity are delivered until pupil reaction exceeds some threshold. This means that the output signal is a quantized signal and that the control design must take this aspect into consideration, as illustrated below. Recently, monitoring pupillometry during anesthesia was shown useful to reduce opioid consumption compared to standard care (Van Santvliet and Vereecke, 2024), showing the relevance of such a measurement method.



2.2.4 Optimal induction and maintenance phase control

Even when closed-loop control strategies are enforced from the initial induction phase, they do not mimic the typical practice of human anesthesiologist who first administer an initial bolus dose of drug and then switch to the maintenance control phase. Few papers have intended to go in that direction, with the idea to mathematically validate the medical strategy. In control terms, the human strategy is a multi-phase control law, with consists first of open-loop bolus dosage during induction, and closed-loop continuous drug delivery during maintenance. Set theory, and in particular invariant sets (Blanchini and Miani, 2008) which ensure that the evolution of a system can be indefinitely maintained within a given set of the state space, have been used in (Fiacchini et al., 2016). The strategy proposed in the paper consists in decomposing the operation into three successive steps as: (i) a high constant value of drug addition; (ii) a zero addition of drug; and (iii) a control loop for the maintenance phase. The stability of such switching control is guaranteed by selecting appropriate instants for switching between the phases. Particularly, the switching instants are related to the trajectory entering the maximal control invariant set and the maximal invariant set.

A similar switching strategy that mimicks human medical practice is proposed in (Queinnec et al., 2019). The paper presents a switched controller that involves, first, optimal open-loop control at the induction phase and, second, closed-loop control for the maintenance phase. The strategy adopted for the first open-loop phase consists in designing a Pontryagin maximum principle-based optimal controller, which brings the fast state to the set-point in minimum time regardless of the slow ones. This indeed resembles the strategy employed by anesthesiologists, namely the initial injection of a large quantity of drug (bolus) for a short time, followed by a phase without addition of drugs. Then, as soon as the trajectory enters the invariant ellipsoidal domain, the controller may switched, with a guarantee of stability, to the closed-loop maintenance phase control.

2.3 The French community on the international scene

The French community active in the design and implementation of control methods for the monitoring and regulation of anesthesia has gained international relevance and recognition within the last decade. After the first results on the application and clinical validation of heuristic control methods in the first half of the 2010s (Liu et al., 2007; Dussaussoy et al., 2014; Liu et al., 2015), several research groups in France, connected to each other, have been contributing on the topic since around 2015. Some of these groups are found, for instance, at the LAAS-CNRS laboratory in Toulouse, GIPSA-lab and VERIMAG laboratories in Grenoble and, more recently, at LAMIH in Valenciennes.

While many excellent groups exist at the European level (see below), a possible specificity of French research in the field is a trend to incorporate theoretical knowledge from advanced control techniques, such as the theory of hybrid and nonlinear systems, machine learning and the theory of model predictive and optimization-based control and estimation, in a way that not only addresses problems that are inherent to anesthesia monitoring but also addresses fundamental properties of stability and controllability in these systems.

This theoretical inclination has provided a basis for collaboration with leading groups at the European level, such as Clara Ionescu and her colleagues from the University of Ghent, or by the team of Antonio Visioli at the University of Brescia. In particular, the GIPSA-lab and LAMIH teams are currently working on the definition and publication of a unified MATLAB/Python simulator to be proposed to the scientific community as a benchmark for implementing and testing control techniques for anesthesia. Common interests regarding the applicability of the theoretical results ensuring the stability are also identified.

Moreover, recent contacts have been established with Libera Fresiello and colleagues of the University of Twente (NL) working on the modeling of cardiovascular dynamics and the prediction of hypotension events during surgery under general anesthesia. This collaboration aims to establish a novel research line regarding the detection and prediction of critical events, so that anesthesiologists can apply preemptive treatment. Regular contacts with Alexander Medvedev (Uppsala university, Sweden) are also held with the aim of developing stochastic versions of the proposed stability algorithms. Finally, one can also mention a connection with Teodoro Alamo from the University of Sevilla, Spain, on the topic of applying learning optimization algorithms for the control of anesthesia.

If a main weakness must be pointed out for research currently conducted in France, it concerns the limited access to proprietary databases and restrictions holding on the clinical validation of our proposed approaches. Indeed, the process to access and exploit real clinical data in France can be potentially rather complex and time-demanding. Moreover, validating new monitoring and control methods in surgical rooms requires complex medical protocols, substantial collaboration with clinical researchers and, most importantly, time. Even in the form of auxiliary numerical assistance to the anesthesiologist and without directly affecting the patients, the requirements to introduce new methods in the operating room remain complex.

The recent establishment or strengthening of collaborations between the teams in Toulouse, Grenoble and Valenciennes and the anesthesiologists at University Hospitals in the three cities is encouraging, though. Several practitioners from the anesthesiology and intensive care unit departments at CHU Rangueil, CHUGA Grenoble and CH Valenciennes are either already involved in control-related scientific research, or have expressed their interest in participating.

2.4 Hot topics and open questions

Although the last decade has seen incremental improvements in the control of anesthesia, several challenges remain before closed-loop control becomes a reality in operating rooms.

First, the need for a clear objective function is still an open question. While most control algorithms are based on the BIS indicator, this does not fully reflect the actual practice of anesthesiologists, who besides BIS rely on the overall patient state, medical history, and the ongoing surgery operations. Most existing control systems are SISO or MISO, but the actual control of anesthesia is inherently a MIMO system. As discussed earlier, the lack of reliable measurements for analgesia is also a significant obstacle to the development of a comprehensive closed-loop control system for anesthesia. While we mentioned in the begining of section 2 new pain indicators such as ANI (Analgesia Nociception Index) or pupillometry, including the hemodynamic system in the control loop might also be part of the solution. For example, the team of Jin-Oh Hahn (University of Maryland) has explored this topic, proposing approaches that incorporate arterial pressure as a measurement variable with hypnotic drugs and crystalloid as input (Hohenhaus et al., 2024; Yin et al., 2025). Additionally, recent models of the effects of propofol and remifentanil on the hemodynamic system, proposed by the team of Douglas Eleveld (University of Groningen) (Su et al., 2022, 2023), could be used to design a MIMO control system. Obtaining more global estimates of patient state might also involve multi-modal data such as video or sound recordings. Recent advancements in multi-modal datasets, such as those published in (Özsoy et al., 2025), provide relevant insights into how next-generation algorithms could integrate information from multiple sources to estimate patient states and improve the anesthesia control.

The second issue is a certain lack of collaboration between the clinical and control communities. Few studies have focused on human-machine interaction with control algorithms. Although closed-loop methods have demonstrated efficiency in controlling the depth of hypnosis, they are not yet widely adopted in clinical practice. Some researchers suggest learning from the aviation industry to improve algorithm interfaces (Jabaley et al., 2020). They emphasize that engineers and anesthesiologists need to work together to design the next generation of clinical devices. The French community could particularly benefit from fostering interdisciplinary collaboration, as clinical trials and the development of new control methods have often been conducted in parallel without sufficient interaction between the two research communities.

Although simulations have improved with the development of open-source simulators and the inclusion of uncertainties in the modeling part, clinical trials are still needed to validate the control methods. This again requires a strong collaboration between the control and the medical community. The team of Antonio Visioli in Brescia is a good example of such collaboration, where the loop of algorithm design is closed with a real evaluation in the operating room. It is especially interesting to observe how their research have shifted from theoretical control methods to more practical considerations in order to satisfy the needs of the anesthesiologists. As stated in (Matias, 2023), "*Hu-*

mans and algorithms work together, so study them together".

Several experts believe that computer methods will help to improve patient safety and comfort during surgery while reducing anesthesiologist workload (Singh and Nath, 2022; Coeckelenbergh et al., 2023; Cai et al., 2025). Especially, data-based methods have shown incredible performances for various tasks in the last decade and will probably be used in anesthesia also. For instance, reinforcement learning (RL) has already been proposed for the closed-loop control of propofol in (Liu et al., 2020). One of the main challenges in the use of data-based methods is the accessibility of data. In fact, those methods rely on important amounts of data which are hard to obtain. Although multiple open-source datasets have been proposed during the last decade, such as VitalDB and Inspire from Korea, MIMIC, e-icu and MOVER in the USA, or AmsterdamUMCdb in the Netherlands, time resolution is often poor (e.g., the 5-minute sampling period in Inspire), data may be lacking (e.g., no bolus information in VitalDB), or documentation may be minimal (e.g., in the MOVER database). In France, accessing medical data is often an arduous task that requires time and connection with the medical practitioners. However, the development of clinical data warehouses such as PREDIMED in Grenoble might simplify the process in the future.

Finally, the ethical aspect of the use of closed-loop control in the operating room is still an open issue. The question of the responsibility of the anesthesiologist in case of failure of the algorithm is still not clear. To answer this question, we might have to learn from the autonomous automotive community, which switched its objective from a fully automated car to a co-piloted car (Awad et al., 2020). In the same way, the closed-loop control of anesthesia could be seen as a co-piloted system where the anesthesiologist is still in charge of the final decision but where the algorithm could propose a control action. This is, for instance, the idea of the AFM system commercialized by Edward LifeScience (Irvine, CA, USA), which proposes bolus volume to inject to the anesthesiologist for hemodynamic system control (Maheshwari et al., 2021).

In such a collaborative framework, the explainability and predictability of algorithms is a key aspect to ensure the trust of the anesthesiologist. For instance, the control algorithms clinically tested in France are mostly decision tree or PIDs which are simple to understand and directly explainable. A first step that could help to build such trust is the open-source sharing of the code. In fact, open-source science has gained significant interest in the last decade, contributing to build reproducible results and to install trust among the scientific community. While some researchers in the control community are still afraid that sharing their code might lead to the loss of their intellectual property, the open-source community has shown that sharing code can lead to more citations and more collaborations. For medical usage, we believe that it is even more important that algorithms introduced in the operating room should be at least tested by an external authority. While some regulations have been proposed, such as the European AI act for instance (see (Aboy et al., 2024) for its implication for medical devices), they are struggling to follow the pace of AI development and international regulation is still needed (Palaniappan et al., 2024). How to certify a control algorithm for medical usage is still an open question, to which we believe that the control community could bring some answers.

Future challenges to be addressed by the control community in the field of anesthesia control are thus numerous and require strong collaboration between the control and medical communities. The development of MIMO control algorithms, the design of human-machine interfaces, the organization of clinical trials, the development of data-based methods, the ethical aspects of closed-loop control, and the certification of algorithms are all topics that need to be addressed in the coming years. In this landscape, the European research community has proved to have the potential to propose innovative solutions and needs to be more organized to tackle those open questions.

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Chapter 3
Control sciences for Cancerology

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3.1 Context and challenges

3.1.1 A role for control in cancer research and treatment

Cancer denotes a set of diseases that are induced by abnormal cells transformation that excessively *proliferate* towards a significant mass of cells called **malignant tumor**. Some malignant cells invade neighboring cells and blood/lymphatic vessels forming the so-called **metastases** which are responsible of 90% of death cases.

Vascular Endothelial Growth Factor (VEGF) is one of the key factors in the initial development, progression and metastasis of tumors. As illustrated in Figure 3.1, VEGF is an angiogenic factor that is responsible for tumor vascularization (also known as tumor angiogenesis), providing a structural basis for the dissemination of cancer cells in the circulation.

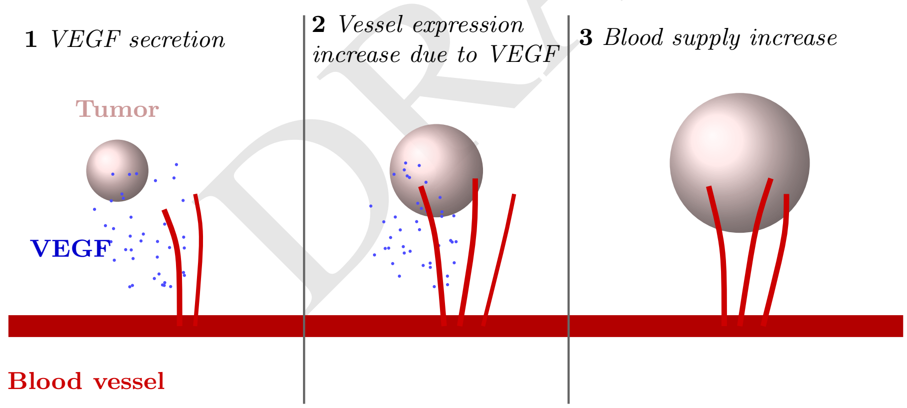

Fig. 3.1 Schematic illustration of tumor growth due to Vascular Endothelial Growth Factor (VEGF) secretion.

Rigorously speaking, cancer is **not a single disease**. Rather, it is a set of different

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pathologies that share the previously described guidelines but which correspond to various forms, origins and consequences. This underlying diversity is the source of major difficulties in handling the different aspects of cancer research, whether it is about diagnosis, modeling, prediction, drug derivation, prognostic and so on.

It comes without saying that cancer-related research is an immensely wide investigation area involving so many different domains such as physiology, biology, pharmacology, chemistry, statistics, membranes behavior, sociology and psychology to cite but few ones.

These different scientific approaches address different objectives, some of them can be sketched in the following definitively non exhaustive list:

- ✓ **Understanding** the detailed physiological phenomena that affect the populations and the states of the different types of cells involved.
- ✓ Building **tailored dynamical models** enabling faithful prediction of the different types of tumor growth or regression (including the drugs effects) as well as a minimal amount of rationalization of the decision making process.
- ✓ **Developing new drugs** and treatment therapies, including combined therapies involving multiple drugs.
- ✓ **Rationalizing & assessing** the chronology and the patient-state dependent drugs injection strategies and more generally the planning of the therapies. Moreover, **certifying** these strategies on a statistical basis.
- ✓ Building **statistics** providing probable causalities between tumors and nutrition patterns.

As far as applied mathematics is concerned (to which belongs the control engineering field for brevity), the early works concerned mainly two topics: *Modeling* and *open-loop Optimal control*. It is only later that works involving true feedback design involving robustness to parameter uncertainties started to appear[4].

Modeling approaches mainly consist in deriving compartmental models which generally take the form of a set of Ordinary Differential Equations (ODEs) (Westman et al., 2001; Bellomo and Preziosi, 2000; Thurber and Dane Wittrup, 2012) in which each compartment contains a single type of cells (healthy, malignant, circulating lymphocytes, natural immune cells, tumor induced immune cells, drug quantity in a specific areas, etc). The role of the model is to describe the growth, death, transfer and interaction between the compartments. Some of the so developed models are validated through comparison between the predicted behavior of measured quantities and the one obtained on real patients from clinical data. This modeling activity is still active given the huge variety of cancers and drugs possible combinations.

Open-loop optimal control-related works (Schättler and Ledzewicz, 2015; Castiglione

[4] It goes without saying that given the huge number of publications on the topics, the references provided in the discussion below are only a tiny set of representative samples.

and Piccoli, 2007; Itik et al., 2009) consider that the model is given and the parameters are perfectly known. The task is then to analyse the mathematical structure of the optimal drug dosage, generally by using the *Pontryagin Maximum Principle*. This enables to come out with some specific *patterns* of the optimal drug injection (intensive therapy, immunity enhancement first and chemotherapy later, etc). These patterns can be associated to different configurations (regions) of the initial state.

In spite of a seemingly relative early awareness of the importance of feedback in cancer treatment (Zajicek, 1980), **Feedback control**-related works appeared relatively lately as a natural answer to the necessary measurement-based adaptation of the drug injection initial planning. This results in a growing contribution of the control community and an increasing amount of work involving different control techniques ranging from model-free (Chareyron and Alamir, 2009b; Fliess et al., 2021), feedback linearization (Chien et al., 2009; Szeles et al., 2013), nonlinear control (Lodhi et al., 2019), Dynamic programming-based feedback (Jeong et al., 2022) to Model Predictive Control (Hirata et al., 2014; Sharifi et al., 2017; Hensley et al., 2015; Chareyron and Alamir, 2009b) and including recently developed learning and certification tools and paradigm that takes into account explicitly the statistics of parameters dispersion (Alamir, 2014; Moussa et al., 2021; Alamir, 2015, 2023).
It is nonetheless worth emphasizing that feedback control for cancer dynamics comes with its own set of challenges, because of the difficulty of measuring all the required information at any time. Therefore, as it will be discussed in the sequel, appropriate feedback schemes have to be developed in order to ensure the realism and the applicability of such control strategies.

3.1.2 Particularities of cancer-related control problems

The control problems related to the cancer therapy show some specific features that make them stand apart from standard control-related problems studied by the control communities, namely:

- Cancer treatment is **not a regulation/tracking** problem in which high gain-like approaches might be used to *compensate* for model *mismatches*. There is no given reference trajectory of the tumor that is to be tracked. One might think that this is regulation problem in which we need to regulate the tumor size at 0 value. While this is true, the need for long term consideration makes the use of high-gain uncertainty-killing approach generally inappropriate: it might for instance be necessary to wait for the immune cell's population size to grow thanks to immunity-enhancing drug before we can force the tumor to decrease.
- When the stochastic aspect is handled, contrary to economic costs that incorporate the expectation of some cost function, the cancer problem involves highly critical consequences of constraints violation. This requires the explicit consideration of the

standard deviation in the definition of the probabilistic cost function. This leads to problem's formulations that are **sensitive to risk**.

- By opposition to human-engineered mechanical or electrical systems (to cite but two examples) where the underlying laws are quite well known, the phenomena underlying the cancer dynamics are only very partially known. Only functional behavioral blocks can be used in the compartmental models with largely unknown relative importance and mathematical structure. The consequence of this is that the only way to compensate for this lack of knowledge is to consider **very high level of parameters mismatches**.
- The medical measurement techniques of the required information for any feedback scheme are widely different, ranging from several types of medical imaging (such as Computed Tomography and Magnetic Resonance Imaging scans) to different biological tests. These measurements have to follow a medical protocol, depending on the type of the cancer, its location and characteristics, making the availability of information about health indicators restricted to specific time instants. Furthermore, drug scheduling for cancer has also to follow a specific medical protocol, that is generally divided in two phases, for treatment and rest, which also adds other restrictions in terms of control actions that are constrained by given time windows, but also in terms of maximal concentration doses for drug toxicity issues. These cancer-related control particularities suggest that not all the standard control approaches are well-suited for cancer treatment scheduling, and that we have to think about **appropriate feedback schemes** that are able to take into consideration the different mentioned **constraints** and **restrictions**.

The cumulative effects of the above features lead to long-term consequences of model mismatches that require an explicit handling of the parametric mismatches. This fact has not been acknowledged sufficiently early in the literature as it is explained in the following section.

A biological primer on Cancerology

Cancer is about the proliferation process of abnormal cells that might be fatal for a human. Understanding how this population grows and interacts with its environment, including the natural defense system enhanced by the different potentially combined drugs is mandatory for a successful treatment.
The goal of a therapy is to decrease the number of proliferating malignant cells while preserving the health and the level of resistance of the patient. This is a critical process that highly depends on algorithms' capacity to correctly predict the consequences of an action in a highly uncertain context.

Due to the complexity of the phenomena and the highly uncertain and time-varying character of any prediction model, the use of appropriate measurement-based feedback is unavoidable in order to compensate for erroneous scheduling that might be induced by the unavoidable specificity of each patient.

In spite of the apparent evidence contained in the previous claim, advanced feedback laws are scarcely (if not never) clinically used because of many reasons, some of which are discussed below with some suggestions towards a better understanding and acceptance by practitioners.

In the discussion that follows, four family of drugs are mentioned which can be briefly described as follows:

– Chemotherapy: it is a type of anticancer that allows targeting the cell division process. A consequence of this is that chemotherapy causes damages to healthy tissues where cells are continually growing and dividing. In practice, several chemotherapeutic agents might be used in order to target cell division at different stages. This treatment is subject to drug resistance problems, due to the fast evolution of cancer cells towards new resistant phenotypes.

– Immunotherapy: this type of therapy helps to enhance the immune response of the body against cancer cells by stimulating it, it gathers many treatments such as monoclonal antibodies, cytokines, vaccines and CAR T–cell therapy, which all have different stimulation mechanisms.

– Anti-angiogenic: this type of treatment allows to reduce the tumor burden by inhibiting its vascular network, starving it of oxygen and nutrients. Although this type of therapy is known to have limited side effects compared to conventional chemotherapy, anti-angiogenic drugs are usually not able to completely eliminate a cancer.

– Vaccine: Cancer vaccines are treatments designed to stimulate the immune system to attack cancer cells by recognizing specific antigens.

3.2 Contribution of the French Control community

3.2.1 Some general facts

Before digging into the technical description of the contributions of the French community to the field of cancer, it is important to underline some major facts that provide the broad picture of the situation. These facts can be summarized by the following items:

1. There are **only few joint works with the practitioners** and hospitals-related research centers (see later for a discussion on the presumed reasons for such a regrettable fact).
2. The cancer research topics in the French control community seems to **serve as a support (an example)** for the validation of methodological control frameworks that might be applied to other domains. This is probably a consequence of the difficulty in establishing joint collaboration with cancer researchers. But it can be also a part of the reason for the lack of multi-disciplinary projects.
3. A highly coupled fact with the previous two items is that not a single contributor to the cancer-related works within the French control community considers the cancer as his/her own personal major research topic. Here again, this fact might be the source of the difficulty of being a part of large multi-disciplinary projects or a regrettable consequence of it.
4. Another highly coupled fact with the previous items is that the access to substantial data-bases is very limited, which might dampen any enthusiasm or motivation on the perspective of achieving substantial and meaningful contributions to the field. The difficulty of data accessibility might be due to the complex regulation in France, with respect to both data collection and use, but also more generally to the considerable variability of cancer-related problems, which makes it hardly achievable to collect a large amount of data related to single specific problems.

This being said, it is also a fact that the cancer paradigm provides a very specific and rich example of validation of many inventive and new solutions due to the particularities discussed in Section 3.1.2 which challenge the standard paradigms of the control community in general.

In order to properly describe the contributions, the following section starts by giving some notation that helps formalizing the problems being studied in a somehow unified way.

3.2.2 Definitions and notation

In the forthcoming presentation, the state vector involved in the compartmental models is supposed to be denoted by $x \in \mathbb{R}^n$. Moreover, let us systematically assume that

- The tumor size T (number of malignant cells) is the first component of the state vector, namely $T = x_1$;

- The number of circulating lymphocytes (a type of immune cells) L is the second component of the state vector, namely $L = x_2$;
- The vector of parameters involved in the compartmental model is denoted by p;
- The vector of drugs' injection rates is denoted by $u \in \mathbb{R}^{n_u}$ where n_u is the number of the drugs involved in the therapy.

Based on the above notation, it is assumed that one disposes of a set of ODEs of the form

$$\dot{x} = f(x, u, p) \tag{3.1}$$

to describe the considered cancer dynamics. This model might be used in the validation step for model-free design or in the control synthesis when model-based feedback control is targeted.

In the next section, the previously defined notation is used to briefly present the classes of contributions of the French control community to the cancer treatment issue. In the reminder of this section, the different contributions are successively described with the appropriate references.

3.2.3 Open-loop optimal control scheduling

The early work of (Alamir and Chareyron, 2007) participated in the flow of studies regarding the design of optimal nominal scheduling by approximating the solution of a constrained optimal control problem via a sequence of unconstrained optimal control problems.

Later on, the works in (Moussa et al., 2020, 2019) used the *generalized moment framework* to address the computation of optimal drugs injection when the parameter dispersion statistics is known. The underlying models are two-dimensional representing the tumor size and the population of immune cells. Obviously the proposed open-loop optimal control computation can be used within a receding-horizon scheme in order to recompute the new optimal injection schedule repeatedly. But this was not explicitly done in the above cited papers probably because of the computational burden associated to a single computation, in addition to the difficulty of accurately recovering the control profiles.

Furthermore, in (Dassow et al., 2021) optimal control of a nominal model representing the tumor-immune interactions was proposed using the Pontryagin's Maximum Principle, together with an a posteriori Monte-Carlo based assessment of the designed control, under some uncertainties on an interaction related parameter.

3.2.4 Nominal model-based feedback control design

In this category, the feedback is designed using the **nominal values of the model's parameter** vector. Then the impact of parameters mismatch is simply simulated in order to evaluate the extent to which the feedback control is able to compensate for model mismatch. This is a rather standard approach in control design. Such a scheme is proposed in (Chareyron and Alamir, 2009a) in which a **nonlinear constrained model predictive control** is designed for the triple immunotherapy/vaccine/chemotherapy. More precisely two different formulations of the underlying optimal control problem are considered:

- In the first, the optimization problem is defined as follows:

$$\mathcal{P}_1 : \quad \min_{u(\cdot)} x_1(t_f) \quad \text{under} \quad x_2(t) \geq x_2^{\min} \tag{3.2}$$

  which amounts at minimizing the terminal value of the tumor under health constraints regarding the minimum admissible number of circulating lymphocytes.
- In the second, the health concerns is used as a performance index under a constraint on the contraction rate ($\gamma \in (0,1)$) of the tumor, namely:

$$\mathcal{P}_2 : \quad \max_{u(\cdot)} \min_{t\in[0,t_f]} x_2(t) \quad \text{under} \quad x_1(t_f) \leq \gamma x_1(0) \tag{3.3}$$

In (Chareyron and Alamir, 2009a), comparison regarding the result of each formulation is provided and a success rate of the therapy is investigated for different control updating periods. Whether to use the one or the other of the above two formulation depends on the general context in which this small part of the problem is incorporated (sensitivity to the health condition versus the available time for the treatment that the person can afford for instance among many other criteria).

Although the nominal design is a standard scheme, the work in (Chareyron and Alamir, 2009a) takes into account the time's structure constraint consisting in systematically having **rest periods within the therapy duration** in order to cope with the real-life practice. This feature is recurrent in many of the forthcoming works that are discussed later on. Notice that the model used in the above mentioned work is the 6-dimensional model proposed and validated in (de Pillis et al., 2006).

In (Fliess et al., 2021), the two-state model of combined immunotherapy/chemotherapy (two drugs) proposed in (d'Onofrio et al., 2012) is used to design a **flatness** based controller that aims at steering the tumor towards its benign equilibrium (stabilization paradigm). A part of the control task uses model-free design as discussed in the next section.

3.2.5 Model-free feedback design

An ultimate acknowledgment of the complexity of modeling the phenomena underlying the cancer dynamics is to come out with a totally model-free design. Obviously, such a design needs to rely on some sort of presumed correlation between the quantity of drug injected and some key variables that are linked to the tumor dynamics that is taken as the target variable as well as the health indicator that needs to be monitored.

Such an approach is used in (Chareyron and Alamir, 2009b) which addressed exactly the same two formulations defined by (3.2) and (3.3) while using an on-line identified simple model governing the two key variables x_1 and x_2. The performances of the so-derived control laws are validated using the same model used in (Chareyron and Alamir, 2009a) leading to rather satisfactory results although no systematic certification is provided.

The model-free approach was partially used in (Fliess et al., 2021) to achieve the tracking of optimal trajectories that are computed using a **flatness** model-based design where the two-state model of (d'Onofrio et al., 2012) is used in the model-based design. Only the tracking task uses local model-free implementation.

3.2.6 Robust nonlinear control design

The work in (Alamir, 2014) is very probably the first academic applied mathematics-like work that addressed the problem of feedback design that takes into account explicitly the presence of parameter uncertainties. The underlying model is a two-state model representing the tumor size and the capacity of vasculature (representing the density of blood vessels). Two drugs are used, namely the chemotherapy and the anti-angiogenic drug (no health-related concerns are studied there).

The control objective is to maximize the tumor contraction under an integral constraint on the quantity of drugs injected. The design is based on the numerical solution of the **Hamilton-Jacobi-Isaacs partial differential equations** (HJI). Such a solution, when available, leads to a cartography of achievable performance in the space of initial states. As a matter of fact, solving the HJI equations provides an explicit solution to the min/max problem in which the control profile attempts to **minimizing the worst-case disturbance** effects on some cost function.

Obviously, this kind of robust min/max approaches is by now rather *deprecated* (or should be so) because of its extremely conservative formulation and is now replaced by stochastic formulation involving probabilities but this was not quite clear in 2014 where the last instances of robust-related point of view were still in the air.

3.2.7 Feedback with explicit handling of uncertainties

Advanced control design addressing problems where the uncertainties show long-term impact on the issue of the closed-loop can benefit from an explicit handling of the statistics of the unknown parameter dispersion.

In (Alamir, 2015), such feedback design is proposed based on a meticulously designed **parameterized control** law of the form:

$$u = K(x, \theta) \tag{3.4}$$

where K is defined via problem-dependent parameterization in which θ gathers the tunable parameters of the control law (gains, threshold, etc.) then the parameter vector θ is computed via **probabilistic certification** (Alamo et al., 2009) in which the success/failure counts depend on the outcome of the closed-loop behavior over a large population of scenarios. Each of these scenarios correspond to a randomly sampled value of the model's parameters vector following the supposedly known statistic of parameters dispersion.

Moreover, it is shown in (Alamir, 2015) that different paradigms can be handled in the problem settings depending on whether focus is put on the quantity of drug being used, the ratio of therapy to rest periods or the contraction of the tumor.

Another option to take explicitly into account the parametric uncertainties is proposed in (Alamir, 2024) via stochastic dynamic programming. This is done by deriving explicit approximation of the value function $Q(x, u)$ that is governed by the following functional equation:

$$Q(x, u) := \ell(x, u) + \gamma \min_{v \in \mathbb{U}} [\mathbb{E} + \alpha \mathbb{S}](Q(x^+, v)) \tag{3.5}$$

where $\gamma \in (0, 1]$ is a discounted factor, $\mathbb{E}$ and $\mathbb{S}$ denote the expectation and the standard deviation respectively associated to the dispersion of the next state x^+ in the expression of which the uncertain parameter vector appears. Once the map $Q(x, u)$ is approximately obtained, the uncertainty-aware resulting feedback can be defined by:

$$u = K(x) := \min_{v \in \mathbb{U}} Q(x, v). \tag{3.6}$$

The work in (Alamir, 2024) proposes a proof of convergence of the associated fixed point iteration together with an assessment of the importance of using a non vanishing weight $\alpha \neq 0$ on the standard deviation term which seems to be a general fact when it comes to handle risk sensitive application as it is the case in cancer therapy.

3.2.8 Estimating regions of attraction of some tumor models

These topics impulsed an important amount of work by some of the french researchers aiming at applying some control specific tools to the examples of cancer dynamics. In this context, estimating regions of attraction (RoA) attempts to characterize the sets (often the largest possible) of **initial health indicators** for which treatment protocols exist, such that the states are driven to a benign equilibrium (characterized also by the dormancy phenomenon), while satisfying some constraints on the states and the control input, in order to account for health and drug toxicity related constraints. This research line joins the previously mentioned stabilization paradigm and has been investigated for both nominal and uncertain models.

For instance, the work in (Riah et al., 2019) used set-invariance tools to investigate the existence of a therapy that steers the state to the benign equilibrium, in the presence of parametric uncertainties in the sense of the robust paradigm *i.e.* uncertainties characterized by bounds and not probability distributions. Furthermore, in (Alaraifi et al., 2024), an individual invariance concept has been used to characterize the RoA of different cancer models, by breaking down the dynamics into different artificial systems.

The stability analysis problem has also been tackled using different Lyapunov-based methods in (Djema et al., 2015; Fridman et al., 2016; Djema et al., 2017, 2018a,b) mainly for nonlinear delayed systems (involving the time needed for the drugs to reach the incriminated cells), allowing to have sufficient conditions on the stability of the locally stable dormancy equilibrium, and therefore to have estimates of the stability regions of such equilibria.

It is important to underline that the above mentioned works do not provide a specific feedback, but rather examine the very possibility of finding such a feedback in the first place. On the other hand, the result consists in sufficient conditions for the existence of such successful control which are generally not necessary. It is also worth mentioning that such methods do not necessarily include all the previously mentioned cancer-related constraints and restrictions on the states and inputs.

In (Moussa et al., 2021), the same goal is achieved by a dedicated analysis of the consequences of using bang-bang control on the boundaries of a meticulously designed set in the 2D space that is inferred by an extensive number of constant-control simulations. Even though this method offers the possibility of mapping the different control strategies to their consequences on the dynamics, it suffers from being hardly scalable to higher dimensional models.

The use of the probabilistic certification paradigm in (Moussa et al., 2022) enabled to introduce an implicit feedback scheme, as being a consequence of many certified open-loop controls over a sequence of certified sets. This framework allowed to estimate the RoA of a slightly higher dimensional dynamical model including up to five states (the additional ones describing the pharmacokinetics), although the certified region is expressed by its projection on the two first dimensions.

3.2.9 Works involving state estimation

The quantities involved in the mathematical models governing cancer dynamics are sometimes only partially measured requiring the use of state observers.

For instance, the work in (Arezki et al., 2022) proposes an LMI-based observer for a three-dimensional model of tumor in the presence of anti-angiogenic treatment where it is assumed that only the tumor size is measured while a correct control design would need the availability of the two remaining unmeasured state, namely the vascular system size and the total amount of already injected drug.

On the other hand, (Alamir and Fiacchini, 2016) addressed the case of cell-cycle-specific drug that efficiently acts on the tumor cells only in a specific phase of its life cycle. An oscillatory cyclic model is proposed in that reference to model these features with a population of cells and a Luenberger observer is used to estimate the average phase of the population in order to maximize the effect of the cell-cycle-specific drug on the tumor contraction.

3.2.10 Works involving reduced modelling

As mentioned earlier, cancer-related works in the control community used quasi exclusively dynamical models developed by the applied mathematics community. Nevertheless, in the context of the French national cancer-related project entitled CATS (Computer-Assisted Therapeutic Strategy) involving the University of Grenoble-Alpes and the INSERM (National Institute of Medical Research), a reduced *mechanistic* model of the 2D propagation of tumor in a network of vessels has been proposed (Alamir and Fiacchini, 2016).

The few parameters of the model have been identified using a high fidelity stochastic computer model which has been itself validated on real-life tumor propagation data. While the dynamics of the tumor size and form fit quite well, the proposed reduced dimensional model acceleration ratio compared to the previously existing automata-like model is beyond 10 000.

3.2.11 Sensitivity analysis via machine learning

Cancer-related models involve many unknown parameters. Moreover, when parameterized control is used in probabilistic certification as it has been done in (Alamir, 2015) (see Section 3.2.7), the number of control design parameters might be quite high. Finally, the more realistic is the model, the higher is the number of states needed in the model.

Given the amount of quantities involved, it becomes important to derive nonlinear sensitivity analysis (in the large) in order to focus on the quantities that really matter. A generic and scalable solution to this problem is suggested in (Alamir, 2023) using the `features_importance` attribute of `random forest` models. Not only this results in a reduced number of control parameters to be computed on-line depending on the state, but also, it allows to focus on a quite few number of initial states which enables the derivation of initial state-dependent dashboard of success/failure of the therapy.

A possible by-product of the scheme proposed in (Alamir, 2023) is the possibility to feed a constraint-based planning of patient admission similar to the one proposed by (Wang et al., 2011) but based on a more realistic, sound and detailed prediction of the outcome of the therapies given the patients' initial indicators.

3.3 The French community on the international scene

The above overview shows that the works on cancer-related control topics within the French control community is **far from being negligible** on the ground of ideas, formulations and algorithms.

Keeping the focus on the positioning within the international scene, it should be acknowledged that the *French* research is rather **methodological and simulation-based** (which is probably a consequence of the facts previously stated in Section 3.2.1). Nevertheless, it can be claimed that, as far as the applied mathematical aspect is concerned, this research is rather **more realistic than the previously prevailing works**[5] **in its handling of practical issues** such as parametric uncertainties, probabilistic certification, stochastic formulations and the presence of time constraints in the therapy schedule (therapy/rest phases).

The **lack of contribution** to the crucial aspect of control-oriented **models** is also an undeniable fact that results from the lack of access to real data which is at least partially due to heavy privacy-related restriction procedures compared to some other countries. The few works in that direction show that there is high potential of decisive contributions.

It might be worth acknowledging the interesting initiative of organizing a tutorial session in ECC23 on Modeling and Treatment of Cancer by French community members, including medical doctors that are also applied maths researchers.

3.4 Hot topics and open questions

In spite of the restricted spectrum of control-related works described above within the many different and challenging problems that are related to cancer studies, a simple fact seems to prevail:

Cancer is not a single disease!

Tumor brain has probably very little to do with leukemia in all aspects that do matter:

[5] Mainly focused on open-loop deterministic optimal control scheduling

tissues nature, flow properties, interaction with the rest of the organism, administration process of the drug, and the drug itself to cite but a limited list.

This fact might explain why while a numerical simulator (Man et al., 2014) has been approved by the American Food and Drug Administration (FDA) to serve as basis of validation of new drugs administration strategies for diabetes (see devoted chapter in this book), **no such approval has been provided for cancer studies** and probably because there was no such a request.

Now, should a specific kind of cancer be considered for its own sake (which would have been more than justified), the question regarding the possibility for a compartmental model to be sufficiently representative remains legitimate. This, coupled with the difficulty of gathering a representative amount of data regarding a specific kind of cancer, makes the assessment of such models even harder.

Consequently, it is probably totally justified that practitioners consider that the toy compartmental models our community was *playing with* for decades are far too simple for the associated results to be worth the examination. This does not mean that the progress in the formulations and algorithms that have been achieved thanks to the cancer-induced instantiation of control problems were useless.

It is probably time to face the reality and acknowledge that the commitment of the control researchers in cancer studies cannot be just *business as usual* where the cancer is just an example among others on which some existing methods are applied with slight accommodations and little refinement here and there.

> *The commitment of the control researchers in cancer studies should be a part of some sort of a Manhattan-like project where dynamic systems specialists are a part of a multi-disciplinary team gathering all the specialities mentioned in the introduction of this chapter.*

In such a framework, the control researchers should start a long period of observation of the specific problems, practices of measurement, drug delivery patterns, decision making determinants, in order to precisely define the needs and the sub-problems where their contributions is the most likely to make a difference.

This would be a long process. This would also be a rather **ungrateful process on the medium term**. But this would be the price to pay to understand the place of our methodologies in this holistic effort against a hugely complex beast!

Now even if we accept to play such a role, there is no reason to succeed tomorrow what we failed in doing along so many years, namely, be a part of such a project. **The**

impulse must come from above, namely from the agencies that provide the funding of such a project, for instance the French National Research Agency (ANR) and the Public investment Bank (BPI). This can be done through projects where multi-disciplinarity is a funding condition and where including control and dynamic systems' specialists is a condition for multi-disciplinarity assessment, among others.

This funding model is already in action in the industrial context. Indeed, it is a common practice to have about 20 million euros BPI-funded industrial projects that are conditioned by the presence of academic research partners to whom 10% of the funding is allocated. It is also true that sometimes, the industrial partners play the game (at least partially) without being totally convinced by our potential impact, but it does not matter, we are in the discussion room and have access to data, project's true pain points, common practices and decision making processes.

In parallel to the above funding of multi-disciplinary projects, it seems mandatory to benefit and especially orient the current public effort towards making accessible to researchers anonymized **public health data hub**. The participation of researchers in data science and dynamical systems in controlling the quality and the content of the so-collected data is mandatory for the usability of the data in consistent progress of our modeling and identification tasks.

Requesting this participation and making it real and effective can be the task of the **French National Research Center (CNRS)** as it is the incarnation of multi-disciplinarity and the first partner that should be convinced of the crucial role of each discipline in the success of such holistic effort.

There is no doubt that many of us (older and younger) would still be thrilled to be part of such a long, painful, dangerous and risky process in terms of career even in the current situation in terms of evaluation process. But obviously, things might be even better if the pressure on the outcome in terms of publication on a short term basis is reduced. Although this seems to be a general process in progress, it should be emphasized and accelerated.

These general comments being said, it might be interesting to examine the following tracks:

- Replace the compartmental models by mechanistic and/or knowledge-based (or a mix of both) 2D dynamical models involving the tissues on which the tumor resides and proliferate following the lines sketched in (Alamir and Fiacchini, 2016). This would be a turning point in the representation of the dynamics which will require associated control paradigms and methods.
- The previous track might trigger a key role for the Partial Differential Equations (PDE) representation of the processes that will be most likely nonlinear with point-wise boundary control actions.

- Consider multi-scale modeling, combining both the micro- and macroscopic behavior in the modeling process, as it is a combined inherent nature of the cancer growth. Such modeling techniques have already been used, for example in (Yu and Bagheri, 2021). Even though such models are not necessarily directly suitable for control approaches, they might remain interesting at least for model reduction and drug scheduling assessment. Indeed, the assessment of the relevance of treatment patterns, in terms of concentration and time scheduling, suggests the ability of carrying out large number of tests. If such models can be developed, they will offer the possibility to avoid time consuming and expensive experimental tests, at least for a first stage. It is also worth mentioning the importance of the large accessibility of such models.
- The access to a huge amount of data representing the evolution of health and tumor indicators over therapy periods would be invaluable in assessing any progress in the new generation of modeling proposals that can be imagined.
- Targeting medical doctors with a mathematical or engineering background (or the inverse), for preliminary collaboration projects, might be a first step to get a good understanding of the inherent problems and to set a reliable and relevant road-map from a technical point of view.

Obviously the above sketched tracks focus on modeling because it is the true bottleneck and the elephant in the room. There is no doubt that once a validated and trusted-by-practitioners models emerge, the control, adaptation, estimation, stochastic and so on algorithms will very quickly pop-up to appropriately address many of the associated remaining questions.

Notice that even the promoters of model-free design would need such faithful models for the sake of validation. This is because there is no chance that any feedback strategy can be tested on humans in a foreseeable future as things go. Proving that any feedback design might successively work on commonly admittedly representative models is the first step towards acceptability by the health system.

On the other hand, it might be argued that modeling biological systems is not necessarily what the control community is the best at. This might be true when knowledge-based models are targeted and when the model is developed by a single partner. On the contrary, when control-oriented models are targeted within a multi-disciplinary project, our role cannot be over-estimated.

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Chapter 4
Control sciences for cardiorespiratory system

Taous Meriem Laleg[1] and Stéphane Victor[2]

4.1 Context and challenges

Cardiovascular and respiratory diseases remain among the leading causes of morbidity and mortality worldwide. According to the World Health Organization, cardiovascular diseases are responsible for approximately 17.9 million deaths each year, accounting for 32% of all global deaths, while chronic respiratory diseases, including chronic obstructive pulmonary disease, asthma, and pulmonary hypertension, affect hundreds of millions of people globally. These conditions place an immense burden on healthcare systems, contribute to long-term disability, and generate substantial social and economic costs.

The need for better understanding, monitoring, and treatment of these diseases has stimulated the development of advanced medical technologies and analytical methods. Among them, control engineering and system modeling have emerged as powerful tools to support clinical innovation. Their value lies in the ability to represent complex physiological systems with mathematical rigor, simulate how these systems respond under different scenarios, and design adaptive mechanisms to support therapy and diagnosis.

The cardiovascular and respiratory systems are responsible for delivering oxygen and nutrients to body tissues, while simultaneously removing metabolic waste such as carbon dioxide. Their close physiological interaction plays a critical role in the onset and progression of many acute and chronic diseases.

From a modeling and control perspective, these systems present significant challenges due to their multiscale structure, nonlinear dynamics, physiological constraints, and intricate neural and hormonal regulatory mechanisms. Nonetheless, these complexities have also made them a rich ground for interdisciplinary innovation.

Over the past decades, the biomedical and physiological modeling communities have devoted sustained efforts to understanding and simulating these systems. More recently, the cardiovascular and respiratory systems have emerged as increasingly prominent application domains for control theory, system identification, and applied mathematics, particularly in the context of patient-specific modeling and real-time feedback strategies.

Mathematical modeling of the cardiovascular and respiratory systems has long been, and continues to be, a key area of active research. Since the pioneering work of Otto Frank (1899), numerous models have been developed to improve our understanding of cardiac and vascular function. These models enable the simulation of a wide range of physiological and pathological conditions, supporting the prediction of system behavior

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under various factors, such as physical exertion, disease progression, or pharmacological intervention. They also play a central role in the design of medical devices, including pacemakers and personalized treatment strategies.

Control engineering and systems theory have played a pivotal role in cardiovascular and respiratory research, contributing to the development of simulators, control strategies, and systems for patient monitoring and therapy. The following examples illustrate how control theory and systems engineering have been successfully applied to address real-world challenges in cardiovascular and respiratory care:

1. Artificial Hearts and Ventricular Assist Devices: These electromechanical devices provide support for the cardiac pump function, and are critical for patients with heart failure. Effective operation requires adaptive control algorithms that can adjust the pump's behavior in real-time to match the patient's physiological needs.
2. Pacemaker: These devices, which deliver electrical pulses via electrodes to one or more of the chambers of the heart, restore normal heart rhythm in patients with arrhythmias. A key challenge lies in ensuring responsiveness to dynamic physiological changes while maintaining real-time control performance.
3. Mechanical ventilation, thermal regulation: Extracorporeal circulation systems support respiration and metabolism through artificial airflow and induced hypothermia. These systems rely on precise control to optimize lung protection and reduce tissue damage.
4. Blood perfusion and Pressure Control: During extracorporeal circulation, dedicated systems replace cardiac output and regulate blood temperature and pressure to ensure systemic perfusion and homeostasis.
5. Remote Monitoring using wearable Devices: The emergence of connected health technologies enables real-time physiological monitoring outside the clinical setting, opening new opportunities for predictive modeling and personalized care.
6. Closed-loop drug delivery system: Closed-loop systems integrating biosensors and control algorithms offer precise, adaptive drug administration tailored to the patient's evolving condition.

A biological primer on the cardiorespiratory system

The cardiorespiratory system is vital to human survival. It delivers oxygen and nutrients to tissues, muscles, and organs, while removing carbon dioxide and other metabolic waste products. It consists of two interconnected subsystems:

- The cardiovascular system, composed of the heart and blood vessels
- The respiratory system, composed of the lungs and airways

The cardiorespiratory system is both fascinating and complex. The heart pumps oxygen-rich blood through the arteries to the rest of the body, a process known as systemic circulation. Veins return oxygen-poor blood back to the heart. In parallel, air enters through the mouth and larynx before reaching the lungs, the central organ of the respiratory system, and pulmonary circulation transports this oxygen-poor blood from the heart to the lungs, where it is reoxygenated before returning to the heart.
The lungs have a branching, fractal-like structure, which enables a vast surface area to exist within a compact volume. This extensive surface facilitates mass diffusion and heat exchange, which are essential for gas exchange. The lungs are closely linked to the cardiovascular system, as they are supplied with blood by two distinct blood networks. A thorough understanding of the pneumatic and thermal behavior of the lungs is critical for anesthesiologists and cardiac surgeons. For instance, during cardiac surgery, extracorporeal circulation (ECC) is often used, employing an artificial heart-lung machine to maintain perfusion and oxygenation. However, this can temporarily exclude the lungs from blood flow, depriving them of oxygen and nutrients. As a result, tissue damage, ischemia, or cell necrosis may occur postoperatively.

4.2 Contribution of the French Control community

The control community in France has made significant contributions to the field of cardiorespiratory systems, bringing together expertise in mathematical modeling, estimation, and control. Research institutions such as the Electrophysiology and Heart Modeling Institute (LIRYC) in Bordeaux, the French National Institute for Research in Digital Science and Technology (Inria), the French National Institute of Health and Medical Research (Inserm), and the French National Centre for Scientific Research (CNRS) have been at the forefront of developing patient-specific models for diagnostic and therapeutic applications.

Although all facets of control theory, modeling, identification, observation, analysis, and control, have been investigated in the context of the cardiorespiratory system, the primary focus across many of these initiatives has been on the development of mathematical models that are both physiologically accurate and computationally tractable, allowing for reproducible cardiovascular simulations.

4.2.1 The heart: Cardiovascular system modeling and identification

4.2.1.1 Overview:

A comprehensive understanding and evaluation of the dynamics of the circulatory system, under both physiological and pathological conditions, requires the development of mathematical models that accurately capture arterial behavior. Among the various approaches proposed in the literature, two principal classes of models have emerged for representing arterial blood pressure (ABP) in large arteries: lumped parameter models (0D) and distributed models (1D–3D).

Lumped (0D) models, such as the classical Windkessel models, abstract the arterial system using analogies with RLC electrical circuits, wherein pressure corresponds to voltage and volumetric flow rate to electric current (Frank and Li, 1989). The simplest configuration, the two-element Windkessel model, comprises a resistor and a capacitor in parallel. To enhance its dynamic fidelity, this model has been extended to three- and four-element variants by incorporating additional elements, such as a series resistance and, optionally, an inductance (Stergiopulos et al., 1999). While these models effectively capture the diastolic decay of pressure, their inherently low order limits their capacity to describe wave propagation phenomena, including the transit delay of pressure pulses along the arterial tree.

In contrast, distributed models, particularly those based on three-dimensional computational fluid dynamics, offer a detailed description of arterial hemodynamics, accounting for spatially varying velocity profiles, wall interactions, and complex geometries. However, due to their high computational cost, 3D models are often reduced to two-dimensional or one-dimensional formulations for practical applications. Moreover, 0D models can be systematically derived from 1D models and are frequently employed as boundary conditions in 1D simulations or as standalone simplified representations for purposes such as signal analysis.

The French community has contributed greatly to the development of advanced and reliable models of the cardiovascular system, allowing the understanding of the functioning of the system and the identification of various interactions within the system, such as mechanical, electrical, and hemodynamic interactions. Various research initiatives emerged, gathering multidisciplinary experts in the field.

Over the past two decades, French researchers have approached the modeling of the cardiovascular system from multiple complementary perspectives, ranging from reduced-order models to highly detailed, multi-physics simulations. Reduced-order models (also called lumped parameter models), such as those developed by Michel Sorine and the SISYPHE team at Inria, aim to capture the essential dynamics of the cardiovascular system using simplified differential equations. These models are particularly valuable for control applications, real-time estimation, and signal interpretation, where computational efficiency is crucial (Djabella et al., 2007; Sisyphe, 2010).

A foundational contribution in this area is the Bestel–Clément–Sorine model, developed in (J. Bestel, 2001), an electromechanical model of the heart, which provides reasonable accuracy with a reduced number of parameters. This model has influenced a wide range of applications in control, monitoring, and patient-specific modeling (Marchesseau et al., 2013).

More recently, from the perspective of proposing a simplified but accurate model of the viscoelasticity of the vessels, Taous Meriem Laleg and her team proposed fractional-order Windkessel models. These models enhance the classical Windkessel approach by incorporating fractional-order calculus, allowing for a more accurate representation of the viscoelastic properties of arterial walls (Bahloul and Laleg Kirati, 2019; Bahloul and Laleg-Kirati, 2021; Bahloul and Aboelkassem, 2022)

On the other end, projects like CardioSense3D have focused on constructing comprehensive, patient-specific models that integrate electrophysiology, myocardial mechanics, and perfusion dynamics. These models, developed by Inria project teams such as Asclepios, REO, MACS, and SISYPHE, utilize data assimilation and imaging to create digital twins of the heart, supporting diagnosis and therapy planning (Delingette et al., 2005), (Delingette et al., 2008). Furthermore, research from institutions such as Inria and Inserm has explored multiscale modeling approaches, incorporating molecular, cellular, and organ-level dynamics to better understand heart-lung interactions and cardiovascular responses to disease (Gall et al., 2020). This spectrum of modeling strategies, ranging from abstracted control-oriented models to biophysically detailed simulations, demonstrates the richness and adaptability of cardiovascular modeling in France.

4.2.1.2 Modeling the electrical and mechanical behaviors of the heart

Several French researchers have worked on modeling the electrical and mechanical behaviors of the heart (Sainte-Marie et al., 2003, 2006; Sermesant et al., 2006). For example, in (Sainte-Marie et al., 2003), heart tissue has been modeled using an electrically activated contraction law formulated by multiscale considerations. The global heart system also incorporated a simplified lumped modeling of the blood compartments. A data assimilation procedure has also been proposed to calibrate the model and estimate unknown parameters that might be relevant for diagnosis. In (Sermesant et al., 2006), a three-dimensional electromechanical model of the two cardiac ventricles was designed both for the simulation of their electrical and mechanical activity and for the segmentation of time series of medical images.

In addition, a reduced-order differential model of cardiac Purkinje fibers' electrical activity has been proposed in (Djabella and Sorine, 2006). This model, comprising eight state variables, effectively reconstructs the action potentials of Purkinje fibers. It incorporates key ionic currents, calcium dynamics, and their interactions with myoplasmic proteins, providing insights into the mechanisms underlying autorhythmicity and excitation-contraction coupling in cardiac cells.

4.2.1.3 Modeling the arterial hemodynamics

During the propagation of the arterial pressure pulse (PP) through the arterial tree, characteristic wave phenomena, such as steepening and peaking, are commonly observed.

These effects have been primarily attributed to the linear superposition of forward- and backward-traveling pressure waves. Backward (reflected) waves are generated when forward-propagating waves—originating from the heart and moving toward the peripheral circulation—encounter impedance mismatches or geometric discontinuities, such as arterial bifurcations or stenotic lesions.

This wave-reflection framework has been extensively studied and constitutes a foundational concept in hemodynamics. One of the earliest and most influential contributions to this area is the work of (Westerhof et al., 1972), who introduced a method for decomposing the arterial pressure waveform into its forward and backward components. This decomposition approach has since been refined and expanded by numerous researchers, including (Li, 1986), (Parker and Jones, 1990), (Berger et al., 1993), (Stergiopulos and Meister, 1993), (Pythoud and Meister, 1995), (Pythoud and Meister, 1996), among others.

On the other hand, the Inria project team Sisyphe has demonstrated that the arterial pressure waveform can be decomposed into two distinct components: a traveling wave that captures the rapid dynamics associated with systolic pulse propagation, and a Windkessel component that accounts for the slower hemodynamic behavior observed during the diastolic phase (Crépeau and Sorine, 2007; Laleg-Kirati et al., 2007). While such a decomposition has previously been explored—most notably in the work of (Wang et al., 2002)—the novelty of the approach lies in the selection of a forward-propagating solitary wave as the representation of the traveling component.

This solitary wave formulation inherently captures key morphological features of the pressure pulse, including the characteristic peaking and steepening phenomena. These solitons, which arise from a balance between nonlinear wave steepening and dispersive effects, possess analytical solutions (a nonlinear dispersive partial differential equation, the Korteweg-de Vries equation Crépeau and Sorine (2007)), making them particularly attractive for model reduction. The resulting reduced-order model of arterial blood pressure is not only physiologically meaningful but also computationally tractable and amenable to parameter identification, which constitutes a significant advantage of the proposed framework.

4.2.1.4 Fractional modeling of the arterial stiffness

Another cardiovascular modeling topic from a control-engineering perspective is arterial stiffness. Arterial stiffness is a key factor in several cardiovascular diseases, such as systolic hypertension, stroke, coronary artery disease, and arteriosclerosis. Therefore, its assessment is crucial in both cardiovascular research and clinical routine. However, there is no standard for measuring arterial stiffness in general and aortic stiffness in particular. Indeed, measuring aortic (central) stiffness is not as simple as the aorta is inaccessible. As a result, several indirect methods for measuring arterial stiffness have been proposed (Segers et al., 2020). Some of these methods provide information on aortic stiffness, while others focus on the arterial stiffness of peripheral vessels, which are more readily attainable. Thus, numerous indices have been introduced and are typically derived by combining mathematical models with accessible measurements of the vessels, such as vessel diameters and Pulse Wave Velocity (PWV). Local arterial stiffness is often assessed using ultrasound and tonometry. Moreover, regional arterial stiffness can be evaluated using PWV, which is recorded at two different arterial sites. If PWV is measured at the carotid and femoral (carotid femoral PWV), then it will provide an estimate of the aortic stiffness (Bortel et al., 2012). Although PWV is currently the most reliable index, it has some limitations. For example, it often produces inaccurate measurements due to the difficulty of measuring the distance between two arterial sites. Additionally, equipment limitations may not permit the simultaneous measurement of PWV at two sites. PWV can also be measured using Magnetic Resonance Imaging (MRI), which provides a more accurate but expensive assessment of the stiffness. Moreover, some recent studies showed discrepancies when comparing various indices in different physiological and pathological situations. For instance, local and regional aortic stiffness measures were compared, and the results show strong correlations in healthy subjects but disproportionality in subjects with cardiovascular risk factors (Paini et al., 2006). Moreover, weak correlations have been obtained in the comparison of stiffness indices in (Kanishcheva and Bilchenko, 2023). In that context, the team of Taous Meriem Laleg (BOOST, Inria Paris Saclay) proposed a modeling framework based on fractional order systems to describe arterial hemodynamics in humans. This model employs an electrical analogy, consisting of a resistance in parallel with a fractional-order capacitor (Bahloul and Laleg-Kirati, 2020a, 2021). The fractional order capacitor is a constant phase electrical element with an impedance phase between $0°$and $-90°$, allowing various behaviors of the vessels ranging from stiff (phase = $0°$) to purely elastic (phase= $-90°$). This range depends on the fractional (non-integer) differentiation order values. Fractional differential order is therefore strongly correlated to arterial stiffness and could provide an accurate and reliable indicator of cardiovascular diseases. However, the fractional framework has only been validated using in-Sillico datasets. This advancement provides enhanced tools for evaluating left ventricular afterload and arterial stiffness, which are essential for understanding cardiovascular health.

Further expanding on this work, the same team explored the application of fractional-order models in the context of hypertension. The study highlighted the model's ability to reflect the complex interplay between arterial compliance and resistance, providing insights into the structural and functional changes associated with hypertension. The fractional differentiation order, in particular, was identified as a potential biomarker for arterial stiffness (Bahloul and Aboelkassem, 2022).

4.2.1.5 Cardiovascular model calibration and identification

Cardiovascular model calibration and parameter estimation have constituted a central research theme within the French scientific community, driven by the objective of constructing patient-specific models with parameters tailored to individual physiological characteristics. Model calibration and identification are integral parts of the modeling pipeline, where the goal is to infer model parameters from observational data and experimental measurements.

The inherent complexity of cardiovascular models, characterized by nonlinear dynamics, time delays, and parametric uncertainties, necessitates the development of advanced estimation techniques. In response to these challenges, various methodologies have been proposed. The M3Disim team (INRIA/Ecole Polytechnique), for example, has addressed the problem through the lens of biomechanical inverse modeling and data assimilation, employing Kalman filtering techniques to achieve robust parameter inference (Chapelle and Le Gall, 2023).

Concurrently, the Boost team (INRIA/Paris Saclay) has built upon prior contributions on observer-based estimation of blood flow and Windkessel model parameters (Bahloul and Laleg-Kirati, 2020b; Bahloul et al., 2021; Boukaf et al., 2024). More recently, their research has focused on integrating physics-informed neural networks (PINNs) with nonlinear observer theory to develop robust and interpretable frameworks for jointly estimating hemodynamic variables and vascular compliance models. This includes efforts to identify the parameters of fractional-order Windkessel models, as well as estimate the fractional differentiation order, which introduces additional modeling flexibility and physiological relevance (Boukaf et al., 2025).

4.2.2 The lung: Modeling and identification of respiratory physiology

As for the heart, a large proportion of research efforts stemming from the control engineering community in the domain of respiratory physiology consists in building identifiable mathematical models that accurately capture respiratory behavior.

4.2.2.1 Pneumatic modeling of the respiratory system

Lungs have a characteristic geometry with an arborescent fractal structure (Weibel, 2005), leading to a fractal dimension between 2 and 3. Helmberger et al. (2014) have linked tortuosity and lung fractal dimension with arterial pulmonary pressure and hemodynamic parameters, but Haitao et al. (2011) have shown a high correlation between hypertension and fractality.

The first dynamical model of lungs are based on their elasticity linking the pulmonary volume and alveolar pressure, its ratio being called as *compliance*. From the analogy with a balloon,Hildebrandt (1970) has shown a dependency between the pressure-volume ratio and time logarithm, and a first pneumatic system identification was then proposed and validated with a constant phase element with cat lungs.

Numerous respiratory impedance models are available in the literature. One of the first original models is the lung impedance model developed by (DuBois et al., 1956), which draws an analogy with series RLC circuits. A visco-elastic model was then proposed by (Navajas et al., 1990), and later, air mass inertia was introduced in (Diong et al., 2007).

Kuwahara et al. (2009) have extended a mechanical model with the help of Murray's law, which establishes recursive laws between consecutive bronchial sections and lengths. This model also considers gas exchanges in lungs, and from the pressure study, an optimal number of bifurcation has been determined, $N = 23$.

Diagnosis of respiratory pathologies have been proposed for pneumatic mechanical models in (Ionescu et al., 2011) with a collaboration between the University of Bordeaux and Ghent University. Such a model makes an analogy between electrical and mechanical impedance models, where the resistance, inductance, and capacitance have recursive relations between two consecutive branches.

Finally, a final mechanical approach was proposed to use pneumatic models in porous media and the finite element technique. The models are derived from fluid mechanics and Navier-Stokes equations for incompressible media (DeGroot and Straatman, 2018). This work has enabled computing the permeability in a 3D lung model.

4.2.2.2 Heat transfer modeling of the respiratory system

Heat transfer in the lungs is also a burning issue. In fact, the ambient air is conditioned through the nose and trachea, and hypothermia has been used to reduce the consumption of lung metabolism for open-heart surgeries. The techniques employed were empirical, and system identification using black-box models was introduced by utilizing fractional models and Havriliak-Negami heat transfer models (Pellet et al., 2011). Experiments on sheep were carried out with the Anesthesiology–Intensive Care Service of the Haut-Lévêque Bordeaux Hospital (Victor et al., 2020).

More generally, there has been a close collaboration between Haut-Lévêque Bordeaux Hospital and IMS laboratory to develop physical models from solving the heat conduction equation on a lung branch (Duhe et al., 2022; Ndreko et al., 2025); to design a suited moving window length of data (Duhe et al., 2023); and to propose system identification in real-time (Victor et al., 2022, 2025).

4.3 The French community on the international scene

4.3.1 French laboratories involved in cardio-respiratory system modeling and control

Several INRIA teams have been working for over two decades on the development of digital and personalized models of the human heart, with the goal of improving the early detection of cardiovascular diseases and supporting patient treatment.

One notable initiative is the Inria Cardiosense 3D project, launched in 2005, which brought together several Inria research teams to develop an electro-mechanical model of the heart for simulation and visualization of the cardiovascular system. This initiative led to numerous publications and software tools (Delingette et al., 2005), (Delingette et al., 2008). The goal of the project was to create a patient-specific cardiac activity simulator adaptable to clinical applications such as pacemaker implantation and the treatment of patients with cardiac arrhythmias (Sainte-Marie et al., 2003, 2006; Marchesseau et al., 2013). The project was followed by several initiatives and the creation of new teams that have continued these efforts, focusing on modeling and characterizing the cardiovascular system, and developing personalized tools for diagnosis and clinical decision support.

The M3DISIM team (INRIA/Ecole Polytechnique) has made significant contributions to the development of a multiscale 3D model of cardiac mechanical contraction in response to electrical activation. By integrating this modeling framework with advanced numerical methods, the team successfully reproduced the behavior of the whole heart, including its interaction with circulating blood during all cardiac cycles (Chapelle and Le Gall, 2023; Genet et al., 2023; Chabiniok et al., 2022).

The recently established BOOST team (INRIA/Université Paris Saclay) focuses on modeling and assessing cardiovascular function, with particular emphasis on arterial risk factors such as arterial stiffness, and on developing new mathematical biomarkers. Among these, the fractional-order Windkessel model has emerged as a promising candidate to represent arterial stiffness (Bahloul and Aboelkassem, 2022; Bahloul and Laleg-Kirati, 2021). BOOST is also investigating the brain–heart interplay by proposing dynamic models that describe mutual physiological interactions between the two systems.

On the respiratory side, the CRONE team at the IMS Laboratory in Bordeaux has focused on modeling the pneumatic impedance of the lungs using an RLC circuit analogy, which is well-suited to the lungs' branching, fractal-like architecture (Ionescu et al., 2011; Oustaloup, 2014). Over the past decades, a close collaboration has developed between this team and the Anesthesiology–Intensive Care Unit of Haut-Lévêque Hospital in Bordeaux. This partnership has enabled the development of mathematical heat transfer models to better understand the thermal behavior of the lungs. Initial black-box system identification experiments were conducted on sheep in offline mode (Victor et al., 2020), but these studies revealed the need for a more accurate dynamic understanding of the lungs during open-heart surgeries. In this context, an interdisciplinary initiative at the University of Bordeaux led to the development of heat transfer models for lung branches (Duhe et al., 2022), as well as online system identification algorithms for real-time use (Victor et al., 2022, 2025), including truncated versions for improved computational efficiency.

4.3.2 Position in the international academic landscape

The CRONE team at IMS can be considered an international leader in modeling heat transfer in the lungs, as well as in developing and designing online system identification methods using fractional-order models. This leadership has enabled close collaborations with the Anesthesiology–Intensive Care Service of the Haut-Lévêque Hospital and the Clinique Saint-Augustin in Bordeaux. These efforts have positioned France as a key contributor to the development of real-time, patient-specific models for intraoperative monitoring and physiological interpretation, particularly in the context of cardiopulmonary dynamics. France is internationally recognized for its pioneering work in fractional-order modeling applied to biomedical systems.

Several French teams have also taken the lead in modeling the electromechanical interaction of the heart, on the one hand, and arterial hemodynamics, on the other. Both reduced-order modeling and distributed approaches have been explored and tested. French researchers have notably contributed to the development of multiscale electromechanical cardiac models that bridge electrophysiology, mechanics, and hemodynamics, and are integrated into simulation platforms for diagnosis, device design, and surgical planning.

Comparatively, work on modeling lung mechanics is relatively under-represented in the French research community. Given the early work of Oustaloup (1995) on fractional (or non-integer) derivatives, RLC circuits, and their link to fractal structures, there was clear potential for a major contribution in modeling lung mechanics. Some developments have been pursued in collaboration with Ghent University (Ionescu et al., 2011), but further advances could have been made, particularly in the detection and diagnosis of pulmonary pathologies. France remains relatively underrepresented in the broader international efforts on lung modeling, especially regarding the integration of data-driven methods, AI-enhanced diagnostics, and experimental validation involving diverse patient populations. While some promising groundwork has been laid, the French community could further strengthen its position by investing in translational research that bridges physiological modeling with clinical application, particularly in areas such as ventilation optimization and early detection of respiratory diseases.

Another under-investigated area is that of control. While the French community has been traditionally strong in terms of modeling and estimation, more extensive work could be pursued in topics such as mechanical ventilation or ventricular assist devices. France is also less visible in large-scale international consortia addressing clinical deployment of closed-loop control systems, especially in respiratory support. Strengthening interdisciplinary links with hospitals and investing in clinically validated prototypes would help close this gap.

4.4 Hot topics and open questions

In the modeling of heat transfer in lungs, a European collaboration could emerge with the University of Novi Sad (Serbia), as they have been developing real-time applications and real-time system identification with fractional models ((Kapetina et al., 2019, 2020)). A collaboration could also be extended with Vrije Universiteit Brussel (Belgium) for pneumatic lung impedance modeling and frequency domain analysis ((Marchal et al., 2024)).

Another promising and underexplored research direction for the French control community lies in the modeling and control of brain–heart interactions, an area in which very few comprehensive models currently exist. The study of this interplay, particularly involving baroreflex mechanisms and the autonomic nervous system's role in cardiovascular regulation, has the potential to open new avenues for understanding the complex and dynamic interactions between key systems. Despite its clinical relevance, this domain has remained relatively neglected. An interest in this area could significantly advance both theoretical modeling and medical applications.

Third, building upon initiatives such as a recently funded ANR project 3CI (Computer-aided assessment of the Cortico-Cardiovascular Interaction for monitoring the stress of athletes) by the BOOST team on stress assessment, there is a clear need to advance integrated models of central and peripheral physiological signals (e.g., ECG, PPG, HRV, EEG) to better understand neurocardiac dynamics under both normal and pathological conditions. A key challenge is the non-invasive, real-time monitoring and diagnosis of stress and cardiovascular risk, which calls for the development of novel signal acquisition strategies—for example, leveraging photoplethysmography (PPG) and other wearable-compatible sensors (Vargas et al., 2025). These technologies offer a low-cost, accessible route for large-scale deployment, but require improved signal interpretation algorithms rooted in robust control, signal processing, and hybrid modeling.

Ultimately, there is a pressing need to develop decision-support strategies that enable clinicians to effectively interpret multimodal data and make personalized therapeutic decisions. A notable example is the ongoing collaboration with AP-HP focused on the assessment of vulnerable carotid plaques, where control-based modeling and estimation methods can inform surgical decision-making by predicting patient-specific plaque rupture risk.

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Chapter 5
Control sciences for Diabetes

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5.1 Context and challenges

Healthy individuals enjoy natural glycemia regulation, *i.e.* the variability of blood glucose (BG) levels throughout the day remains within the physiological 70-180 mg/dL range. The endogenous insulin needed for this glycemic control is produced by the β-cells of the pancreatic islets.

5.1.1 Worldwide situation about diabetes

Diabetes is a chronic disease characterized by a sustained time spent above range (> 180 mg/dL) for BG, leading to long-term complications. According to the International Diabetes Federation, there were 588 million cases of diabetes worldwide in 2024, expected to rise to 852 million by 2050. In France, the number of patients with diabetes covered by health insurance in 2022 was 4,331,400, for an annual cost of around 10 billion euros. From the medical literature, there are several forms of diabetes, such as Type 1 Diabetes (T1D), Type 2 Diabetes (T2D), gestational diabetes and rare diabetes (*e.g.* MODY: Maturity Onset-Type Diabetes of Youth) to name a few. In the context of this work, the focus is put on the two main forms of diabetes for which control sciences have been able to provide scientific contributions: T1D and T2D. Type 1 diabetes, about 8% of the world's population with diabetes, is an autoimmune disease associated with the death of pancreatic β cells, so that no endogenous insulin is produced. Blood glucose is no longer absorbed by muscle tissue and hepatic glucose production no more regulated. BG concentration, or blood glycemia, increases with carbohydrates intake and may reach dangerous levels. People living with T1D must get a suitable amount of exogenous insulin to maintain glycemia close to the normoglycemic levels. Type 2 diabetes accounts for 90% of all cases of diabetes in the world. T2D is characterized by the development of insulin resistance, coupled with a deterioration in the pancreas ability to produce the adequate amount of insulin to compensate this insulin resistance. Ultimately, the defect of insulin secretion can lead to the need of exogenous insulin delivery.

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5.1.2 Brief overview of worldwide contributions

According to (King and Rubin, 2003), the first record of diabetes is found in the Egyptian ”Ebers Papyrus” document circa 1500 BC, which describes what is believed to be diabetes mellitus. Although diabetes is thus as old as antiquity, it really started to be understood at the end of 19th century. The key milestones can be sketched as follows: i) 1889, discovery of the role of the pancreas in diabetes, ii) 1921-1922, discovery of insulin and its role in diabetes, iii) 1961, Bolie’s model on insulin-glucose homeostasis (regulation) in individuals without diabetes (Bolie, 1961), iv) 1963, the prototype of an insulin pump was designed by Dr. Arnold Kadish, v) 1984, the Biostator glucose controller which delivers insulin or dextrose to an individual while providing continuous monitoring of the blood glucose level (Young and Herf, 1984), vi) 1989, the minimal model for T1D (Bergman, 1989), vii) 1999, the first Continuous Glucose Monitoring (CGM) sensor, Minimed, was released on the market (Clarke and Foster, 2012), (Didyuk et al., 2021), viii) 2006, use of Model Predictive Control (MPC) algorithm for BG regulation (Hovorka, 2006), ix) 2006, Closed-loop insulin delivery using implanted insulin pumps and sensors in T1D patients (Renard et al., 2006), x) 2008-2013, UVA/Padova simulator (Kovatchev et al., 2009), (Dalla Man et al., 2014) shown in Fig. 5.1.A, has been accepted by Food and Drug Administration (FDA) as a substitute for pre-clinical testing of new treatment strategies for T1D, xi) 2018, the estimation of physiological parameters (insulin sensitivity, etc.) (Blanc et al., 2019; Scharbarg et al., 2022), and xii) the development of T2D in silico simulator (Visentin et al., 2020, 2024) introduced in Fig. 5.1.B to name a few.

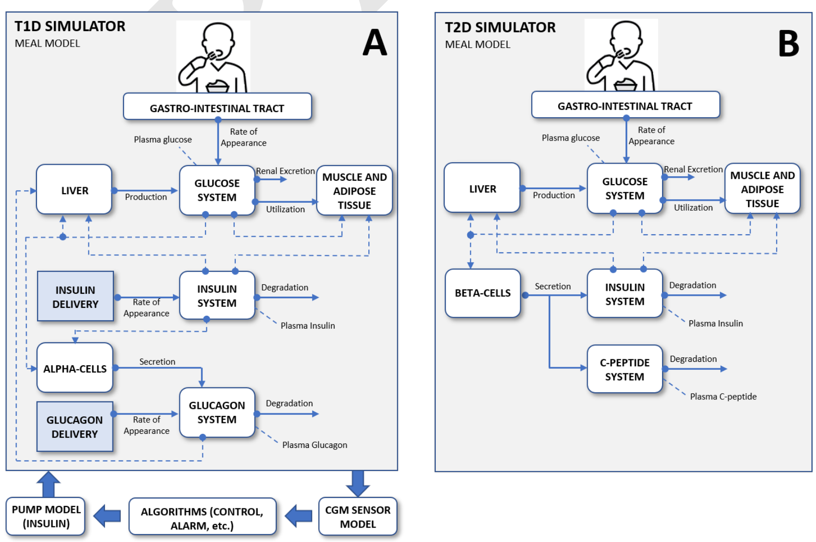

Fig. 5.1 T1D (A) (Dalla Man et al., 2014) and T2D (B) (Visentin et al., 2024) simulators for testing new therapeutic care

5.1.3 Challenges and on-going researches

Biological solution: transplantation of pancreatic islets

Over the past two decades, advances have been made in cell replacement therapy for T1D. By substituting impaired β-cells with functional ones, this approach can help T1D patients to recover their insulin needs and achieve better glycemic control. Human islet transplantation involves the purification of islets from cadaveric donors and infusion into the portal vein. This invasive procedure is only recommended for unstable cases of T1D (Brittle Diabetes) due to associated risks, *e.g.* portal vein thrombosis and need for immunosuppressive drugs. Furthermore, the limited availability of human islets restricts its widespread application. To overcome this weakness, an alternative approach currently under development involves the use of induced pluripotent stem cells (iPSCs), which can be expanded and differentiated into β-like cells for transplantation. However, the process of generating iPSCs into functional β-like cells is complex and costly. Moreover, it is not possible to replicate the essential network interactions between β- and non-β-cells within the native pancreatic islets, and there is a potential risk of tumorigenicity.

Engineering solution: Automated exogenous Insulin Delivery (AID)

To circumvent the aforementioned difficulties, the use of AID systems – also known as *Artificial Pancreas* (AP) – is now well established as the most promising practical therapeutic approach for T1D care. Especially, technological advances in diabetes management have led to the development of semi-automated (so-called hybrid, see Fig. 5.2) insulin delivery systems for BG regulation. These AID systems are hybrid solutions, since they require manual intervention by patients to announce meals and physical activity.

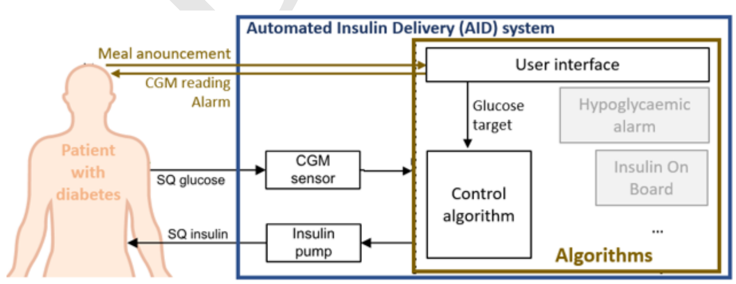

Fig. 5.2 Principle of an automated insulin delivery system

These solutions are based on the principle of insulin therapy, *i.e.* they use a CGM sensor for glucose measurement in the subcutaneous (SQ) compartment and a pump that infuses insulin at a rate decided by a control algorithm to maintain BG level in the normoglycemic range (Phillip et al., 2023). In addition, AID systems also incorporate other algorithms (estimation of active insulin in the body, hypoglycemic alarms, etc.) to increase the reliability and efficiency of such medical care.

According to (Trevitt et al., 2016), there are 6 stages in the development of AID systems:

- **Step 1: Insulin off pump for very-low-glucose**. Pump shuts off when user not responding to low-glucose alarm.
- **Step 2: Hypoglycemia minimizer**. Predictive hypoglycemia causes alarms, followed by reduction/stop of insulin delivery before low BG.
- **Step 3: Hypoglycemia/Hyperglycemia minimizer**. Same product as Step 2, with added features allowing insulin dosing above high threshold.
- **Step 4: Automated basal / Hybrid closed loop**. Closed loop at all times meal-time manual-assist bolusing.
- **Step 5: Fully automated insulin closed loop**. Manual meal-time bolus eliminated.
- **Step 6: Fully automated multihormone closed loop**.

The current challenge is step 5, *i.e* the new generation of AID system aims to completely remove the need of patients to announce meals or physical activities. This represents a major step towards fully automated solutions (Jacobs et al., 2024; Hughes and Levy, 2025). To reach this objective in the context of meal management, there exist different on-going investigations. For instance, the use of meal detection and carbohydrate (CHO) intake estimation can be useful to schedule, in real-time, the control algorithm which drives the insulin pump. However, most meal detection algorithms can identify a meal 25–45 minutes after it is consumed. By considering the different delays inherent to a care with an AID system using subcutaneous glucose monitoring and insulin delivery (*e.g*. 5–10 minutes for subcutaneous route, approximately 20 minutes for insulin diffusion between injection and bloodstream entry, etc.), the benefit to hyperglycemia mitigation is small. In addition, the accuracy of glucose measurement provided by the CGM sensor in real-time can have an error of ±20% (see the difference between magenta and red curves in the top of Fig. 5.3), in spite of a mean absolute relative difference of blood glucose around 10% for current CGM sensor. To overcome this weakness, some attempts aimed at transforming the Single Input / Single Output (SISO) BG control problem into a Multiple Inputs / Multiple Outputs (MIMO) one, including the infusion of the antagonist hormone glucagon. Unfortunately, this way is still limited in terms of stability of glucagon, validity of additional physiological sensing in a medical device and the cost for society to name a few.

These limitations are confirmed by the directions taken by industry actors, as demonstrated by Diabeloop which launched a multi-country clinical study in February 2023 to assess the effectiveness of unannounced meal management, despite a 5% loss of time spent within the normo-glycemia target (Lachal et al., 2021). In this context, the development of a fully implantable physiologic high-precision insulin delivery system connected to a multi-sensing device has been recently granted in the Horizon Europe (EIC Pathfinder 2023 - MuSiC4Diabetes - *Unobtrusive Continuous Multi-Metabolite Monitoring for a Physiological Care of Insulin-treated Diabetes*). This project involves French hospital practitioners and Italian researchers in control sciences. The interest in

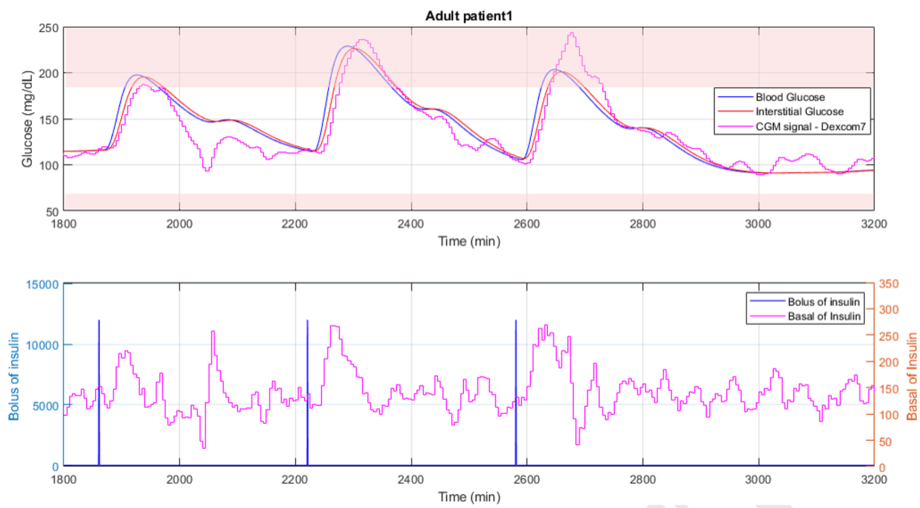

Fig. 5.3 A simulation from FDA-approved simulator (Dalla Man et al., 2014)

such an approach lies in an implantable device*, i.e.* inside the body. Thus, such integration should reduce the delays of the AID system for a potential improved management of diabetes.

On-going investigation for treatment guidance in T2D population

The insulin deficiency linked to T1D has clearly offered a privileged framework to highlight the benefit of control sciences in the field of diabetes, especially on the modeling of glucose-insulin dynamics and BG regulation. As a result of these remarkable contributions to accelerating innovation for T1D care, initiatives are being developed to T2D. In this context, recent studies focusing on closed-loop therapies such as the EU Horizon 2020 CLOSE project - *Automated glucose control at home for people with chronic disease* and the development of new in silico simulator for such pathology (Visentin et al., 2020, 2024).

A biological primer on Diabetes

The natural blood glucose regulation in an individual without diabetes essentially results from the action of two antagonist pancreatic hormones. Insulin is the hypoglycemic hormone produced by the β-cells of the pancreas. It plays a role after carbobydrates intake since it allows blood glucose consumption by the muscles and blocks hepatic glucose delivery. Thus, the effect of insulin is to decrease the level of glucose concentration in blood plasma.

To balance the action of insulin, especially between two meal intakes, and to avoid severe hypoglycemia, the α-cells of the pancreas produce glucagon which is the hyperglycemic antagonist hormone. Glucagon is required to trigger glucose release by the liver and thus to avoid hypoglycemia.

The focus is put here on the two main types of diabetes. Type 1 diabetes (T1D) is an auto immune disease, *i.e.* the immune system destroys the β-cells so that no more endogenous insulin is produced. In type 2 diabetes (T2D), the quantity of insulin is no more sufficient and its hypoglycemic effect becomes limited. T2D may follow from aging or a non suitable diet. Summarizing (Pirog, 2017),

- T1D i) is often diagnosed in childhood, ii) is not associated with excess weight, iii) is associated with a high level of ketone bodies at the time of diagnosis, iv) is treated with insulin injections and v) cannot be controlled without insulin therapy.
- T2D is i) generally diagnosed in people over the age of 30, ii) often associated with excess weight, iii) often associated with high blood pressure and/or high cholesterol, iv) generally treated initially without medication and v) sometimes treated by intermittent medication.

5.2 Contribution of the French Control community to the field of Diabetes

5.2.1 Academics highlight

French control community contributions in diabetes really began when the glucose-insulin dynamics simulator (called UVA/Padova) has been developed (Dalla Man et al., 2007) and continuously updated/improved (Kovatchev et al., 2008), (Dalla Man et al., 2014), until its FDA approval for testing new control strategies as a substitute for pre-clinical animal trials. Here, we review some key contributions of the French community, classified according to the terminology introduced in Chapter 1.

Modeling: knowledge-based or data-driven methods

Mathematical models for the glucose insulin dynamics are subject to physical constraints, such as the positivity of the state variables (blood glucose concentration, insulin concentration in various compartments), of the control input (insulin infusion rate) and of disturbances (carbohydrates intake). To fit medical practice, a mathematical model should display the so-called *basal insulin infusion rate* I_b. The latter has to be defined, using an engineering terminology, as the single constant input which is able to stabilize the BG concentration G, away from meals (at night e.g.). To summarize, the set of equilibria of the mathematical model is $\{(G, I_b) \,:\, G \geq 0\}$. Within an advanced time-varying model, the basal insulin rate may be time dependent so that the basal insulin rate may adapt to different periods over 24 hours, for instance night and day.

One of the first French initiatives comes from a collaboration between researchers at Supélec Rennes and hospital practitioners at University Hospital Center of Rennes. The authors in (Ben Abbes et al., 2011) introduce a two-compartment model that involves a notion of basal glucose concentration. A basal insulin infusion then yields the stabilization of blood glycemia at the so-called basal glucose concentration. Although the latter is arguable by practitioners, satisfactory identification was performed on ten virtual patients to give credit to this model.

Next, the joint venture between the control group of LS2N laboratory in Nantes and Nantes University Hospital focused both on modeling, identification, and control, taking advantage of the practice of clinicians and the availability of clinical data. The central feature within those works is the Flexible Insulin Therapy (FIT) which is the worldwide well accepted methodology among clinical practitioners. FIT implicitly assumes some linear dynamics, both from carbohydrates intake to blood glucose concentration and from exogenous insulin injection to blood glucose concentration. In this context, a so-called long-term model of the glucose-insulin dynamics has been derived in (Magdelaine et al., 2015a). This long-term model has been validated in (Magdelaine et al., 2015b, 2016) using clinical data from 12 patients with T1D to demonstrate its ability to predict the behavior of glycemia and insulinemia dynamics. More recently, FIT model has been extended to be able to manage BG during aerobic physical activity (Scharbarg et al., 2022) by using heart rate sensors (watches) in a fully AID system. One research output is a so-called metamodel that includes aerobic physical activity and its use in a metamodel-based FIT for patients with T1D subject to aerobic physical activity.

Furthermore, an analysis of several models has also been performed in (Califano et al., 2019) for patients living with diabetes with or without gastroparesis, which is a delay in the digestion process and which affects 4% to 12% patients with diabetes. Finally, further contributions on modeling, such as a fractional-order model, can be found in (Aounallah et al., 2021).

Identification/estimation of physiological parameters

In (Scharbarg et al., 2020) and (Scharbarg et al., 2022), a patented identification methodology (Magdelaine et al., 2019) is given to estimate FIT parameters (the BG level, the plasma insulin rate, the subcutaneous compartment insulin rate, the carbohydrate flow in the duodenum or the carbohydrate flow in the stomach) from some standard ambulatory clinical data.

Based on Bergman Minimal Model (BMM) (Bergman et al., 1981), an adaptive observer is derived in (Franco et al., 2023b) to simultaneously estimate states of BMM and the parameter corresponding to the insulin-independent glucose disappearance rate p_3 of the BMM. This estimated parameter could be next used to derive an estimate of the ”insulin-sensitivity index” to provide an additional signal for BG management.

Such results have interest *per se*, and open the door to adaptive control solutions, which can modify the dosing rules of insulin for an improved BG regulation.

Observation

The design of observers has often been discussed as a part of the solution to the state feedback problem. It is one of the main motivations of the adaptive nonlinear observer given in (Franco et al., 2023b), already mentioned above. Efficiency of the standard Luenberger observer has been highlighted in (Magdelaine et al., 2020). Under the assumption that the intake of meals can be approximated as an impulse disturbance and given that current AID systems still require the injections of insulin bolus (impulses) with meal announcement, *ad hoc* notions of observability were also investigated for impulsive nonlinear systems in (Rivadeneira and Moog, 2015) to derive specific mathematical tools for analysis, observation and control.

Control design

After the registration of a patent in 2009 (Cormerais et al., 2009), the working group of Rennes developed a new control law (Poirier et al., 2010; Richard et al., 2010) based on the principle of Error Dynamics Shaping (EDS). EDS is a nonlinear control principle based on direct adjustment of the dynamics of the servo error, in particular through its degree of damping. It stands out for its robustness to disturbances, with the aim of suppressing the need for meal announcements (*i.e*. no information on the time and content of meals). To raise the level of maturity of the solution, a new control-oriented model has been derived (Ben Abbes et al., 2011). This model has been next used in (Cormerais et al., 2011) to design explicit feedback control laws that require few computational resources. The EDS controller has to be tuned with two parameters (different for each patient) by a trial-and-error procedure (Cormerais and Richard, 2012). Note that the glycemic target has been used as a time-varying parameter for a better BG management during the day or at night. Using the first version of UVA/Padova simulator (Kovatchev et al., 2009), the robustness of the EDS controller was tested in several scenarios over a week, with meal variability.

In parallel, the same research group also designed a Proportional-Integral-Derivative with double phase lead controller (Ben Abbes et al., 2013), tuned from the frequency approach of control theory. *In silico* assessment shows BG values in the target range for 77% of the time for a 36 h scenario, including six unannounced meals, on the cohort of adult patients of the UVA/Padova simulator (adult 9 has been excluded). In both solutions, the authors underline, however, a need to develop a generic procedure to tune the controller in a systematic way. In addition, robustness against new variability introduced in a release of UVA/Padova simulator (Dalla Man et al., 2014) (Visentin et al., 2018) has to be studied before clinical trial assessment.

From the long-term model developed at Nantes (Magdelaine et al., 2015a), a positive Sliding Mode Control (SMC) (Menani et al., 2017) has been proposed. In (Menani et al., 2017; MohammadRidha et al., 2019), necessary conditions are derived to design a SMC which achieves the largest positively invariant set (PIS) for the insulin dynamics. Then, BG regulation can avoid an hypoglycemia event for any trajectory initiated in the PIS. In (Magdelaine et al., 2020), a state feedback control law is proposed to compute the required insulin correction bolus in real-time to avoid any hypoglycemia event. From this theoretical result, an international cooperation between Nantes and Argentinian researchers has been initiated to take advantage of the impulsive zone model predictive control (iZMPC) (Gonzalez et al., 2020) based on the long-term model (Magdelaine et al., 2015a). In parallel, a model-free intelligent proportional-integral-derivative (iPID) has been also investigated in (MohammadRidha et al., 2018), without considering the circadian variability.

Alongside, a research initiative led by biologists, bioelectronics and hospital practitioners has been patented at the University of Bordeaux in 2011 (Lang et al., 2011). The first contributions in control sciences were developed at IMS laboratory, during the French grant ANR DIABLO and the ECOS Nord Project (Grant M18M01) with Mexican researchers. Investigations focused on developing proofs of concept for a paradigm shift in insulin therapy, *i.e*. an *in silico* validation of a closed loop based on a static model of the patented biosensor (Lang et al., 2011; Perrier et al., 2018). By integrating pancreatic islets inside a bio-electronic device, the goal was to capture the influence of hormones on the glucose level. Such feature is currently not possible with the marketed CGM sensor. In (Olçomendy et al., 2020), a Proportional-Derivative controller has been tuned by minimizing the blood glucose risk. Assessment of the proposed solution has been next performed for both intravenous and subcutaneous roads (Olçomendy et al., 2021) in the UVA/Padova simulator. To tackle the variability between and within T1D patients, the construction of an uncertain Linear Time Invariant (LTI) control-oriented model - which can be seen as a family of linear models - from a cohort of adult patients was proposed in (Cassany et al., 2021a). The Linear Fractional Transformation (LFT) formalism was next used in (Cassany et al., 2021b) to formulate the robust control problem by using H_∞ mixed-sensitivity control approach. Due to the LTI feature, meal announcement is still needed, but it is possible to avoid asking T1D patient to estimate the amount of ingested carbohydrate, thanks to a patient-specific insulin bolus calculator (Olçomendy et al., 2022). In parallel, a nonlinear Model Reference Adaptive Controller (MRAC) has been studied (Franco et al., 2021b) and the assessment of SMC solutions for T1D patients in intensive care unit has been investigated (Franco et al., 2021a, 2023a), but only for the intravenous road.

5.2.2 Involvement of hospital practitioners at the interface of control and medical sciences

The main focus of clinical research is within a partnership between hospital practitioners and the pharmaceutical/medical device industry with regard to the testing of new molecules or systems. Basically, all major university hospitals in France participate in multicenter clinical trials (Renard et al., 2024b), and regularly publish practical rules for AID system (Renard et al., 2024a; Bismuth et al., 2025).

In addition to this standard framework, several transdisciplinary research projects emerged, as a result of the cooperation between biomedical science and engineering science. One historic reference is certainly provided by the long-standing cooperation between Montpellier University Hospital, the University of Virginia and the University of Padova (Kovatchev et al., 2010). The whole spectrum of research was considered, from modelling (Dalla Man et al., 2007) to adaptive control algorithms design and implementation (Renard, 2002). Another multinational cooperation in this field has been supported by the EU-funded project "*AP@Home - Bringing the Artificial Pancreas Home*", (Heinemann et al., 2011), in which Montpellier University Hospital was a research partner (Renard et al., 2016).

Furthermore, there are also the following initiatives: ***i)*** between the control research team of Supélec Rennes, and Dr. Isabelle Guilhem and Pr. Jean-Yves Poirier which are hospital practitioners at the University Hospital of Rennes, ***ii)*** between the control research team of LS2N laboratory, and Dr. Lucy Chaillous, Pr. Anne-Laure Fournier-Guilloux, Dr PhD Emeric Scharbarg and Pr. Michel Krempf working on clinical research, ***iii)*** between control and bio-electronic research groups of IMS laboratory, with the support of a biologist research team (Pr. Matthieu Raoux, Pr. Jochen Lang) of University of Bordeaux, Pr. Bogdan Catargi (diabetologist), Pr. Alexandre Ouattara (anaesthetist) and Pr. Edouard Gerbaud (cardiologist) with University Hospital of Bordeaux, ***iv)*** between a control research team of Paris Saclay, Air liquide group and Pr Jean-Pierre Riveline which works at APHP, Paris and ***v)*** between several hospital practitioners and CEA Leti, as part of the Diabeloop story discussed in the next subsection.

5.2.3 Positioning of French private sector

French government has supported an initiative launched in 2011 by Dr Guillaume Charpentier, diabetologist and chairman of the *Centre d'Étude et de Recherche sur l'Intensification du Traitement du Diabète* (CERITD). The initiated translational research project aimed to improve the day-to-day management of T1D by developing a closed-loop AID system. After the promising preliminary evaluation of a semi-closed-loop insulin therapy system (Quemerais et al., 2014), the company Diabeloop was created by Dr Guillaume Charpentier and Erik Huneker in 2015. The company formed a joint research laboratory with CEA-Leti. That year was also marked by the funding granted by the ANR to the DIABELOOP AP project, which focused on modeling the relationship between insulin, blood glucose levels and physiological data (heart rate, etc.) during an episode of stress and physical activity in T1D patients. In particular, ***i)*** an automatic classification algorithm to discriminate between 8 activity classes (lying, slouching, sitting, standing, walking, running, and cycling) was proposed in (Bastian et al., 2015), ***ii)*** Personalization of the compartmental physiological model used in the MPC algorithm has been proposed in (Jallon et al., 2017) to improve BG regulation, and ***iii)*** the first autoregressive with exogenous input (ARX) model using energy expenditure, carbohydrates on board, and insulin on board has been proposed for glucose prediction during and after physical activities (Romero-Ugalde et al., 2019).

First clinical trials, fund-raising, CE marking and rapid growth

Highlighting the combination of '*artificial intelligence*' and '*medical innovation*', Diabeloop launched its first clinical trials and raised an initial €13.5 million in 2017. Investors included ALIAD, the Air Liquide Group's venture capital investor, as well as funds managed by Supernova Invest, Sofimac Partners, Kréaxi, and Crédit Agricole's regional funds, which have subscribed to a €7.5 million capital increase. In 2018, the first medical device developed by Diabeloop obtained CE marking, enabling it to be marketed in Europe. This recognition was followed by a support of €2.8 million under the H2020-EIC Accelerator pilot program, with D2P project (*Diabeloop to Patients: An Artificial Pancreas solution to improve the balance, safety and autonomy of 20 million people*). This has led to the modeling of the variability of insulin sensitivity (Blanc et al., 2019) for the FIT paradigm and the design of a meal detection algorithm by using the extended isolation forest (EIF) concept (Zheng et al., 2020). In 2019, a funding of €31 million, the largest in Europe in the field of therapeutic artificial intelligence, has been obtained as part of Programme d'Investissements d'Avenir (PIA) program. An original closed-loop solution has thus highlighted an improvement for patients with T1D exposed to gastronomic meal intakes or to sustained physical exercise (Hanaire et al., 2020). In (Franc et al., 2021), it has also been shown that there is no more hypoglycemia on days with physical activity and a non-restricted diet when using a closed-loop system for 12 weeks.

Internationalisation and business

In 2020, Diabeloop opened a subsidiary in Germany (Diabeloop GmbH) and signed an exclusive development agreement with Terumo Corporation for the Japanese market. The CE marking of DBL-hu - an automated solution for the management of highly unstable T1D - has been obtained. The company began its commercial launch in Europe in 2021, with a presence in France, Germany, The Netherlands, Switzerland, Spain, Italy and other countries. In 2022, Diabeloop raised a third round of funding of €70 million to accelerate its international expansion. In 2024, Diabeloop obtained a further €15 million to continue its development and expansion. In January 2026, Diabeloop announced in a press release that it has received the 510(k) clearance from the US-FDA for DBLG2 algorithm, officially opening the doors to the US market for the company.

5.3 The French community on the international scene

While there are French contributions in the field of diabetes, it is honest to say that French researchers in control sciences need to make better headway on the international scene. This is particularly clear from the International Program Committee of the 1st IFAC Workshop on Engineering Diabetes Technologies (8 - 9 May 2025, Valencia), which includes only Eleanore Maeva Doron from CEA Leti as the French representative. This situation can be explained by a strong national priority focused on Diabeloop (a remarkable funding of over €100 million, as described above), without succeeding in fully bringing on board the researchers attached to the CNRS research laboratories. As a consequence, France's impact on the international scene remains limited.

Despite this situation, there are two encouraging points to highlight:

- Diabetologists are working with control researchers, and some of them have already collaborated with European control teams, see '*Involvement of hospital practitioners at the interface of control engineering and medical sciences*' section. This is particularly true for Prof. Eric Renard, who has been working for several years now with Prof. Claudio Cobelli (University of Padova) on modeling and closed-loop solutions.
- There are currently 5 hybrid AID systems available on the French market, including one French solution: Diabeloop. In addition, there is a French up-and-coming start-up (Eclypia) developing a noninvasive glucose sensor. Therefore, there is a level of technological maturity which can be of interest for the sovereignty of France.

Hence, there exists an opportunity to structure a French branch of the control community around the challenges posed by diabetes, by identifying original contributions, that would be complementary to the works being carried out:

- by Marc Breton's team at the Center for Diabetes Technology, University of Virginia, US, which works also on modeling and control engineering. A tight and long-standing collaboration between French clinical investigators and this group has been active through a series of clinical research projects led by Montpellier University Hospital and supported by the French Ministry of Health (*Programme Hospitalier de Recherche Clinique National*): Stop Hypoglycemia at Night (2014) (Renard et al., 2019), Freelife Kid Artificial Pancreas (2017) (Renard et al., 2022; Coutant et al., 2023; Bismuth et al., 2024), Artificial Pancreas at Diagnosis (2021) and the US National Institute of Health: *A Randomized Clinical Trial to Assess the Efficacy of Adjunctive Closed Loop Control Versus Sensor and Pump Therapy in the Management of Type 1 Diabetes Prone to Hypoglycemia* (2020) (Renard et al., 2023).
- in Claudio Cobelli's team at the University of Padova, Italy, which includes work on modeling (Prof. Dalla Man), control (Prof. Del Favero) and fault detection / alarms (Prof. Andrea Facchinetti), to name a few.
- in Francis J. Doyle's team at the School of Engineering and Applied Sciences of Harvard University, US, to model and analyze circadian rhythms, and control drug delivery for diabetes;
- by the Argentinian school (Prof. Ricardo Sánchez-Peña) with so-called automatic regulation of glucose (ARG) validated with clinical trials;

- at the Imperial College of London, UK, with Prof. Pantelis Georgiou and Pau Herrero (now with Roche diabetes care).
- by Prof. Thomas Desaive and his colleagues from the University of Liège, Belgium, to design model-based therapeutics and estimate insulin sensitivity in Intensive Care Unit (ICU);
- by Jorge Bondia's team with the Universitat Politácnica de València, Spain, working on modelling and the multiple drug delivery for diabetes;
- in J. Geoffrey Chase's group at the University of Canterbury, New Zealand, with a projection towards the concept of digital twins;
- in the team led by Levente Kovács at the University of Obuda in Hungary, with the use of model-based tools;
- by the Artificial Pancreas Trondheim research group coordinated by Prof. Anders Lyngvi Fougner with Norwegian University of Science and Technology,
- or at the Universidad Nacional de Colombia in Medellin with Prof. Pablo S. Rivadeneira which designs meal detection and impulsive model predictive control solutions for BG management.

5.4 Next challenges and open questions

5.4.1 Topics for convenient and effective day-to-day care

This section focuses on the implementation of effective treatment for the day-to-day life of patients with diabetes. The aim is to be compliant with the recommendations of hospital practitioners, *i.e.* to guarantee 70% of the time in normoglycemia (when glycemia is in the range 70-180 [mg/dL]). For a sustainable effect on metabolism, some studies (Zhang et al., 2025) suggest aiming for a smaller target: the so-called time in tight range (TITR) where BG has to be in the range 70-140 [mg/dL].

Whatever the targeted glycemia zone, the first hot topic is to define a T1D care to reach a full autonomy (Step 5), as highlighted in Section 1. To counteract the delays inherent to a AID system based on subcutaneous road (5–10 minutes of delay for glucose behavior in subcutaneous road, 20 minutes for insulin diffusion between injection and bloodstream entry, accuracy of CGM measurement), there are two on-going projects in France which involve a least one French researcher (medical or control sciences), with expected contributions in control engineering:

- ANR-MIMICbio (2024, *Mathematical modeling of human pancreatic islet electrical activity for bio-inspired and fully automated insulin delivery system*) proposes to i) build new bio-inspired dynamic models able to mimic the electrical activity of human pancreatic islets (with a main focus on β and α cells), ii) learn from patient's lifestyle to generate precursor signals that will enable meal intake anticipation under probability distribution framework, and iii) integrate both contributions for a health-aware bio-inspired control in a fully AID system.
- EIC Pathfinder MuSiC4Diabetes (2023, *Unobtrusive Continuous Multi-Metabolite monitoring for a physiological care of insulin-treated diabetes*) focuses on the de-

velopment of a fully implantable physiologic high-precision insulin delivery system connected to the multi-sensing device. This project involves a French practitionner and control researchers of Padova (Italy). The main interest will be the design of a technological innovation that avoids the aforementioned delays of current AID solutions for an improved BG regulation.

In this context, it could be interesting to follow the contributions obtained by these two consortia in the near future, to identify if an interesting collaborative research topic can emerge for the management of T1D.

While control sciences have its natural legitimacy in closed-loop AID systems, it could also make valuable contributions to pancreatic islet transplantation. One opportunity would be to focus on the control of quality of pancreatic cells (Raoux et al., 2023) used for transplantation. This would involve modeling and observation to detect, for example, an abnormal variation in the natural behavior of a pancreatic islet. Such detection could identify and eliminate poor quality islets to ensure a successful transplantation. This framework could therefore be carried out using tools from control sciences, at the interface of the PEPR MED-OOC which promotes islet-on-chip, organ-on-chip or organoid platforms for sustainable healthcare.

5.4.2 Diabetes in intensive care unit: positioning future needs

Despite technological advances to improve the daily life of patients with diabetes, there is still too little work carried out to integrate these new technologies into the management of diabetic patients undergoing surgery. A working group of the *Société française d'anesthésie et de réanimation* (SFAR) and the *Société francophone du diabète* (SFD) has established practical guidelines for the peri-operative management of diabetic patients (Gheisson et al., 2017; Cosson et al., 2018). One of the key messages of these documents is that an estimated 20% of patients hospitalized for general surgery and up to 40% for cardiovascular surgery (Adams et al., 2005) have known or unknown diabetes. Preoperative testing of glycated hemoglobin (HbA1c) (an indicator of the patient's glycemic stability) is therefore important to ensure glycemic control during the surgery, and in some cases to recommend an automated closed-loop intravenous system for administering insulin. This protocol is necessary, for example, to prevent the rapid onset of ketosis in patients with T1D and to combat longer hospital stays (Carles and Raucoules-Aimé, 2011).

Recent studies (Gerbaud et al., 2022; Baudu et al., 2022) seem to show that monitoring glycemic variability (GV) of patients with diabetes in cardiac intensive care units is a key factor in preventing complications and co-morbidities. More specifically, GV corresponds to variations in blood glucose level over the time, and its increase may contribute to cardiovascular complications (such as acute coronary syndrome). The dynamic feature of this GV indicator tends to make it highly relevant to address this health issue by using control sciences. Considering the research being carried out in France on the topic of anaesthesia (see the Chapter 2 of this volume) and the funding of an ERC to anaesthesia control (AMICAS - *Adaptive Multi-drug Infusion Control system for* *general Anesthesia in major Surgery*), there is a relevant research area for control community to position itself at the convergence of several clinical domains. For example, the use of some drugs in anaesthesia leads to hyper- or hypoglycemic effects. Ignoring these coupling effects means being vulnerable to uncontrolled glycemic variability. There is therefore a promising research area to address challenges of personalised medicine, at the frontier of the PEPR *Santé numérique* program.

5.4.3 Towards the prevention of other diabetes-related diseases

A cross-reading of the Interdisciplinary Health Research CNRS roadmap, coupled with the 2025-2030 strategic project of the *Haute Autorité de Santé*, which highlights two key themes: *Prevention* (Item 1) and *Digital and AI in health* (Item 3). This context opens the door to prognosis, a topic linked to control sciences. Now that health data is being structured, it would be interesting to initiate some opportunities to easily identify multi-pathology patients who are subject to regular health check-ups. Since diabetes can induce serious cardiovascular problems (such as stenosis and atherosclerosis) (Adams et al., 2005), this positioning should be of interest. For instance, one approach could be to develop a multi-scale/multi-physics model capable of describing the dynamical evolution of stenosis and atherosclerotic plaque for patients with diabetes. The parameters of this model could be estimated by using parametric identification algorithms. The model could then be used to predict the characteristic changes of atherosclerosis for patients with diabetes and to estimate the remaining time, before surgery is required. It can be made an analogy with the property of Remaining Useful Lifetime (RUL), defined by the Prognostics and Health Management (PHM) society. Thus, there is a great opportunity to position the French control community at the convergence of two clinical fields (cardiology and diabetes), to act in key areas identified as being in the society interest.

Closing words

From the discussions throughout this chapter, it is clear that there is a promising environment for positioning French initiatives in control sciences on diabetes-related issues. This chapter therefore serves to highlight this potential, and can be an input for initiatives aimed at bridging the gap between basic research and the needs of industry to meet the expectations of healthcare professionals in a context of national sovereignty.

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Chapter 6
Control sciences for medical robotics

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6.1 Context and challenges

Robotics has been a progressive answer to many issues encountered in the medical field across a wide range, and also opens new surgical solutions not feasible without it. Nowadays, the most famous and widespread robot is the *Da Vinci* (Intuitive Surgical) robot designed for assisting surgeons in laparoscopy. Nonetheless, there has existed a wide variety of medical robots since 1985 when a PUMA 200 robot was first used to help perform a biopsy in the brain of a patient under Computed Tomography (CT) imaging (Kwoh et al., 1988). The last 4 decades of robotic integration into the operating rooms have helped evolve many medical disciplines: surgery, interventional radiology, cardiology, radiotherapy ... As J. Troccaz tells in (Troccaz, 2024), the robot has become the ultimate link between the patients and their digital medical data, which opens to the surgeons a vision of their anatomy before and during operations that is not achieved without it. It also opens the way to assessing the right gestures and training novice staff. This chapter provides a short overview, focusing on French contributions of the research community in this domain.

Historically, the main motivation for using robots during surgical operations emerged with the arrival of Minimally Invasive Surgery (MIS) techniques that revolutionized open surgery practice during the '80s. MIS approaches and technical challenges are analyzed in (Vitiello et al., 2013; Troccaz et al., 2019). Indeed, the manual use of MIS tools imposed fatigue and musculoskeletal disorders on surgeons during long operations, and also required an assistant to hold the endoscope and follow the tools as the surgeon had his two hands occupied. Therefore, one of the first robots' objectives was to enable the control of the pose of the endoscope (Wang et al., 2023), sometimes commanded by the voice of the surgeon or pedals (such as AESOP[4]. Then, for the same reasons, followed the control of the position of surgical instruments, teleoperated by the surgeons located at their console nearby the patient (see PROBOT (Harris et al., 1997)). Across all medical disciplines, surgeons consistently face a set of common challenges:

1. Long procedures generate fatigue that raises hand tremors. Robotic systems can compensate for this and provide better stability (Csókay et al., 2009).
2. Getting precise real-time information can be complex with current medical imaging systems. Besides the aforementioned endoscopy, ultrasound, X-ray and Magnetic

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[4] AESOP: Automatic Endoscopic System for Optimal Positioning

Resonance Imaging (MRI) techniques find benefits with robotic help (Salcudean et al., 2022).

3. Navigating some anatomical areas is challenging, such as in pelvic fracture repairs and spine surgeries. To illustrate this, recent advances in robotics offer a higher degree of dexterity in confined spaces for MIS, such as concentric tube flexible robots (Girerd et al., 2020a), and untethered small-scale robots (Daguerre et al., 2022). Flexible robots are designed in such a way as to have a continuously deformable structure, which makes them ideal for navigating complex environments and performing delicate tasks in MIS. They have a significant impact on medical procedures (Schegg et al., 2022). Also, more targeted medicine can be delivered at the micrometric scale: for instance, targeted drug delivery, with untethered small-scale robots (Boudaoud et al., 2013; Daguerre et al., 2022), or nanoparticles steered by external magnetic actuation servoing (Abbes et al., 2023).
4. Some operations require sub-millimeter accuracy with risks of tissue disruption. Robotic systems enable surgeons to tailor, plan and execute such procedures, improving surgical outcomes. For instance, Computed Tomography (CT) or MRI guided needle insertion in interventional radiology procedures is a critical issue as more than 600,000 acts are performed each year in the USA. In more than 10% of the cases, the target is not reached, and it is often necessary to insert the needle more than once to successfully reach the target (between 10 and 30% of cases, depending on the difficulty) (Éderson Dorileo et al., 2022).
5. Surgeons and patients need to be protected. Typically, fluoroscopy-based operations induce X-ray exposure to patients and surgeons. Inserting a robot between the patient and the surgeon offers reduced radiation exposure to the surgeon (Wang et al., 2021) but also to the patient, such as in the radiotherapy context (Gerlach and Schlaefer, 2022).
6. Medical students, surgeons, and healthcare professionals must remain proficient in their abilities to respond effectively to all professional situations and need to stay current with the latest advancements. They require regular skills training to learn new medical protocols and stay updated on infrequent cases. More specifically, they need realistic, iterative, and continuous practice in a risk-free environment; the training involving real patients and animals should be phased out. Given the constraints on their time, they demand facilities that offer immediate feedback and assessment while minimizing reliance on experienced colleagues (Giovanelli et al., 2024).

Out of the operating room, robots can also relieve the physical burden on the therapist by taking charge of the conventional rehabilitation work of the patient (Courtois et al., 2021). They can be implanted in/on the patient body as medical devices, such as artificial pancreas-like closed-loop insulin pumps (Scharbarg et al., 2022), active therapeutic devices to combat scoliosis (Ray et al., 2023) and cardiac assist devices (Hammoud et al., 2024). Less intuitively, robots can provide nursing and assistance (Christoforou et al., 2020), and train medical students and expert physicians on difficult medical gestures, with the help of haptic (kinesthetic or tactile) feedback, and help respect the principle "never the first time on the patient" (Cuvelier, 2018; Zara et al., 2025). Robots bring new imaging means such as mass spectrometry imaging (MSI), which is conventionally performed *ex vivo* from tissue sections, and can be realized *in vivo* only with the help of a robot (Ogrinc et al., 2021).

To do so, and to provide novel mechatronics compliant with medical usage including safety, reliability, and precision, the following scientific questions need to be investigated.

1. Microrobots require complex control laws. Improving their control efficiency and precision, while they are limited by their small scale, computing power, power supplies, and sensors is complex (Jiang et al., 2022). Also, Machine Learning is expected to enable microrobots to adapt to more dynamic environments and undertake more complex medical tasks (Yang et al., 2024).
2. Soft robot control often leverages other scientific disciplines, such as continuum mechanics, material science, computational mechanics and computer graphics (Armanini et al., 2023). Controlling these robots is still an open challenge due to underactuation, environmental interactions, actuator dynamics, task space control, and using data in a model-based framework (Della Santina et al., 2023). The modeling of *continuum robots* (Tummers et al., 2023; Xun et al., 2024) and control (Zhang et al., 2019; Chikhaoui and Rosa, 2022) have become a very active research topic recently. Also, the control of cable-driven robotic endoscopes, which present significant friction (Abdelaziz et al., 2017) and backlash (Poignonec et al., 2023) is still a challenge.
3. In the medical context, control law design approaches include model-referenced control, sensor-referenced control, advanced control (ie adaptive, robust, AI-based) and motion generation (Bamaarouf et al., 2024). One of the difficulties lies in determining the control parameters without resorting to techniques that are either empirical or require too high a level of knowledge of automatic control (Bamaarouf et al., 2024). Typically, precise medical data are rare, often obtained from cadavers or animals. The diversity of patient cases motivates for adaptive control strategies, such as in gait assistance devices (Arnez-Paniagua et al., 2019).

6.2 Contribution of the French Control community to the field of medical robotics

Over the past decade, the French Control community has significantly contributed to advancements in medical robotics, addressing critical challenges in areas such as haptic training simulations, flexible, continuum and soft robotics, and modeling and control for surgical assistance. This section, even if not exhaustive, highlights part of the key contributions, showcasing their impact on improving healthcare technologies.

Haptic Training Simulations

The French Control community has established an empirical design process for haptic training simulators by leveraging multidisciplinary expertise. This process (see Fig. 6.1) begins with professional practice analysis to identify procedural skills and didactic objectives. These insights are then used to define simulator specifications, which guide the didactic/robotic co-design phase. This approach also involves trainee gesture evaluation for objective assessment, followed by simulator validation and the development of control laws for both pneumatic and hybrid (pneumatic-electric) actuation systems (Khalek et al., 2021; Alamilla et al., 2022; Vadcard, 2022; Gosselin et al., 2013; Bouchigny et al., 2020; Zara et al., 2025).
Recent technological advancements have significantly enhanced haptic training simulations. For instance, hybrid actuation, combining pneumatic and electric systems, has improved kinesthetic feedback (Sénac et al., 2019), while the development of novel tactile actuators has enhanced tactile feedback mechanisms (Gil et al., 2022) (see Fig. 6.2). Additionally, researchers at institutions like the CEA have worked on advanced actuation technologies, such as using the piezoelectric effect or magneto-rheological (MR) fluids. The integration of these actuators into robotized simulators allows for ”Human in the loop” interaction, and requires the consideration of control algorithms that remain stable, even when cycle times exceed the typical limits of haptic interaction.

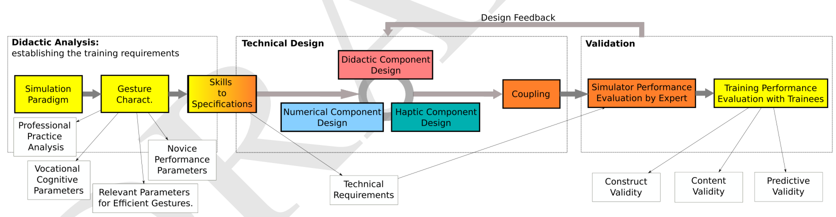

Fig. 6.1 Haptic Training Simulation Process Proposal

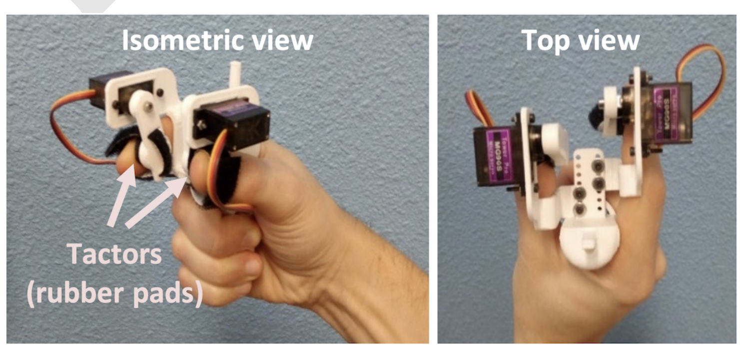

Fig. 6.2 Portable haptic device for robotic surgery training, (Gil et al., 2022).© LIRMM.

Flexible Robotics

Flexible manipulators have undergone significant advancements in recent years due to their versatility, compliance, and safety. Research in Flexible Robotics encompasses various systems such as continuum robots, tensegrity mechanisms, and soft manipulators made from hyperelastic materials. Despite their numerous advantages, these systems pose substantial challenges in modeling and control due to their combination of geometric and material nonlinearity, as well as the leverage provided by their inherent compliance.

... for endoscopic surgery

In the context of minimally invasive surgery (MIS), endoscopic robots are revolutionizing how surgeries are performed by providing better standards of care for patients. These robots typically feature a tubular system comprising a flexible passive proximal section and an active distal section. The distal section can bend continuously along its length, forming an equivalent structure of an infinite number of joints with zero link length, known as a continuum robot (CR). The impact of CRs on the medical field is increasing due to their small size, high dexterity, flexibility, accuracy, and ability to navigate complex paths (Benoist et al., 2024). French research teams such as TIMC-Grenoble, iCube-Strasbourg, LIRMM-Montpellier, and FEMTO-ST-Besançon labs to name a few, have made significant advancements in addressing critical challenges in the design, modeling, and control of these systems. Notable progress includes system identification, state estimation, and closed-loop control based on ultrasound images, which have been applied to needle steering robots used in brachytherapy (urology) (Lapouge et al., 2018, 2021). Modeling based on a geometrically-exact approach derived from Cosserat rod theory has been intensively investigated for tendon-actuated continuum robots (Tummers et al., 2023), concentric tube continuum robots (CTCR) (Boyer et al., 2024), and continuum concentric push-pull robots (Tummers et al., 2024) (cf. Fig.6.3). Robot calibration and closed-loop, model-based control of CTCR were performed using long-term ultrasound feedback. A comprehensive literature review on modeling and control of continuum robots, which recalls recent advances in the field, is provided in (Chikhaoui and Rosa, 2022).

In (Zorn et al., 2018), a telemanipulated robotic assistant for surgical endoscopy, named STRAS, was introduced and evaluated with a preclinical application to endoscopic submucosal dissection. In (Girerd et al., 2020a), an automatic tip-steering approach for concentric tube robots based on visual SLAM (simultaneous localization and mapping) was presented. This approach enables a closed-loop control scheme to compensate for open-loop errors and allows the surgeon to focus on the medical procedure, simplifying deployment management. A combination of navigation by SLAM and follow-the-leader (FTL) deployment for controlling concentric tube robots (CTRs) was also proposed in (Peyron et al., 2019; Girerd et al., 2020b).

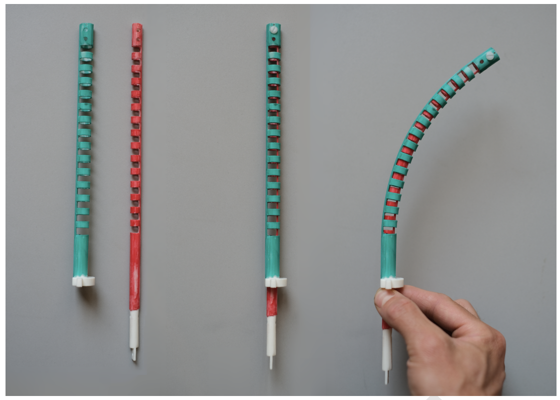

Fig. 6.3 Photo of a two-tube continuum concentric push-pull robot developed at TIMC, (Tummers et al., 2024). © TIMC.

In (Chen et al., 2009), the development of pneumatic-driven flexible robotic manipulators for colonoscopy, known as ColoBot, was presented. This work introduced a sensor-based position control system for guiding the robot through a tubular, compliant, and slippery environment. A collaborative research project through a CIFRE (industrial+academic) thesis between the LIRMM Lab and the French Caranx Medical Company focused on the design and control of a flexible robot for minimally invasive surgery and endoluminal navigation. In (Benoist et al., 2024), a design combining 3D-printed flexible notched tubes with rods routed in their walls was presented, aiming to reduce axial compression in tendon-driven robots and allow for more precise control over the robot's length (cf. Fig. 6.4).

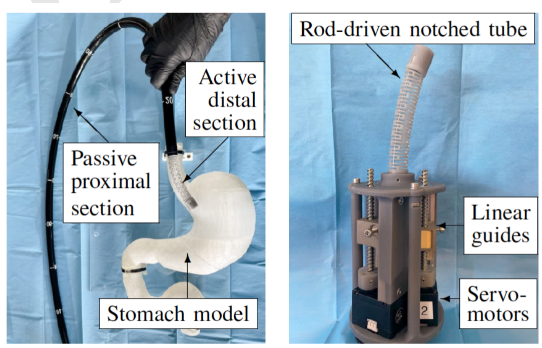

Fig. 6.4 (Left) Photo of the proposed flexible endoscopic robot concept, and (Right) photo of the proposed rod-driven notched tube robot prototype, (Benoist et al., 2024). © Caranx Medical.

Another interesting strategy was proposed in (Calme et al., 2023), where the design and control of a discrete snake-like robot based on Shape-Memory Alloy (SMA) actuation were introduced (see. Fig. 6.5). Each module of the robot features three stable states, providing a discrete workspace and simplified open-loop control. This approach combines the mechanical stability of the modules with an easy-to-use direct kinematic model, avoiding the need for complex control strategies. In (Awada et al., 2024), a thick cylindrical pneumatic actuator was considered in the context of a soft parallel robot for clinical applications, specifically in digestive/gastric surgery (see. Fig. 6.6). The analytical solutions for the manipulator's models were derived using the Yeoh strain energy density function. The advantage of this model is that it guarantees the existence of an analytical solution regardless of the material used to fabricate the actuator. The control of the system will be addressed in future work.

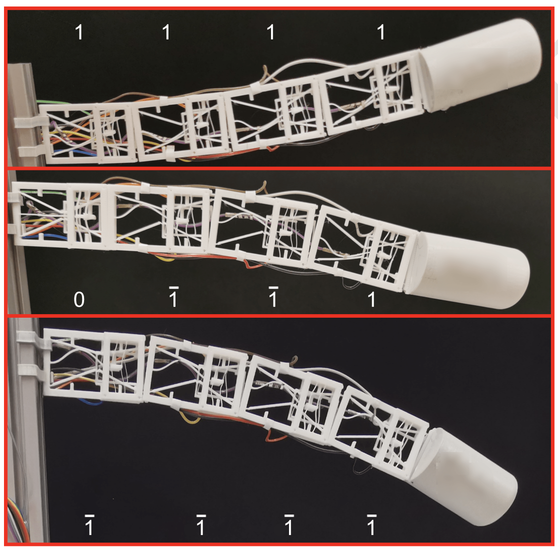

Fig. 6.5 Prototype of the discrete snake-like robot based on Shape-Memory Alloy (SMA) actuation developed at LIRMM, (Calme et al., 2023). © LIRMM.

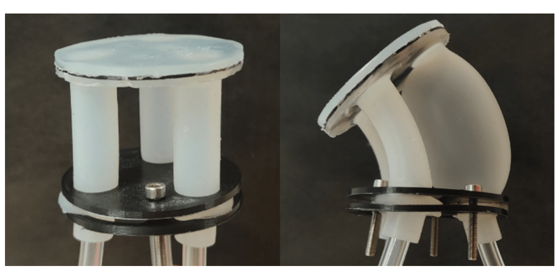

Fig. 6.6 Prototype of the soft parallel robot with 3 soft thick cylindrical pneumatic actuators developed at LIRMM, (Awada et al., 2024). © LIRMM.

Furthermore, a new type of soft robot, known as tip-extending, everting, or 'vine' robot, is under active development in the soft robotics community, with applications in the medical field. Inspired by the growth of biological systems such as plants, these robots consist of long inflatable bodies that deploy in their environment by growth, with the principle of material eversion (Hawkes et al., 2017; Harthy et al., 2025). This technology is particularly interesting for reaching challenging areas of the human body, such as the bronchial pathways, the depths of the lungs (Davy et al., 2024) or the digestive tract (Giri et al., 2025). Researchers at LIRMM and FEMTO-ST are working on applying these soft everting robots to urology (ANR JCJC EXTRACT 2024, LIRMM) and patient intubation (ANR PRCE RESPIRE 2025, collaboration between FEMTO-ST and LIRMM).

... for cochlear implantation

In the context of ear surgery, the optimal design of cochlear implants has been a highly active research area in recent years. Numerous articles have addressed topics such as modeling, control, and design, employing various actuation strategies (magnetic, tendon, fluid actuation, concentric tubes, etc.), which have led to promising outcomes. For example, in (Thuillier et al., 2024), a tendon-driven robotized cochlear implant, defined as a Soft Micro-Robot (SMR), has been modeled and designed with optimal bending stiffness to achieve a specified clinical objective (see Fig. 6.7). This work has been conducted in collaboration between the LIRMM Lab. and Stanford University within the CNRS International Research Project (IRP) LIRMM-Stanford collaboration and a CNRS-MITI PhD thesis.

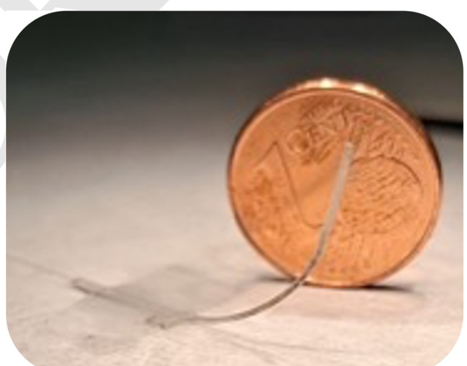

Fig. 6.7 Lab. prototype of a tendon-driven robotized cochlear implant, (Thuillier et al., 2024).© LIRMM.

... for interventional radiology

Interventional radiology (IR) is an image-guided percutaneous intervention used for both diagnostic and therapeutic purposes. The clinical demand for such interventions is growing, as they are minimally invasive. In the field of IR, the interaction modeling between clinical tools (typically needles) and patient tissues, as well as robot design and control, are critical for planning and performing safe procedures. Several French research teams are addressing some of the scientific challenges in this domain.

- Regarding tool/tissue interaction modeling, works proposed in (Barbé et al., 2007) and (Barbe et al., 2007) (iCube lab.) present robust methods for online force estimation in typical percutaneous interventions and model estimation of the interaction between tissues and a surgical needle. In (Éderson Dorileo et al., 2022) (LIRMM lab.), the researchers propose an image-based interaction model that is compatible with both CT and MRI constraints in clinical scenarios. A key feature of this approach is that it does not rely on force measurements.
- In terms of robot control, notable work includes the collaborative efforts between LIRMM and iCube labs within the LabEx CAMI framework, focusing on the design and control of Remote Center of Motion (RCM) tensegrity mechanisms for needle manipulation. In (Jurado Realpe et al., 2021), a Model Predictive Control (MPC) approach is introduced for trajectory tracking and stiffness modulation in a 1-DOF RCM mechanism. Building on this work, (Realpe et al., 2020) introduces an asynchronous and decoupled position and stiffness control strategy for a novel 2-DOF RCM tensegrity mechanism.
- Needle insertion procedures under ultrasound guidance are commonly employed for diagnosis and therapy. Ultrasound is an appealing imaging modality for both diagnostic and interventional purposes due to its non-invasive nature, affordability, and real-time capabilities. However, the quality of ultrasound imaging, and thus needle positioning, heavily relies on the clinician's expertise. To address this limitation, robot-assisted ultrasound systems have been developed, with tele-echography emerging as a key solution to facilitate remote examinations by specialists, particularly for patients in medically underserved or isolated areas (Vieyres et al., 2006) (PRISME lab.). Also, in (Daniel et al., 2020), the Ampère lab has developed a haptic simulator designed to help primary care physicians master the synchronization between the hand holding the ultrasound probe and the hand manipulating the needle.
- Image control has also become a point of interest to facilitate the manipulation of the ultrasound probe and optimize the quality of robotic ultrasound imaging while tracking an anatomical target. For example, in (Chatelain et al., 2016) (Inria/IRISA Project-Team, Rennes), a multitask control framework is proposed to control the in-plane motion of a convex probe mounted on the end-effector of a robotic arm. This framework is based not only on the target's position in the image but also on features extracted from an ultrasound confidence map.
- Flexible needle path planning, steering, and precise positioning in moving biological tissue using ultrasound and/or force feedback have also been explored within the French community (Chevrie et al., 2018; Dorileô et al., 2015; Bernardes et al., 2011) (Inria/IRISA Project-Team, Rennes, LIRMM lab.).

Surgical Assistance and Automation

Motion Compensation and 3D Reconstruction ...

... for Minimally invasive surgery (MIS)

As mentioned in the introduction, MIS has gained significant popularity in recent years. The use of advanced robotic systems to assist surgeons can enhance the accuracy of surgeries and reduce patient risk. However, physiological motions continue to pose a challenge for robotic-assisted surgery, and no comprehensive solutions for compensating these motions are available in existing surgical robotic platforms. Breathing and heartbeats are the two primary sources of physiological disturbances. Against this backdrop, several French research teams such as i-Cube, LIRMM, ISIR labs. have been working to address some of the scientific challenges in this field and alleviate the issues associated with physiological motion. For instance, in (Ginhoux et al., 2005), an adaptive disturbance predictor is introduced, using visual tracking of the heart surface. Artificial markers are placed on the heart to track its surface motion; the predicted disturbance values are then used in a Generic Predictive Control system to anticipate the disturbance effects. In (Ott et al., 2011), visual servoing is employed to control flexible endoscopes, enabling them to automatically track an area of interest despite breathing motion.

In (Richa et al., 2010, 2011), a robust visual tracking method is proposed to estimate the 3D temporal and spatial deformations of the heart surface using stereo endoscopic images. This method aids in the estimation and compensation of heart movements during cardiac surgery. The novelty of this work lies in combining a visual tracking method based on a Thin-Plate Spline (TPS) model to represent heart surface deformations with a temporal heart motion model based on a time-varying dual Fourier series. This combination helps overcome tracking disturbances or failures. In (Cagneau et al., 2007), a force controller based on Iterative Learning Control (ILC) is proposed to compensate for breathing motions. In (Zarrouk et al., 2010), a feedback force control system based on Model Reference Adaptive Control is introduced, and its effectiveness and robustness are validated through simulations. In (Cortesao and Poignet, 2009), a control scheme based on Active Observers (AOB) is proposed for compensating beating heart motion. This scheme uses two AOBs: the first guarantees desired closed-loop dynamics for force, while the second compensates for physiological motions without taking control actions. In (Moreira et al., 2012), a force control scheme using an Active Observer based on the Kelvin Boltzmann interaction model is presented. The scheme includes a feedforward term and disturbance estimation to improve compensation for disturbances.

In (Bachta et al., 2007), an alternative solution is proposed, involving a mechanical stabilizer to locally suppress heart excursion. This work proposed the design, modeling, and control of an active stabilizer capable of compensating residual heart motion. The system consists of an actuated cardiac stabilizer and an exteroceptive active vision measurement. Using this feedback, the stabilizer was controlled to cancel out residual cardiac motion. Similarly, in (Gagne et al., 2012), the modeling, observer-based control, and validation of an alternative solution that uses a control moment gyroscope to generate compensatory torque and an accelerometer for sensing are discussed. This approach makes the system completely independent from the stabilizing instrument and any external measurement sources.

... for *In-Situ* Robotic Bio-Printing

In the context of deep skin lesions caused by burns, an emerging solution is *in situ* robotic bio-printing, which involves printing skin cells directly onto the wound to accelerate the healing process. Studies have shown that this approach improves both the speed and quality of healing compared to traditional methods. However, the human body is subject to respiratory movements, which can compromise patient safety and negatively impact the quality of deposition, especially in mobile areas.

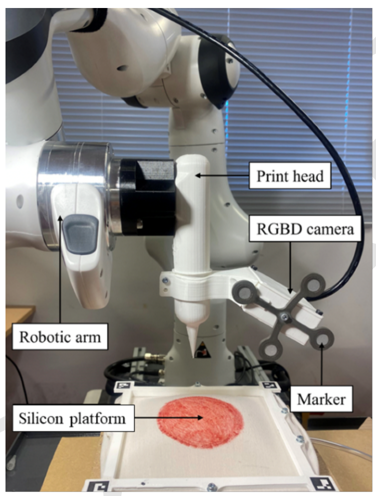

Fig. 6.8 Robotized *in situ* bio-printing platform developed in the BlocPrint 2 ANR project, (Cuau et al., 2024). © LIRMM.

The aim of the French ANR collaborative project (BlocPrint 2 ANR project: a collaboration between LIRMM Lab and Labskin Creations) is to enhance *in situ* bio-printing by using a robotic platform that compensates for physiological movements (cf. Fig. 6.8). In this project, the team proposed and implemented a predictive path following control (PPFC) within the developed robotic bio-printing platform, which controls five degrees of freedom (DoFs) of the end-effector. The remaining (decoupled) translational degree of freedom is controlled by an external controller (Santos et al., 2023). To estimate and compensate for respiratory motion, the team also proposed modeling 3D non-rigid surface deformation using a Thin Plate Spline (TPS) model, observed via an RGB-D camera (Cuau et al., 2024).

Gesture guidance for surgery...

... through comanipulation

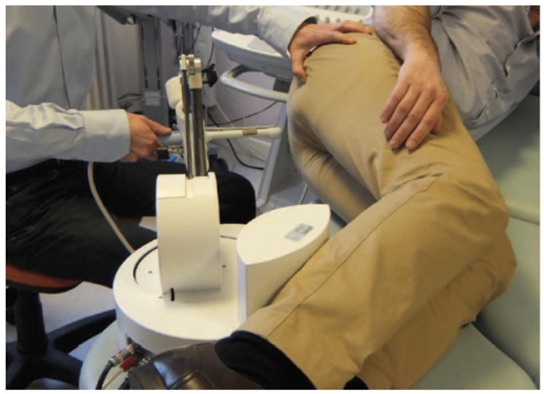

Fig. 6.9 The 6-DOFs Apollo robot assisting an urologist who comanipulates an endorectal ultrasound probe with virtual fixtures constraints, (Vitrani et al., 2017). © ISIR.

Co-manipulation is a paradigm in which a robot and a subject simultaneously hold a tool and collaborate on performing a task, enabling gesture guidance. In particular, virtual fixtures—geometrical constraints imposed on the tool by the robot—have garnered significant interest in surgical applications. So far, this concept has been successfully implemented in open surgery and applied in minimally invasive surgery, including assisting endorectal prostate biopsies (Vitrani et al., 2017, 2016), where the tool is inserted into the patient through a fulcrum. A key challenge in this context is to return the forces felt by the surgeon that are virtually applied at the instrument's distal tip, while the robot is physically attached to the instrument's proximal handle.

In (Bamaarouf et al., 2024), a new collaborative assisting system was introduced specifically for ultrasound examinations (Institut Pascal). The primary objective is to develop a transparent co-manipulation strategy that allows clinicians to maintain their natural gestures during the procedure. To achieve this, a novel co-manipulation control strategy has been devised, which computes a virtual solid's path based on the operator's interaction. This approach offers several advantages over conventional control techniques: it improves accuracy, reduces task execution time, facilitates intuitive parameter adjustments, and requires less force exertion from the operator.

... through teleoperation

A teleoperated surgical robotic system enables surgical procedures to be performed over long distances using both wired and wireless communications, offering a wide range of capabilities that can significantly impact surgical outcomes. While these systems have driven significant advancements in surgery over the past decades, they are not without limitations. For example, time delays—commonly caused by data transmission within the communication channel connecting the master and slave in bilateral teleoperation—can destabilize the entire teleoperation system.

To address the instability caused by time delays, a wave variable transformationstructure was proposed in (Guo et al., 2019) to passivate delayed communication channels, ensuring system stability. More recently, researchers in (Almasalmah et al., 2023) leveraged advancements in adaptive robust Model Predictive Control (MPC) to design a controller for bilateral teleoperation systems (LIRMM lab). Their approach focused on guaranteeing transparency, robustness to environmental uncertainties, and controller safety. To achieve this, they incorporated polytopic tube controllers into the MPC design and utilized online learning methods to dynamically model the environment.

In the context of vertebroplasty — an intervention involving the injection of bone cement into the vertebral body — (Lepoutre et al., 2016) presents a bilateral teleoperation control system designed for slow and precise orthopedic cement delivery under fluoroscopic guidance. This system employs a rate-control strategy with force feedback, ensuring stability and transparency while accommodating the non-linear, time-dependent behavior of the injected material.

... through automatic gesture execution

Autonomous robotic surgery is an emerging field focused on integrating robotic systems with various levels of autonomy to execute surgical procedures. In the context of robotic-assisted spine surgery, where robotized assistants are employed to position physical guides based on pre-operative planning and per-operative image-based registration, the work presented in (Da Silva, 2022) explores advancing robotic assistance in spine surgery towards automated gesture execution by integrating appropriate sensory feedback (ISIR lab). More specifically, the study investigates the use of bony tissue bioelectrical impedance measurements during drilling, leveraging an electrical conductivity sensor and a Bayesian-based algorithm to enable real-time detection of spinal canal perforations. The focus has been on developing an algorithm capable of detecting a bone breach and immediately stopping the robot to prevent damage to the spine or surrounding soft tissues.

Ongoing Works

Several areas are still under development, such as the integration of advanced control strategies in flexible robots and the increasing automation of surgical systems. The automation paradigm shift is being driven by the progressive integration of artificial intelligence (AI) and machine learning (ML) into the field of surgical interventions. Regarding flexible robots, despite their potential, their practical use is limited by issues such as lower precision, difficulties in sensor integration, and an incomplete understanding of their environmental interactions, which hinder autonomous task performance. These challenges remain active research topics for the French control community.

However, there is a strong belief that, in the near future, human health will increasingly be managed at the cellular level, rather than at the organ level through surgery. Microsurgery, drug delivery, and cellular therapy are already emerging as pivotal research areas where robotics and control engineering play a crucial role (Abbes et al., 2023; Massoud et al., 2025).

Robotic assistance seems to be a promising approach to enhance inner ear treatments and, more particularly, to enable precise and effective drug delivery into the human cochlea. For instance, in (Abbes et al., 2023) (in PRISME lab, see Fig. 6.10), a study investigated nanoparticle steering in the cochlea using push/pull forces, achieving accurate dosage and controlled drug delivery via magnetic actuation. In (Thuillier et al., 2024), a soft micro-robot was developed for cochlear implantation and drug delivery, providing an innovative tool for addressing inner ear challenges (LIRMM lab).

In the context of *in vitro* fertilization (IVF), (Gerena et al., 2024) presents a comprehensive mini-review exploring the advantages, recent advancements, and future prospects of robotisation in IVF. The review highlights the transformative impact of robotics on addressing the evolving demands of Assisted Reproductive Technology (ART) laboratories. Similarly, (Yin et al., 2017) introduces a novel 3D force-sensing method for optical tweezers. This development enhances automated biological tasks, enabling real-time, interactive biomanipulation.

In the realm of microrobotics, innovative systems continue to emerge. A novel family of microrobots capable of moving in liquid media to perform tasks in interaction with biological samples in a Petri dish has been developed as part of the ANR project Optobot (Interactive Optical Robots for Biophysics, 2022-2026). Moreover, the CoDiCell ANR project (2018-2021) focused on developing innovative methods for trajectory control of large populations of biological cells inside fluidic chips at high speed. This project has paved the way for applications such as adoptive cell therapy (ACT), an emerging anticancer treatment approach.

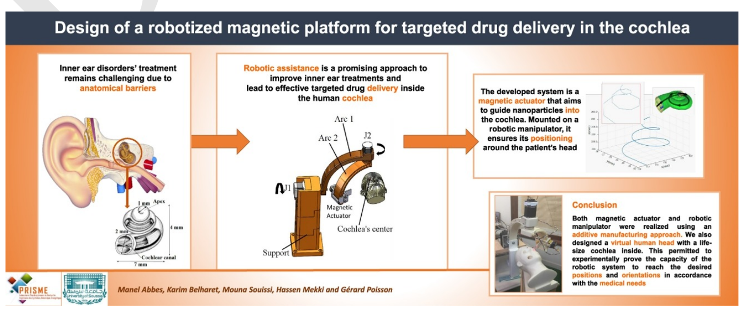

Fig. 6.10 Example of robotized targeted drug delivery (Abbes et al., 2023).

6.3 The French community on the international scene

French robotics research teams have established collaborations with laboratories worldwide. This section aims to provide an objective overview of these partnerships, categorized by geographical regions. The collaborations vary in duration, with some being long-standing and others newly initiated. The density of these partnerships reflects the research capabilities and strengths of the countries involved.

On the European scale, for space reasons, let us cite only a few European projects in the medical robotic theme:

- μRALP (Micro-Technologies and Systems for Robot-Assisted Laser Phonomicrosurgery, 2012-2015): Pioneered research towards a complete redesign of current **laser microsurgery systems**, focusing on the development of robotic micro-technologies to enable endoscopic operations (Mattos et al., 2021): it involves Femto-ST (France), two Italian teams: the Istituto Italiano di Tecnologia (IIT) and the Università degli Studi di Genova (UNIGE), and one German lab: Leibniz Universität Hannover (LUH).
- H2020 FAROS (Functionally Accurate RObotic Surgery, 2021-2024): Aimed to develop surgical robots with advanced sensing capabilities for complex surgical tasks. It included the ISIR laboratory, KU Leuven in Belgium, King's College London in the UK, and the University of Zurich in Switzerland.
- Horizon Europe REGO (Cognitive robotics tools for human-centered small-scale multi-robot operations, 2019-2023): Aimed to develop an innovative set of AI-powered, microsized, untethered, stimuli-responsive swarms of robots. It was coordinated by IRISA lab and included teams from the University of Twente, Nederlands, la Scuola Superiore Sant'Anna, and the IIT in Italy, and Helmholtz-Zentrum Dresden-Rossendorf in Germany.
- TEF-Health (Testing and Experimentation Facility for Health AI and Robotics, 2023-ongoing): Aims to test novel AI approaches in real-world scenarios. It involves partners from nine European countries and is led by the Berlin Institute of Health at Charité.
- ATLAS (AuTonomous intraLuminAl Surgery) Marie Curie European Joint Doctorate school (813782): targets the training of experts in a very specific branch of Robotic Surgery, coordinated by the University of Leuven, and implemented by a consortium of seven Universities and industrial partners.
- IRISA and Max Planck Institute for Biological Cybernetics (Germany) on topics including motion control for mobile robots, visual control, and shared control.
- Spirits project (2017-2020), a three-country collaboration between ICube (France), the Furtwangen University and the Heidelberg University (Germany), the University of Applied Sciences and Arts and the EPFL (Switzerland), on the topic of Robotics for surgery and interventional radiology.
- COBRA project (57 months): featuring notably the TU Delft (Nederlands), and the University of Portsmouth (UK), and the CRIStAL lab (France) to improve the practice of brachytherapy through the design of a robot intended for the diagnosis and treatment of localized soft tissue cancers such as prostate cancer.

At a smaller scale, we can cite some European bilateral collaborations, with labs in England. For instance, LS2N and SYMME labs work with the Imperial College, London respectively on EMG signal processing for robotic hand prostheses. There is also an initiative on simulation and modeling in Medicine and Surgery, and TIMC works with St Thomas' Hospital in London.

On the other side of the Atlantic, numerous collaborations exist with American research centers. For instance, ICube and LIRMM both work with Stanford University (more precisely with Pr. Allison Okamura and Pr. Oussama Khatib within the IRL between the LIRMM and U. Stanford), ICube with the University of Houston and the University of Montreal. TIMC is involved in the International Associated Laboratory (LIA) "EvoAct" with the Michigan State University focusing on "Evolution In Action with Living and Artificial Organisms". In Canada, Ampere has collaborated with the University of Alberta, more specifically with Pr. M. Tavakoli of the Telerobotic and Biorobotic Systems Group and Pr. I. Cheng of the Multimedia Research Group.

In Asia, the JRL (Joint Robotics Laboratory) is a joint laboratory, created in 2003 and established between the CNRS (Centre National de la Recherche Scientifique) and the National Institute of Advanced Industrial Science and Technology (AIST) located at Tsukuba, Japan. The researchers from both countries are closely collaborating to increase robot's functional autonomy, especially using the humanoid platform. Also, the LAAS lab is linked to the Laboratory for Integrated Micro-Mechatronics Systems (LIMMS) in Tokyo, focusing on micro-nano technologies for bioengineering and biosensors. We have not found any exposed collaboration between Korean and French research labs even though IRIS lab in the Korea Advanced Institute of Science & Technology (KAIST), located in Daejeon, is very active in this research topic.

There also exists Oceanian collaborations. For instance, IRL Crossing (frenCh austRalian labOratory for humanS / autonomouS agents teamING) is an international research laboratory created by the CNRS gathering three Australian universities (Adelaide University, the University of South Australia, and Flinders University), a French Engineering school IMT Atlantique, and the industrialist Naval Group. It has been created in 2021 and it aims at designing new ways for humans to work with robots and autonomous systems.

Concerning Africa, we can cite a collaboration between the MICA laboratory of the University of Bordeaux Montaigne with the University Institute of Applied Sciences and Technologies of Man (UISTAM) in the Ivory Coast, on the topics of artificial intelligence and autonomous robotics. However, we could not find as many samples as in other continents. We can guess that there must exist collaborations between French labs and, at least, Submediterranean countries, but they are not highlighted.

Due to space constraints, this overview is not exhaustive. We apologize for any significant collaborations that may have been inadvertently omitted. It is important to note that public information about many smaller collaborations, particularly between France and African and Middle Eastern countries, may be limited, likely because they are not funded by large-scale programs. Nevertheless, there is a significant exchange of robotics students between universities worldwide, and it is reasonable to assume that a similar exchange occurs among researchers.

6.4 Hot topics and open questions

Robotics has revolutionized medical procedures by enabling tasks to be performed with greater precision and introducing innovative treatments (Dupont et al., 2021). This has led to improved patient care, expanded treatment options for complex conditions and training new generations of practitioners. Control engineering has played a crucial role in their development. However, several technological challenges remain, preventing robotics from reaching their full potential in healthcare (Troccaz et al., 2019). Control engineering will continue to be a driving force in addressing these issues, ensuring that medical robotics evolves to meet the needs of modern healthcare. In this section, we highlight the key research areas in automatic control that the French community should prioritize to maintain an active and leading role in the development of medical robotics. We outline critical technological issues that must be addressed by the Automatic Control community to fully unlock the potential of robotics in healthcare (See Figure 6.11.). We also address non-technological challenges related to funding, training, data accessibility, and bridging the gap between research and clinical deployment.

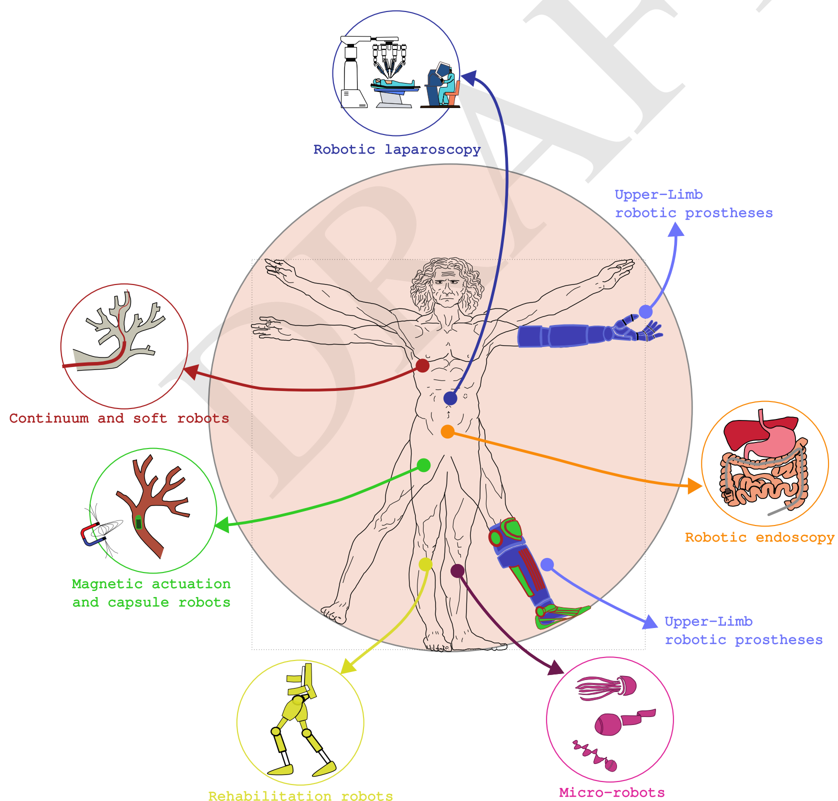

Fig. 6.11 Examples of hot topics of medical robotics.

6.4.1 Key Technological Challenges in Medical Robotics

Surgery

Over the last 30 years, surgical robotics has emerged as one of the most impactful and transformative areas in medical robotics. It has evolved from being restricted to the academic and research fields to becoming an essential part of modern clinical practice. Systems such as the Da Vinci surgical system from Intuitive Surgical have revolutionized minimally invasive surgery by enhancing precision and reducing recovery time. Surgical robots are evolving from simple tools to intelligent and efficient assistants (Yang et al., 2016). This transformation will make them more clinically relevant, enabling surgical procedures to become more reliable and patient-specific, especially with the resurgence of AI technologies. However, challenges such as limited force feedback, restricted visualization in confined spaces, and the high cost of robotic systems remain significant barriers (Simaan et al., 2018). For instance, high-quality force feedback has been shown to assist surgeons in maintaining safe tissue interaction forces, ensuring uniform knot tying, and minimizing trauma. However, most surgical systems lack force feedback due to challenges such as the high cost and uncertainty associated with indirect force estimation algorithms (Patel et al., 2022).

In interventional robotics for vascular, neurological, and gastrointestinal procedures, performance depends on advanced algorithms and sensing for precise navigation. However, challenges remain in adapting to dynamic environments, such as blood flow in vascular systems, tissue deformation in neurosurgery, and localization in flexible organs like the gastrointestinal tract. The automatic control community should help address these issues, enabling surgical platforms to achieve greater autonomy, while incorporating adaptive systems driven by advanced control techniques, incorporating AI and enhanced sensing technologies.

Autonomy in medical robotics remains a medium to long term challenge, with limited clinical applications and studies demonstrating the advantages in clinical practice (Attanasio et al., 2022; Haidegger, 2019). The journey toward integrating fully autonomous and intelligent robots into clinical workflows will be challenging and gradual. It will require advancements in control algorithms, data-driven decision-making, and regulatory frameworks. In particular, control systems must ensure stability, safety and reliability in autonomous tasks, especially in high risk applications.

Flexible Robotics

Flexible robots have shown significant potential in several medical applications such as MIS surgery. This is mainly due to their compliance and adaptability, which allow them to have safe interactions with tissues in complex environments. However, the non-linear behavior of soft materials and the complexity of contact dynamics present significant challenges for modeling and control. For instance, dynamic modeling of soft and continuum robots, as well as active compliance control, remain active research topics and are essential for developing advanced control algorithms. Robust and optimization-based control strategies will play a key role in addressing these challenges, particularly in surgical applications. Additionally, the use of data-based and emerging AI-based control strategies represent promising and active areas of research.

Electromagnetic-Based Robotics

Electromagnetic actuation systems represent a highly promising technology that could enable transformative solutions for in-vivo diagnostics and targeted therapies by eliminating the need for mechanical connections. Examples of applications include capsule endoscopy, microrobotic drug delivery systems and targeted interventions in vascular and gastrointestinal surgeries. Nonetheless, several problems in this domain remain unsolved, such as controlling the magnetic fields while ensuring reliable force and stiffness control, and managing interactions with the anatomy.

Innovative control algorithms and enhanced feedback sensors will be necessary to address these issues and achieve precise navigation and interaction with soft tissues while maintaining compact designs that are suitable for clinical use. Optimal control methods could help overcome energy limitations.

Physical Human-Robot Interaction (pHRI)

Since the emergence of collaborative robots, the goal has been to facilitate interaction between the robot, the patient, and the doctor, ensuring safe assistance without replacing the clinician. Research on controlling the dynamics of pHRI has become very active. This is essential in order to make the robot adapt to human movements and intentions while ensuring stability and safety of the interaction. Designing such control strategies would push forward the applicability of medical robotics in several applications, such as orthopedic surgery (Li et al., 2023).

Another important application is rehabilitation and assistive wearable devices, where robotics is transforming care for individuals with neuromuscular disorders or those in need of movement assistance. Exoskeletons and prosthetic devices are increasingly designed with personalized control strategies and wearable technologies to enhance user comfort and functionality. Achieving ergonomic and safe physical human-robot interaction is a key challenge in this domain. It requires the collaboration of interdisciplinary teams. See, for example, the project Reinvent, one of the French Priority Research Program and Equipment (PEPR) projects under Organic Robotics (O2R), which aims to create a new paradigm of robotics capable of interacting more naturally with humans. Control engineering is definitely a major element in such interdisciplinary research, providing smart control systems that adapt in real-time to the user's needs and progress.

Teleoperation

Significant challenges still persist for teleoperated robots for complex surgical procedures. This includes robot design, human-robot interaction, sensing, and control. For instance, designing intuitive interfaces and control strategies for multi-arm, highly articulated robots remains an active area of research. Additionally, control algorithms should enhance the speed and the accuracy while guaranteeing safety by implementing methods such as passivity-based control and control barrier functions. This is particularly challenging in surgery due to the complexity of anatomical constraints and limited sensing capabilities. Finally, enabling effective collaboration between multiple surgeons in a teleoperation framework presents an underexplored area with interesting applications, such as collaborative haptic training.

6.4.2 Needs and Future Directions

Medical robotics has evolved significantly over the past three decades, becoming a major driver of innovation, research, and development. However, realizing its full potential requires addressing critical non-technological challenges, particularly in funding, collaboration, training and data accessibility.

Funding and Collaboration

Despite the rapid advancements in medical robotics, translating novel technologies into clinical practice remains challenging, especially for emerging applications such as AI-based control and autonomous robots. Their widespread adoption and clinical translation require further funding and stronger collaborations between the different actors. Indeed, closer interaction between researchers, the industry and medical institutions should be highly encouraged. This will make it possible to focus on developing medical devices with a realistic socio-economic impact and ensure that they meet clinical needs. Such interdisciplinary collaboration could be further strengthened through national funding programs such as the PEPR O2R and PEPR *Santé Numérique*, as well as the *Agence Nationale de la Recherche* (ANR) projects. At the European level, Horizon Europe calls (Cluster 1 - Health) and European Research Council (ERC) provide relevant frameworks for advancing such research. Finally, organizing research specialized workshops at major robotics and automatic control conferences could attract new researchers and strengthen innovation in this field.

Training the Next Generation of Engineers and Doctors

Medical robotics is inherently cross-disciplinary, integrating diverse fields such as automatic control, image and signal processing, computer vision and data science. Specialized training for researchers, developers and future practitioners should address the needs at both the engineering and clinical levels. For engineers, programs should focus on robotics, AI, control engineering and healthcare, offering dual-degree programs and clinical internships to build the skills necessary for tackling real-world challenges in medical robotics. For clinicians, training should introduce and integrate new technological innovations as early as possible, in order to push forward the adoption of new robotic technologies. Current developments in training facilities should be enhanced, particularly through the increased integration of Virtual and Augmented Reality coupled with haptic feedback, both kinesthetic and tactile, interacting with advanced and real-time biomedical simulations. This will significantly enhance the training, pre-operative planning and experimental experience. These efforts will ensure the development of skilled personnel capable of driving innovation in both research and clinical practice.

Data Accessibility

Access to high-quality datasets from academic and clinical research is crucial for the development, validation, and benchmarking of robotic control and learning algorithms. Open data initiatives play a key role in facilitating data sharing and collaboration within the research community, ensuring the reproducibility and comparability of results and accelerating advancements in AI-driven medical robotics.

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Chapter 7
Control sciences for Neuroscience and Neurology

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7.1 Context and challenges

Neuroscience, and its associated clinical field of neurology, is concerned with the study of the structure and function of the nervous system which, in humans, includes the brain and spinal cord (the so-called *central nervous system*) as well as the peripheral system of neuron and nerves that innervate other organs.

Neurophysiological systems at different spatial scales: from individual neurons to the cortex

The physiology of the human nervous system, and that of the human brain in particular, involves several levels (or spatial scales) of organization (Fig. 7.1-top). These levels of interest correspond to different subfields of neuroscience, each with their own models and methodologies, and which do not always easily communicate with one another. **At the cellular level**, neuroscientists study the molecular and electro-chemical interactions between neural cells, which in the adult human brain include about 70-90Bn neurons and about as many supportive glial cells. Neurons are unique in their ability to send signals to other cells in the form of electrochemical pulses, called *action potentials*, transmitted over *axon* fibers that extend from their cell body and connect to other cells by electrochemical interfaces called *synapses*. There are many techniques available to record brain activity (Toga and Mazziotta, 2002) – including electroencephalography (EEG), magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI) or near-infrared spectroscopy (fNIRS) – but these do not allow for single-neuron resolution. Cellular mechanisms (e.g. synaptic transmission, action potential generation) were historically studied in-vitro, but now mostly with in-vivo single-unit recordings, in which microelectrodes record changes of voltage in the extracellular space close to the cell membrane, with a field of view of about 1μm (1 cell).

At the population level (i.e. ensembles of 100s or 1000s of neural cells), neuroscientists study the emergent mesoscopic activity of interconnected neurons, such as their firing rate and local field potentials, and how it is modulated by excitatory or inhibitory connections from other populations of neurons in their neighborhood. In humans, although progress in high-resolution imaging (e.g. ultra-high field fMRI) offers hopes

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to image populations of neurons non-invasively, population recordings are typically done using surgically-implanted electrodes (stereoencephalography, SEEG) or devices (deep-brain stimulation, DBS, which can also be used as a sensor), which have a field of view of 50-500μm (10-100s of cells) but can so far only be used for research on patients who have a pre-existing medical condition that require such surgery (typically pharmacoresistant epilepsy for SEEG; movement disorders such as Parkinson's disease and neuropsychiatric conditions like obsessive-compulsive disorder for DBS).

Finally, **at the organ level** (i.e. whole brain), neuroscientists study how large networks of neural populations cooperate macroscopically to implement such high-level cognitive functions as learning, memory, behaviour, perception or consciousness. Research at that level often involves recordings of sensory inputs (e.g. sounds or images presented to freely behaving participants) and behavioral outputs (e.g. speech, facial expressions, subjective reports) simultaneously with brain activity, using non-invasive imaging techniques such as EEG, MEG, fMRI or fNIRS. Whole-brain, non-invasive imaging techniques allow more experimental flexibility, but vary in their temporal (milliseconds to seconds) and spatial (millimetric to centimetric) resolution. A current frontier of neuroscience research even aims to extend such research **at the organism level**, by studying the two-way interactions between the brain and other organs such as the heart (e.g. heartbeat-evoked potential, a brain response to each heartbeat thought to be linked to internal body awareness) or the gut nervous system (using electrogastrograms, the stomach/intestine equivalent of EEG).

Some challenging properties of neurophysiological systems for control engineering

From a control engineering perspective, neurophysiological systems at each of these spatial scales have a number of complex features that make them both interesting and challenging research objects.

Multiphysicality: Neurophysiological systems communicate internally and externally via an intricate network of electrical, chemical/molecular signaling. When an electrical signal arrives at a chemical synapse, neurotransmitter molecules are released and then bound to specific receptor proteins in postsynaptic cells, causing the generation of electrical or chemical signals which further propagate down the network. The behavior of synapses (their so-called short-term plasticity) is further modulated by other signaling from surrounding neurons and, as is becoming increasingly apparent, supporting glial cells (Williamson et al., 2025).

Non-linearity: The building block of neurophysiological systems, the individual neuron, is an intrinsically non-linear system. Its input-output mapping (current in, membrane potential out) essentially has an integrate-and-fire phenomenology, and has given rise to a large variety of mathematical models in the form of nonlinear dynamical equations (derived from the seminal work of Hodgkin & Huxley Hodgkin and Huxley (1952)). At the population level, the microscopic behaviour of neurons interconnected with excitatory or inhibitory connections also gives rise to coarse-

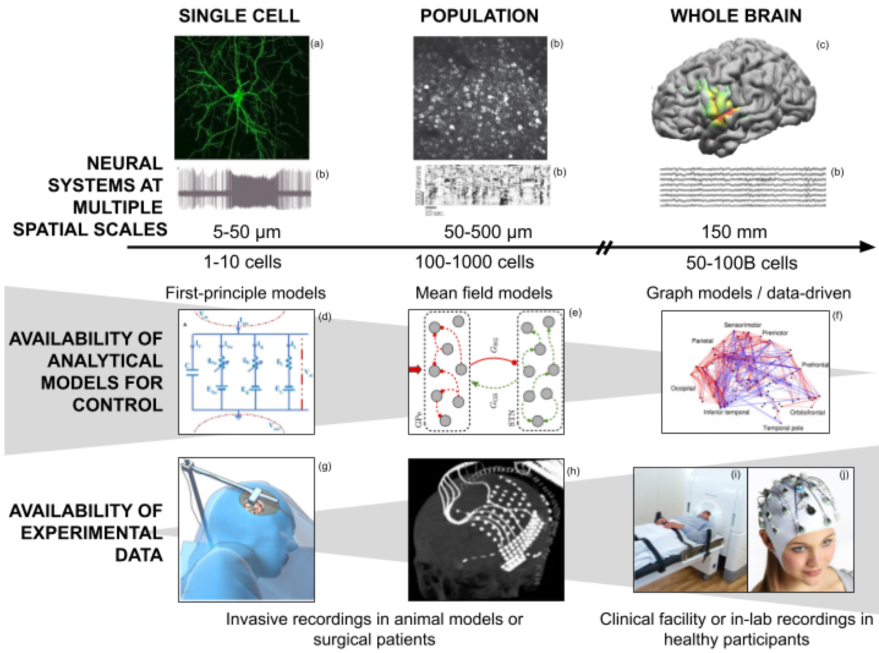

Fig. 7.1 The multiple spatial scales of neural systems. The physiology of the human brain involves several spatial scales of organization, which correspond each to specific methodologies and challenges for the science of control. At the cellular and population level (left), rich analytical models exist (such as, as illustrated here, the Hodgkin-Huxley model of axon signaling (Hodgkin and Huxley, 1952) and the Wilson-Cowan (Wilson and Cowan, 1973) field model). However, data and opportunities to experiment at these scales are scarce and constrained by considerable ethical, regulatory, and practical barriers. At the other extreme (right), data at the whole-brain scale have never been more accessible: non-intrusive imaging and affordable EEG systems allow the rapid collection of neural signals in healthy participants, often under lightweight ethical oversight and at minimal cost. However, dynamics at these scales cannot be succinctly represented by first-principle models, and instead require data-driven representations, which remain an active domain of study. *Credits for illustrations: (a) Piatkevich et al. 2019 (Piatkevich et al., 2019); (b) Stringer & Pachitariu, 2024 (Stringer and Pachitariu, 2024); (c) source: www.amnahyder.com (d) Fang et al. 2021 (Fang et al., 2021); (e) Madadi Asl et al. 2022 (Madadi Asl et al., 2022); (f) Achard et al 2006 (Achard et al., 2006); (g) Coughlin et al 2023 (Coughlin et al., 2023); (h) Hill et al. 2012 (Hill et al., 2012), (i) source: clevelandclinic.org; (j) source: brainproducts.com.*

grain non-linearity when modeled as a mean field (e.g., Wilson & Cowan Wilson and Cowan (1973)). The extent whether such macroscopic and/or whole-brain dynamics can be described/predicted/controlled with linear models is the topic of much current research (Nozari et al., 2024).

Feedback: Backward connections (i.e. that re-ascend the information-processing pathway) are ubiquitous in the human cortex and play a central role in computational formulations of brain function, because they are necessary to explain macroscopic phenomena such as event-related potentials (Garrido et al., 2007). At the behavioural level, the brain also *implements* important feedback functions, in which e.g. efferent signals (motor commands, speech) are compared continuously to reafferent monitoring signals to compute prediction errors and achieve a target, i.e. essentially a form of optimal control (Todorov and Jordan, 2002).

Strong intrinsic activity: The brain has a key function in homeostatic regulation, which means it is continuously monitoring and modulating various aspects of the organism's metabolism, such as food intake, energy expenditure and cardiorespiratory activity (Kim et al., 2018). This activity manifests itself as an intrinsic oscillatory activity (so-called 'resting-state' activity) which, at any level of observation, accounts for a substantial fraction of variability in e.g. single-unit firing rates, population mean-field activity or event-related responses to external stimuli. In terms of system identification, this means that the 'perturbation' signal acting on any input-output relationship may be several orders of magnitude greater that the stimulus' influence, and have a non-random structure with strong spatio-temporal correlations (e.g. traveling waves; (Raut et al., 2021)).

Stochasticity: Noise is pervasive at every level of the nervous system, from thermodynamic/quantum noise acting on sensory receptors (e.g. photons hitting retinal photoreceptors at random rates), variability in the strength and timing of neuronal action-potential transmission (e.g. 'background' spontaneous neurotransmitter release in synapses), up to macroscopic variability in motor actions and behaviour (Faisal et al., 2008). Whether such variability is intrinsically stochastic or results from a deterministic process that is too complex to grasp (and thus better modeled as random), advances in the analysis and control of stochastic dynamical systems are of relevant use in the neuroscience context. In particular, the functional role of noise in sensory systems is an active research question in biology, with mechanisms such as stochastic resonance showing that the addition of an optimal level of noise to a weak input can enhance its detectability (Russell et al., 1999).

Spatial structure & connectivity: Finally, one additional complex feature of brain dynamical systems is that their networks are strongly constrained by brain anatomy. Detailed anatomical studies have documented a complex mesh of pathways (bundles of axons) linking neurons between distant cortical areas (the so-called *connectonome*; (Sporns et al., 2005)), while sometimes restricting interactions between areas that are spatially (but not functionally) closer. This graph structure is, for a large part, shared across individuals (e.g. the *corpus callosum*, a large bundle of more than 200 million axons that connect the two hemispheres) but may also be genetically inherited and modulated during/by behavior. It constitutes a complex, only partly-understood substrate for the dynamic interactions between cell populations and, because these connections are mostly reciprocal, they largely determine what spatiotemporal correlations can be observed between populations. Even within populations, the non-local nature of brain dynamics has led to the development of analytical and numerical tools for the study of spatiotemporal patterns, based on partial differential equations (PDEs) or integro-differential equations (Coombes et al., 2014).

The role(s) of control engineering in neuroscience

While not usually considered a mainstream research tool in neuroscience (as would e.g. signal processing or artificial neural networks/machine learning (Sanei and Chambers, 2021)), the theory and metholodology of control science (and its subfields of modeling, analysis, identification, observers and control/command) offers important opportunities for the study of neurophysiological systems, both at the fundamental (understanding normal brain function) and applied/clinical level (diagnosing/curing abnormal brain function).

Because they are essentially dedicated to the study of complex non-linear systems, the control subfields of **modeling** and **analysis** provide a strong framework to understand neurophysiological systems, both at the level of the individual neuron and within-between cell populations. In addition to providing conditions for e.g. stability and controllability that may explain why such biological structures evolved the way they did, analysis may also provide causal explanations for emergent phenomena. For instance, models that include or don't include certain backward connection can be compared in their ability to generate mean field activity consistent with experimental data (Garrido et al., 2007). In such a role, control engineering shares a lot of similarity with research described as ‘computational‘ or ‘mathematical‘ neuroscience (Sejnowski et al., 1988), although the two communities perhaps do not communicate as much as they could/should.

The control subfield of **system identification** offers important opportunities to study and model experimental data, as measured e.g. by single-unit, local-field or whole-brain recording. In addition to providing realistic parameter estimates for computational models (see Fig. 7.2 for an early example of nonlinear system identification with white noise applied to a three-stage neuron chain in the catfish retina (Marmarelis and Naka, 1972)), system identification also offers unique opportunities to extract parameters at the individual patient level and see if these parameter values can serve as biomarkers to e.g. differentiate patients from controls, or cluster different phenotypes of patients (see e.g. (Adl Zarrabi et al., 2024) for an application to cognitive deficits after a brain stroke). In such a role, the field of control appears especially close to the emerging so-called ‘data-driven‘ methods in the field of psychophysics and sensory neurophysiology (reverse correlation (Schyns et al., 2009); temporal response functions (Crosse et al., 2016)), which essentially (and somewhat confusingly) propose to identify impulse-response models - and would probably benefit from using a more consistent terminology.

Like system identification, the **observer** subfield potentially provides an important framework to uncover brain states from experimental data. Measurements from brain imaging (e.g. up to 256 EEG sensors distributed across the scalp) are typically high-dimensional and highly redundant, and provide only a poor proxy to the state of the underlying dynamical system. Much recent research in neuroscience has focused on learning lower-dimensional ‘state-space‘ embeddings of brain imaging data in which one can uncover causal links with other physiological signals (e.g. auto-encoders to learn a 1-d embedding of arousal that's common to both pupil size and neuronal calcium-imaging time series (Raut et al., 2025)), or better separate phenotypes of patients than with surface features (Pourdavood and Jacob, 2024). In such a role, the field of control

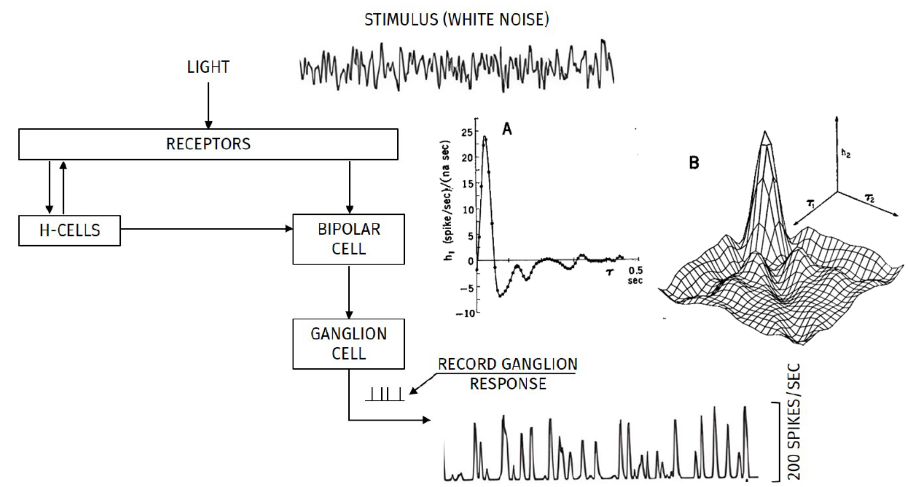

Fig. 7.2 White-noise system identification in an experimental chain of three retinal neurons. An early 1970s example of using system identification to characterize the equivalent system of how the catfish retina converts light intensity to neural spikes in the visual ganglion. An in-vitro montage of the cells is stimulated experimentally with visual white noise, and the input-output system is modeled with Volterra kernels. The first order kernel (A) is the impulse response of the linear part of the transfer function of the chain. The second order kernel (B) describes the nonlinear behavior of the system. *Figure adapted from (Marmarelis and Naka, 1972).*

appears close to recent neuroscientific applications of ‘scientific machine learning’ (Brunton and Kutz, 2022), which aim to learn state-space representations, or even complete functional descriptions (i.e. ODEs) of a dynamical system in a purely data-driven manner (e.g. using symbolic regression (Champion et al., 2019)). The subfield of observers is also linked to the notion of compressed or virtual sensing, a topic especially relevant for neuroscience applications where the number of sensors may be practically limited and one would like to estimate hidden state variables (Williams et al., 2024).

Finally, the subfield of **control design** opens opportunities to construct control signals adaptively, either in the form of electric or sensory stimulation, in order to bring neurophysiological systems into a desired trajectory or regime. While an experimental science such as neuroscience requires the ability to test the consequences of experimentally-manipulated variables, such manipulations are typically only done in a simple open-loop way (e.g. inhibiting the activity of a neural population by applying transcranial magnetic stimulation - (O’Shea and Walsh, 2007)) or, at best, with discrete stimulations triggered by predefined threshold on the output. For instance, in the sleep-neuroscience method confusingly called ‘closed-loop stimulation‘, short bursts of acoustic noise are triggered in synchrony with the onset of EEG slow waves occurring in deep sleep, in an attempt to accentuate their amplitude and test their role for memory consolidation, often with limited success (Antony et al., 2022). The objective of altering, or even controlling, the response of neuronal ensembles in a genuine closed-loop manner, notably by exploiting the stimulation capacity of implanted SEEG or DBS systems, would open the door to a wide range of possible therapeutic interventions, including in Parkinson's disease or epilepsy. In such a role, the field of control appears close to the research concerns of the *brain computer interface* (BCI) and *neurofeedback* communities, although the latter tend to focus on letting individuals learn to induce certain patterns of brain activity, (which are then detected and transcoded into some form of feedback), rather than on techniques that directly manipulate that activity (Wood et al., 2014).

7.2 Contributions of the French Control community to the field of Neuroscience

As early as the 1950s and 1960s, French researchers in the spirit of cybernetics began to conceptualise the brain as a regulatory system, with pioneers such as Louis Couffignal exploring analogies between nervous function and machine feedback (Le Roux, 2009). In the decades that followed, the community of French control scientists increasingly engaged with questions at the interface of neuroscience and neurology and, with the advance of brain imaging technology in the 2000s, contributions from this community have become both more frequent and more diverse. We review here a number of research topics that appear particularly active in the current French community.

Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disease which causes the progressive degeneration of nerve cells in the subcortical region of the *substantia nigra*, with the consequence of deregulating neuronal dynamics in the *striatum*, another subcortical region involved with voluntary motor control, and to which the substantia nigra normally provides dopamine neurotransmitter. This deregulation cause a variety of motor symptoms, such as tremor, rigidity and bradykinesia (slowness of motion), as well as non-motor disorders, such as dementia.

Significant efforts have been made by the French control community to counteract motor symptoms in PD. The main developments rely on Deep Brain Stimulation, a symptomatic treatment developed by the team of Prof. A.L. Benabid in Grenoble in the early 1990's (Benabid et al., 1991). This treatment consists in inserting electrodes in deep brain regions to deliver low-voltage high-frequency electrical impulses (3-5 V, 130 Hz).

In clinical practice, the electrical signal is delivered in open loop, i.e. it is the same regardless of the patient's brain state or macroscopic activity. As reviewed in (Carron et al., 2013), several attempts have been made to go closed-loop, namely to adapt the stimulation signal based on real-time measurements of the patient's brain activity. Until recently, most of these attempts have been confined to fundamental research, either of a computational or experimental nature. However, closed-loop systems have recently come closer to medical practice since the first device allowing for closed-loop DBS

(BrainSense, by Medtronic) has received CE mark approval in January 2025, which may also create larger opportunities for experimentation for control research.

Contributions from the French control community first aimed at analyzing the mechanisms by which parkinsonian brain activity is generated. It is well documented that motor symptoms severity correlates with the intensity of specific brain waves in deep brain regions, particularly in the beta frequency band (13-30 Hz) (Boraud et al., 2005). By relying on computational models of the neuronal populations involved, notably derived from biophysical models of the subthalamic nucleus (STN) – globus pallidus pars externa (GPe) network (Holgado et al., 2010), the link between these pathological oscillations and the synaptic weights between STN-GPe has been formally evidenced, with explicit account of axonal propagation delays (Haidar et al., 2013, 2014) and of the spatiotemporal nature of the neuronal populations (Brivadis et al., 2023). A resonance effect, which may explain the amplification of activity in the pathological frequency band, has also been studied with incremental stability techniques (Chaillet and Detorakis, 2017). From a more microscopic viewpoint, the synchrony properties of an assembly of interconnected neurons has also been addressed, in which each neuron is modeled by an oscillator (Franci et al., 2011c,d, 2012c).

Based on these analytic results, some feedback-control strategies have then been developed to attenuate parkinsonian brain activity. Control in PD is made challenging by both practical and theoretical aspects of the disease. Practically, available data and opportunities for experimentation (e.g. during electrode positioning) are scarce in order to limit surgical intervention time, and safety concerns also require bounded control, for stimulation not to propagate to neighboring regions. Theoretically, models for pathological neuronal dynamics remain imprecise, and present several control-theoretical challenges such as the presence of time delays due to axonal propagation and the high spatial heterogeneity of the considered neuronal populations.

At the microscopic scale, it has been shown that a feedback proportional to the mean activity of the neurons is enough to desynchronize them (Franci et al., 2011a, 2012b,a, 2011b,c). At the mesoscopic scale, it has been shown that stimulating the subthalamic nucleus (an excitatory deep brain region) proportionally to its own activity is enough to disrupt oscillations (Haidar et al., 2016; Chaillet et al., 2017; Detorakis et al., 2015; Chaillet et al., 2019). Moreover, this proportional gain can be adaptively adjusted in order to limit the stimulation influence when oscillations are in a non-pathological frequency range (Or lowski et al., 2018, 2022; Fleming et al., 2020) (Figure 7.3). It has also been shown that this stimulation can be made less energy consuming and more physiologically respectful by using observers to estimate averaged synaptic weights and the activity of unmeasured populations (Brivadis et al., 2022).

Epilepsy

It has already been mentioned that most neuroscience mathematical models, although sharing a common formalism with those typically used for control purposes, are developed by researchers who would probably not claim to belong to the control-theory community, such as computational neuroscientists or physicists. Epilepsy models do

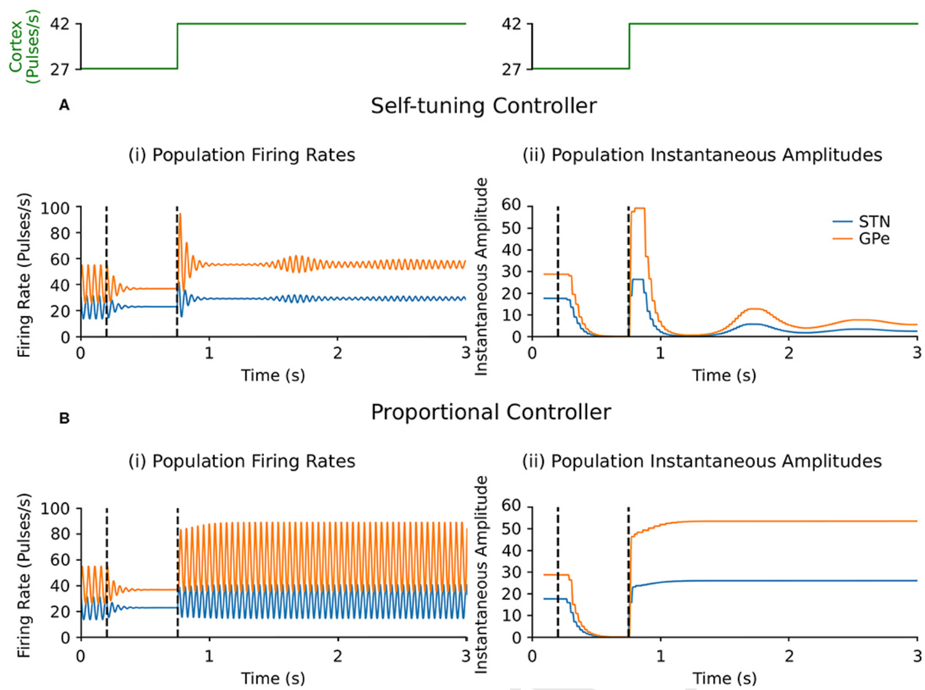

Fig. 7.3 Controlling pathological dynamics in models of Parkinson's Disease (PD). Synaptic weights between populations of neurons modeling the STN and GPe brain regions can simulate pathological beta oscillations associated with PD. Closed-loop control algorithms simulating the effect of deep-brain stimulation (DBS) devices acting on the STN can attenuate these oscillations. Shown here: a comparison between proportional (bottom) and self-tuning controlers (middle), after being switched on (t=200ms), and after the introduction of additional oscillations at t=750ms. While the self-tuning DBS automatically adapts the proportional gain to maintain the attenuation of beta oscillations, pure proportional DBS is unable to do so. *Figure reproduced from (Fleming et al., 2020).*

not escape the rule, whether they are operating at the level of phenomenology (Jirsa et al., 2014), biophysics (Destexhe, 1998) or mean-field dynamics (Meijer et al., 2015) (for a review, see (Depannemaecker et al., 2023)). One notable exception is (Alamir et al., 2011), in which authors from the French control community propose to model the considered brain region as a network of interconnected sub-regions, each modeled by a nonlinear oscillator. Seizures then occur due to the activation of short-term plasticity mechanisms, whose threshold would be abnormally low for epileptic patients, opening the possibility to control seizures with a closed-loop stimulation architecture.

Beyond modeling, most of the recent contributions on epilepsy in the French control community have exploited observer theory. In (Chong et al., 2012b,a), the authors rely on neural mass models to estimate hidden state variables, such as the mean membrane potential of neuronal populations, based on EEG measurements. A local, but probably more constructive, approach was proposed in (Hamid et al., 2015) by relying on linear parameter-varying systems techniques. A hybrid approach, mixing continuous and discrete dynamics, has also been proposed and additionally allow to estimate synaptic weights (Chong et al., 2015). While all these approaches aim at precise estimation of

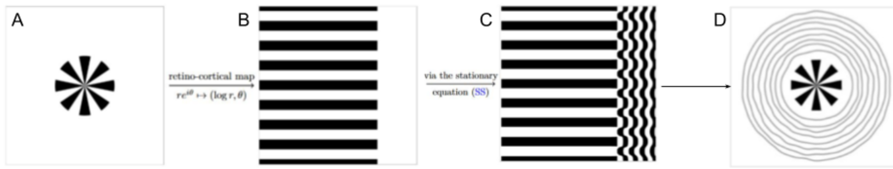

Fig. 7.4 Mathematical analysis of neural field models of the visual correct explains visual hallucinations. The so-called "MacKay" family of visual illusions induces the illusory perception of concentric rings in the visual periphery (right), when one fixates a funnel-shaped stimuli in the center of the retinal field (A). By converting stimuli to a retinotopic model of how the visual cortex encodes visual scene (middle-right), and analysing how a neural field model (of the Cowan-Wilson family) propagates that stimuli, one can simulate cortical representations that correspond to the illusory percept. *Figure adapted from (Tamekue et al., 2025).*

specific state variables or parameters, seizure onset detection and prediction are mainly concerned by a qualitative shift in the brain region dynamics: evolving from a normal state to a pathologically excited one. This idea gave rise to the notion of qualitative detection (Tang et al., 2019), which aims at estimating the overall dynamical behavior of the considered system (resting, oscillating, bursting, spiking, etc.) regardless of the exact value of the parameters which underlie them.

Vision and perception

The primary visual cortex (V1) is a brain area involved in the processing of visual information transmitted by the retina. It is organized in columns, that code not only the intensity and color, as would a television screen, but also for the orientation of contours. A mathematical model of V1 has been proposed by A. Sarti, G. Citti and J. Petitot, in which each point in the perceived image is enriched with information about local contour orientation, thus embedding the image in the higher dimensional manifold $SE(2)$, which corresponds to translations and rotations in the plane (Sarti et al., 2008).

By relying on this model, the French community has developed neuro-inspired image processing algorithms by relying on control-theory tools. In particular, the state of each image point (containing both contrast and direction) can be combined to diffusion dynamics in order to restore a significantly degraded image (Prandi and Gauthier, 2018) or for object recognition (Bohi et al., 2017). By combining this model with a spatio-temporal version of Wilson-Cowan model mentioned above, a mathematical analysis of the neural processes involved in the generation of visual hallucinations (Fig. 7.4) has also been proposed (Bertalmío et al., 2020, 2021; Tamekue et al., 2023, 2025), including a controllability analysis aiming at identifying the type of hallucinations that can be emulated by this model (Tamekue et al., 2024). A similar approach was adopted for sound reconstruction (Boscain et al., 2021).

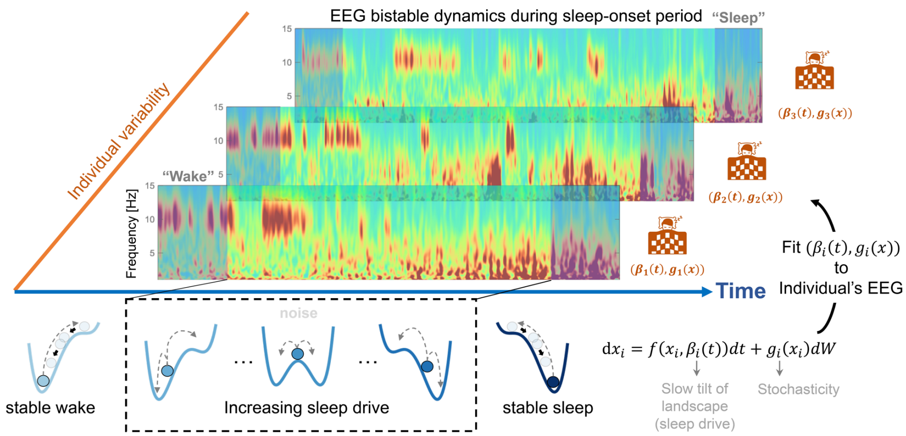

Fig. 7.5 Cortical dynamics during the transition to sleep modeled by a stochastic bistable system. The sleep-onset period has a strongly bistable phenomenology, marked by a non-monotonous decrease of the electroencephalogram (EEG) frequency and high inter-individual variability, seen here in wavelet spectrograms of three illustrative participants' EEG (top). For control purposes, these dynamics can be modeled as the motion of an noisy overdamped particle in a slowly tilting bistable landscape. *Figure reproduced from (Hu et al., 2025).*

Circadian rhythms and homeostasis

One primary function of the central nervous system is to maintain homeostasis - i.e. control over the internal environment of the organism - and circadicity - i.e. its adaptation to external environmental cycles. Because they are essentially bistable dynamical phenomena, these processes have attracted a number of mathematical modeling efforts, which typically model circadian and homestatic drives as coupled non-linear oscillators (for sleep/wake cycles, see e.g. S. Strogatz's PhD Thesis (Strogatz, 1987)), or - more generally - simplified cubic systems (Fig.7.5) that bifurcate, potentially stochastically, between states (Hu et al., 2025).

Unsurprisingly, this modeling framework has provided a fruitful playground for control-theoretic approaches. Recent work in the French control community have focused for instance on system identification, where techniques were proposed to characterize the adaptation speed of the circadian system based on temperature measurements (Bonargent et al., 2018), and on analysis, where the impact of homeostasis regulation processes have been included in population models of neural dynamics (Harnack et al., 2015).

Locomotor rehabilitation

Beyond the cortex, neural injury at the brainstem or spinal-cord level may lead to severe locomotor deficits, or even complete limb paralysis. In the past 5-10 years, progress in stimulation neurotechnology has made it possible to deliver trains of electrical stimulation directly to the spinal cord, on demand, letting patients regain some level of voluntary control over previously paralyzed muscles (Wagner et al., 2018a).

This emerging clinical context has opened an opportunity for the development of closed-loop control strategy for locomotor rehabilitation, for which some authors of the French control community have started contributing. For instance, closed-loop control strategies have been developed to reduce the time-variance of muscle response under functional electrical stimulation (Hayashibe, 2016). Closed-loop approaches were also developed to control diaphragm of patients with *cervical spinal cord injury* (Zbrzeski et al., 2016).

Hemodynamic response

Finally, a number of neuroimaging methods such as fMRI or fNIRS estimate neural activity by measuring metabolic proxies, such as the increase of cerebral blood flow that support this activity. Estimating the brain hemodynamics response - essentially a transfer function - is key to the precision of such methods, and has seen a number of control-theory contributions, both in terms of modeling (e.g. coupled ODE-PDE models (Belkhatir et al., 2019)) and identification (e.g. time-varying autoregressive models (Sood et al., 2016)). More generally, the hemodynamic response is at the core of closed-loop strategies for *transcranial direct current stimulation* (tDCS) (Sood et al., 2016).

7.3 Perspectives and open questions

The "dynamical renaissance" in neuroscience is an opportunity for control science

The field of neuroscience is undergoing a profound conceptual shift toward frameworks rooted in dynamical systems theory which, although reminiscent of early achievements such as the Hodgkin–Huxley and FitzHugh–Nagumo models, has been described as a "dynamical renaissance" (Favela, 2021). Notions such as latent states (Cai et al., 2021), bifurcations (Sergent et al., 2021), embeddings (Raut et al., 2025) and attractors (Vinograd et al., 2024) are increasingly used to describe neural computations and brain states in mainstream neuroscience work. Yet, these concepts are often invoked qualitatively, as observations made from empirical data, without being connected to formal modeling or analysis as dynamical systems – tools that control theory can provide. This convergence presents the control community with a pivotal moment and an opportunity to integrate control-theoretic principles such as stability analysis, feedback design, observability, and controllability into emerging dynamical models of brain function (Kumar et al., 2016; Chaillet and Frégnac, 2017; Kao and Hennequin, 2019).

A critical trade-off between the need for models and the need for data

The field of control-engineering approaches to neuroscience faces a fundamental trade-off between the need for models and the need for data (Fig. 7.1-bottom). On one hand, experimental data is indispensable: it provides inspiration for model formulation and allows the calibration of parameters; beyond access to pre-recorded data, the opportunity to experiment is also needed for identification purposes and to validate control procedures. On the other hand, control science, both for analysis and command, has historically relied on first-principle mechanistic models, typically expressed as systems of ordinary or partial differential equations. Such biophysical models of brain function, however, are usually only available at the neuronal-population level, where data are scarce and experimentation is constrained by considerable ethical, regulatory, and practical barriers. For instance, although theoretical work has explored the control of the subthalamic nucleus–globus pallidus externus (STN–GPe) network in Parkinson's disease, advancing beyond simulation would require access to pre-recorded deep-brain stimulation data or, ideally, the ability to test control schemes in live patients, both of which remain formidable challenges.

At the other extreme, data at the whole-brain scale have never been more accessible: affordable EEG systems and brain–computer interface toolkits allow the rapid collection of neural signals in healthy participants, often under lightweight ethical oversight and at minimal cost. However, such data do not lend themselves naturally to classical model-based analysis, as whole-brain dynamics cannot be succinctly represented by low-dimensional ODEs or PDEs, but instead require data-driven representations such as NeuralODEs (Chen et al., 2018). For these recent data-driven models, much work remains to be done in the domain of analysis and control: for instance, providing strong evidence for the dynamical properties of the learned systems, developing procedures to enforce physical laws (e.g. stability) during training, or developing methods for uncertainty quantification and robustness to noise.

In short, the field faces a methodological gap: where data is abundant, the tools remain underdeveloped; where these tools exist, data is scarce.

Progress will likely require movement along one of two complementary paths: first, finding new, ethically and practically accessible experimental paradigms at the cellular-population scale (e.g., organ-on-chip models, which are increasingly being developed in academic engineering departments and could provide opportunities for easier collaboration); or developing a new methodological corpus that integrates control theory with scientific machine learning, enabling principled analysis and control of complex, data-driven models (Beregi et al., 2023).

A two-way theoretical opportunity

The application of control-science principles to neuroscience presents a two-way opportunity for novel theoretical contributions in both fields.

For the field of neuroscience, the ‘internal model’ principle (Annaswamy et al., 2025) is one illustration of how control theory can help understanding neuronal mechanisms and guiding experimental design to test biological hypotheses. Many sensorimotor mechanisms (e.g. producing and monitoring one’s own speech, (Pickering and Garrod, 2013)) are indeed consistent with the use of internal models of either the organism or its environment. Knowing the mathematical ground of internal models allows to predict fundamental ingredients of their neuronal implementation (Bin et al., 2022; Broucke et al., 2022). A close collaboration between experimental neuroscientists and control theorists has the potential to address fundamental questions pertaining to the level at which internal models are explicitly coded in the nervous system and whether internal models and feedback control are coded on separate neuronal substrates.

Another key theoretical neuroscience question is whether the brain, or some of it structures, operates close to a critical state, meaning at the edge of qualitatively different behaviors. While some experimental evidence pleads for this hypothesis (Hesse and Gross, 2014), other authors object that the employed statistical signatures of self-organized criticality (such as the power-law distribution of neuronal avalanches) can be reproduced far from any critical behavior (Touboul and Destexhe, 2017). In mathematical terms, self-organized criticality can be translated as the ability of a dynamical system to autonomously tune its parameters to a bifurcation value. It is thus a feedback mechanism, thus particularly well suited to control theory tools, the challenge lying mostly in the distributed nature of the control law implementation (each neuron adapting only its own dynamics, with a very limited knowledge of the overall population dynamics). Despite this familiarity, the control community has not yet devoted significant effort to this question, with the notable exceptions of (Moreau et al., 2003; Efimov and Fradkov, 2006).

Conversely, biological neuroscience can be of great inspiration to advance control theory (Madhav and Cowan, 2020). Precision, rapidity, robustness to uncertain and fluctuating environment, energy efficiency, adaptability, redundancy, distributed computing, . . . : the brain is by far the greatest controller device we can think of. Progresses in the understanding its working mechanisms can therefore be of decisive inspiration for enhanced control design. A promising avenue in that direction lies on the specificity of the elementary brain computation primitive: the action potential or spike. This fast response of a neuron to a sufficient stimulation constitutes a continuous-time signal. Yet, it also endows a digital component, as the number of spikes generated by a neuron can be counted. This hybrid nature could provide a fundamental bridge between automata (discrete events) and physical systems (continuous time). The idea of post-digital computing devices relying on spikes and rhythms, rather than bits and clocks, is not new (Mead, 1990), yet spiking control systems is recently receiving a growing attention (Sepulchre, 2022). Systematic control design tools and performance guarantees are still needed in that framework.

The promise of clinical applications in neurorehabilitation

Recent neuroscientific work at the interaction with machine-learning has produced spectacular proofs of concept in neuroprostheses able e.g. to restore the capacity of walking (Hankov et al., 2025) or speaking (Littlejohn et al., 2025) in patients with severe paralysis. Many of the obstacles separating these prototypes from mainstream applications - issues of safety, robustness, adaptation to inter-individual differences and intra-individual plasticity - are topics related to control theory. Two particular domains where we see opportunities for important contributions of control engineering are brain-machine interfaces and neuromodulation.

Brain-machine interfaces (BMI) relate to developments aiming to allow direct interaction between the central nervous system and a computer or a robot. In these applications, neural activity is measured, decoded, and exploited by decoder to send appropriate commands to the artificial device. Feedback is most often visual (Shanechi, 2016), although more elaborate sensory feedback is sometimes employed for research purposes (Goueytes et al., 2022). Brain-machine interfaces have a wide scope of possible applications, covering rehabilitation, diagnosis, assistive technology, robotics, and gaming. They fit ideally the classical framework of control theory, in which the controller is the brain, the control signal is the neural activity, the system is the machine, and the measurement results from the considered biofeedback. Despite this analogy, control theory is not yet fully exploited to enhance brain-machine interfaces, particularly in terms of robustness to the non-stationarity of brain signals, safety, shared control between the brain and a possible artificial control device and appropriation of the prosthesis.

A related topic that still requires deepened investigations is neuromodulation, meaning the ability to steer neural activity in specific brain regions. Different types of actuation can be used for that purpose, including electrical stimulation, magnetic stimulation, and optogenetics. The possibility to artificially influence brain activity is a key instrument for fundamental brain research, for instance to determine the role of a given brain structure on a specific function. Neuromodulation proves also useful for medical applications, including spinal chord injury (Wagner et al., 2018b), epilepsy (Fisher and Velasco, 2014), Parkinson's disease, essential tremor, depression, and obsessive compulsive disorders (Krauss et al., 2021). More and more research effort is devoted to its use in more advanced cognitive processes, such as attention and memory (Gupta et al., 2023). While neuromodulation has traditionally been achieved in open-loop, strong benefit is expected from a closed-loop approach in which the delivered stimulation signal is adapted in real time to measurements from the brain or other body parts (Guidotti et al., 2024; Carron et al., 2013). As already mentioned, the first medical device allowing for closed-loop deep brain stimulation has been approved just a few months ago in Europe. Here also, the relevance of control theory catches the eye: the plant is the targeted brain structure, the actuator is the stimulation device and the sensor is the recorded biofeedback. Significant collaborative effort is still needed to go beyond the envisioned on-demand approaches, in which a predefined stimulation is delivered upon the detection of some specific biomarker.

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Chapter 8
A roadmap for Control4health: concrete steps for researchers, laboratories and operating agencies

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Building on feedback received from the 2022 GdR MACS questionnaire, as well as observations made by contributing authors of this volume for each of their specific research activities, we end this volume by a number of structural recommendations that provide a roadmap for the development of Control4Health research. The recommendations are accompanied by suggestions of concrete steps/actions that can be taken at each level of the community: individual researchers, laboratories, and operating institutions.

8.1 Recommendations

8.1.1 Dedicated networks and funding schemes

11% of respondents to the 2022 GdR MACS questionnaire on control applications to health mentioned the absence of dedicated funding opportunities for Control4Health as an important barrier to developing such research. As evident from the chapters in this volume, control engineering offers unique advantages for health research by applying versatile mathematical frameworks to diverse physiological domains, from brain activity to glucose regulation. Its ability to provide guaranteed robustness and performance through mechanistic models ensures reliable and adaptable solutions, making it ideal for addressing the safety and variability challenges inherent in biological systems.

Yet, the field of control sciences, and in particular its application to health research questions, appears to lack visibility. While the ability to solve interdisciplinary problems is clearly a major strength of control sciences (Lamnabhi-Lagarrigue, 2011), the most visible outcomes of such research is often on the applicative side, and the specific methodological contributions of control remains often hidden. The rapid growth of Artificial Intelligence (AI) has also shifted some focus away from control sciences. For example, institutions like INRIA, originally founded as the *Institut National de Recherche en Informatique et en Automatique*, have evolved to emphasize digital sci-

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ences more broadly, reflecting the changing landscape of technological research. Similarly, the French Research Agency (ANR)'s 2026 'digital sciences' call for projects includes axis E.01, which supports research in computer science, control, signal and image processing, robotics, and AI. While this reflects a broad commitment to digital research, the distribution of recent funding, such as the 2025 JCJC Phase 1 results shown in Fig. 8.1, indicates that AI and data-science projects have secured a significant share of resources. This is also witnessed by the so-called PRCE projects (*projet de recherche collaboratif entreprise*), which involve industrial collaborations, in which AI and data-science represent a 9:1 ratio with control and signal processing projects. To ensure that control sciences continue to thrive, it is essential to highlight their unique contributions and advocate for proportional support, maintaining France's leadership in diverse areas of digital research.

Axe	CES	Intitulé	JCJC %	JCJC Retenus Phase 1	JCJC Total éligibles	PRME %	PRME Retenus Phase 1	PRME Total éligibles
Axe E.01	CE48	Fondements du numérique : informatique, automatique, traitement du signal et des images	55,1	27	49	50,0	1	2
Axe E.02	CE23	Intelligence artificielle et science des données	49,4	39	79	55,6	5	9
Axe E.03	CE25	Sciences et génie du logiciel - Réseaux de communication multi-usages, infrastructures numériques	41,0	16	39	100,0	1	1
Axe E.04	CE33	Interaction, robotique	47,1	16	34	0,0	0	2
Axe E.05	CE46	Calcul haute performance, Modèles numériques, simulation, applications	50,0	12	24	0,0	0	1
Axe E.06	CE47	Technologies quantiques	52,4	11	21	100,0	3	3

Axe	CES	Intitulé	PRCE %	PRCE Retenus Phase 1	PRCE Total éligibles	PRC %	PRC Retenus Phase 1	PRC Total éligibles
Axe E.01	CE48	Fondements du numérique : informatique, automatique, traitement du signal et des images	25,0	1	4	46,4	13	28
Axe E.02	CE23	Intelligence artificielle et science des données	39,1	9	23	48,6	17	35
Axe E.03	CE25	Sciences et génie du logiciel - Réseaux de communication multi-usages, infrastructures numériques	58,3	7	12	45,5	10	22
Axe E.04	CE33	Interaction, robotique	50,0	2	4	53,6	15	28
Axe E.05	CE46	Calcul haute performance, Modèles numériques, simulation, applications	_	0	0	38,5	5	13
Axe E.06	CE47	Technologies quantiques	50,0	1	2	40,9	9	22

Fig. 8.1 Results of phase 1 of the 2025 generic call for projects in the digital sciences field. On average, 50% of selected projects have eventually obtained funding approval.

Some national initiatives that aim at supporting interdisciplinary research are particularly relevant in the development of Control4Health. In particular, the CNRS *Mission for Transversal and Interdisciplinary Initiatives* (MITI) has launched an interdisciplinary PhD scholarship program specifically devoted to health research (Doctoral contracts 2025: CNRS Health roadmap). To be eligible for funding, each PhD project must be co-supervised by two scientists (researchers, professors, associate professors, etc.), each attached to a different discipline (as institutionally embodied by the CoNRS/CNU sections that preside over their recruitment and evaluation). Also within CNRS, the CoNRS interdisciplinary commissions (*commissions interdisciplinaires*, or CIDs) play a pivotal role in the recruitment and evaluation of researchers whose work bridges biology and informatics, including control sciences.This is notably true for CID 51 ("computational, physical and mathematical modeling for the life sciences"). In particular, CIDs ensure that research efforts spent on interdisciplinary work do not penalize careers compared to colleagues whose research profile is more disciplinary (Joulian et al., 2005).

That said, additional efforts could be made towards increasing the share of Control4Health projects in funding and recruitment schemes, even when they specifically target interdisciplinarity. First, evaluation committees could benefit from a greater awareness of the specific epistemic advantage of control sciences as a modeling strategy for biology (i.e. of its ability to ask and answer key biological questions such as stability, controllability, etc.), complementary to other, possibly more notorious, data-driven methodologies. Second, the discipline of control sometimes presents some degree of institutional ambiguity as to whether it belongs to computer science, engineering or applied mathematics. In France, CNRS laboratories are attached to disciplinary operating institutes, which also serve as perimeters to attribute funding. For instance, of the 17 CNRS laboratories among which researchers responded to the 2022 GdR MACS questionnaire on Control4Health (Chapter 1), roughly one half (10/17, 58%) were affiliated (*"rattachement principal"*) to the *CNRS Sciences Informatique* institute and one fourth (4/17, 24%) to the *CNRS Ingénierie* institute. The institutional structure of CID51, for instance, which receives funding from the former but not the latter institute, makes teams from the latter category of labs ineligible for such funding.

Recommendation 1: Increase the presence of Control4Health projects in national funding programs by aligning keywords and ensuring expert representation in review committees. Prevent institutional disciplinary structures from accidentally excluding researchers from interdisciplinary funding programs.

The France 2030 program, with its €54 billion investment, aims to position France as a leader in innovation. Within this initiative, more than 25 priority research programs (PEPRs) and over 20 exploratory PEPRs have been launched, with a combined budget of €2 billion for the former (3.7% of the total France 2030 budget), and another €1 billion for the latter.

Unsurprisingly, several of these programs focus on heath-related challenges. This includes programs primarily operated by the French Medical Research Agency (INSERM), such as *Alimentation - microbiomes*, *Santé des femmes, santé des couples*, *Biothérapies* or *Identité et destins Cellulaires*, but also programs that are co-operated by Agencies or Institutes that support computer sciences and mathematical research, such as *Mathématiques en interaction* (CNRS), *Santé numérique* (INRIA/INSERM), *Psychiatrie de Précision* (INSERM/CNRS), *Robotique organique* (CNRS/CEA/INRIA) or *Organes et organoïdes sur puces* (CNRS/CEA/INSERM). However, none of the present programs explicitly address control, despite the unique contributions of the field in ensuring safety, robustness, and provable performance. Incorporating control science perspectives into new or existing programs could therefore provide a valuable complement to existing approaches and further strengthen France's leadership in health innovation. Besides control, the core theoretical framework of dynamical systems is inherently interdisciplinary, spanning other communities such as applied mathematics, scientific machine-learning and computational neuroscience. Despite its broad relevance, this perspective, especially in the context of health, appears like a particuliar salient gap (*"trou dans la raquette"*) in the current funding landscape.

Recommendation 2: *Establish a PEPR project dedicated to modeling, analysis, identification, observation, prediction and control of dynamical systems for health.*

8.1.2 Access to data

In addition to funding, 16% of respondents to the GdR MACS questionnaire mentioned important challenges in collecting and accessing medical data for control research. Respondents cited a lack of information, difficulties navigating administrative procedures, and constraints related to ethical approvals and data confidentiality.

In France, the legal framework for using clinical data in control engineering research is shaped by *Loi Jardé* and the General Data Protection Regulation (GDPR). Research involving new data collection for control engineering typically falls under the 'observational' or 'interventional' categories of Loi Jardé. Observational research (Category 2 or 3) requires submission to a *Comité de Protection des Personnes* (CPP) for ethical review, designation of a research promoter, and compliance with methodological and regulatory standards, including informed consent. Interventional research (Category 1) involves additional steps, such as authorization from the *Agence Nationale de Sécurité du Médicament et des Produits de Santé* (ANSM) and mandatory insurance coverage (Table 8.1).

A lesser-known fact is that research using pre-existing clinical data, collected for purposes other than the current study, actually falls outside the scope of Loi Jardé and does not legally require CPP approval, insurance, registration as a clinical trial, or even patient consent under this law. However, it remains subject to a number of obligations under other laws:

- GDPR, which requires lawful, transparent data processing based on valid legal grounds, most commonly explicit consent. If consent for reusing data was not obtained at the time of data collection (e.g., through broad consent clauses mentionning e.g. subsequent algorithmic development or automated analyses etc.), researchers (or, most likely, their clinical collaborators) must either re-contact participants to seek new consent, or rely on another legal basis, such as public interest or scientific research exemptions (Art. 6 and 9 GDPR).
- Project declaration/authorization at France's data protection authority (*Commission nationale de l'informatique et des libertés*, CNIL) or a signed commitment to compliance with the MR-004 Reference Framework ("*engagement de conformité MR-004*"), a technical framework for organizations processing health data.
- Even though ethical clearance by a CPP is not formally required, medical practice recommends to seek approval from CESREES (*Comité éthique et scientifique pour les recherches, les études et les évaluations dans le domaine de la santé*).

Note that in practice, even hospital research services (*directions de recherche clinique*) sometimes prefer to err on the side of caution and advise practitioners to seek CPP approval for reusing preexisting data, although it is not formally required. This conservative approach reflects the complexity of navigating legal and ethical considerations in clinical research.

Beyond clarifications on these general guidelines, many steps could be taken to facilitate how control science researchers can access clinical data, including identifying resources that already exist. For instance, it is often unclear whether the data protection regulations already in place in laboratories cover some or all the requirements of

GDPR and CNIL in the case of clinical data. In particular, France has been engaged since 2013 in the deployment of *Zones of Restricted Regime* (ZRR), which aim at protecting the nation's scientific and technical potential by controlling access to sensitive areas, particularly in defense, research, and high-tech industries. According to a recent Senate report, more than 900 ZRRs are spread across 66 establishments, many of which overlap the control engineering community. It is therefore possible that control laboratories that are already enforcing ZRR regulations also straightforwardly meet the requirements of GDPR and CNIL. Similarly, research engaging with data stored and managed by datahubs, such the HealthDataHub (`https://www.health-data-hub.fr`), may benefit from streamlined procedures to authorize access to data.

Recommendation 3: *Establish, document and publicize within academic and clinical institutions what is the existing legal framework to allow the sharing of health data with French research laboratories, including those already subject to ZRR or linked to Data Hubs.*

<table>
<tr><th colspan="3">Inside Jardé law</th><th>Outside Jardé law</th></tr>
<tr><td colspan="2">Interventional Research</td><td>Non-interventional research</td><td rowspan="2">Pre-existing data, humanities and social sciences studies, satisfaction surveys, care practices</td></tr>
<tr><td>Drug and health product research</td><td>Research with minimal risks and constraints</td><td>Observational research</td></tr>
<tr><td colspan="3">Requires approval from the Committee for the Protection of Persons (CPP)</td><td>Ethics committee opinion recommended</td></tr>
<tr><td>ANSM authorization mandatory</td><td>ANSM authorization not required: notification sufficient</td><td>ANSM authorization not necessary</td><td>INDS submission for CEREES opinion</td></tr>
<tr><td colspan="2">Information and written consent of participants mandatory</td><td>Information and non-opposition of participants mandatory</td><td>Information and non-opposition of participants recommended</td></tr>
<tr><td colspan="2">CNIL declaration, CNIL authorization,or MR001 compliance commitment</td><td colspan="2">CNIL declaration, CNIL authorization, or MR003 compliance commitment</td></tr>
<tr><td colspan="2">Insurance mandatory</td><td colspan="2">Insurance not mandatory</td></tr>
<tr><td colspan="3">Clinical Trials registration mandatory</td><td>Clinical Trials registration not mandatory</td></tr>
</table>

Table 8.1 Summary of legal and ethical requirements for research in France. Data translated from *Plateforme nationale de la recherche sur la fin de vie*.

Second, access to health data does not always ensure its suitability for control engineering applications. The quality and characteristics of the data can significantly impact collaboration between clinicians and control researchers. For instance, if the time intervals between recordings are inappropriate for modeling dynamical systems, the sampling frequency may be insufficient to capture the variability of physiological parameters. Consider the impracticality of attempting to model a patient's heart rate during surgery using measurements taken only every 30 minutes. . .

Under the France 2030 initiative, the 'Tiers lieux d'expérimentations' program was launched, with €63 million in funding over four years, to address the shortage of testing environments for digital health innovations. The primary aim of this program was to accelerate the market launch of digital solutions developed by SMEs, mid-cap companies and large industrial groups. While this is a commendable effort, a complementary program tailored to research laboratories would further strengthen its impact. Such a program could focus on supporting clinical trials designed for fundamental research, thereby accelerating innovation in emerging areas. This new program would then make it possible to focus on smaller cohorts of patients, with a shorter sampling period to be compliant with the studied problem. Balancing cohort size and sampling frequency would be essential to ensure the program remains aligned with principles of responsible digital technology.

A relevant illustration of the potential of this approach is the development of an in-silico simulator capable of reproducing glucose-insulin dynamics of a human metabolism (Dalla Man et al., 2014). This simulator, developed by the University of Padova and the University of Virginia, has been approved by the US Food and Drug Administration (FDA) to test and evaluate control strategies, replacing pre-clinical trials on animals. Beyond the obvious ethical benefits, this approach has proven its efficiency in accelerating the market launch of medical devices capable of regulating blood glucose levels for patients with diabetes. This analysis leads to the following recommendation.

Recommendation 4: *Facilitate the collection of medical time-series data that are specifically suited for control research, possibly inspired by 'Tiers lieux d'expérimentations' clinical program.*

8.1.3 Training

17% of questionnaire respondents identified challenges linked to interdisciplinary dialogue: this includes difficulties identifying medical collaborators (11%) but also generally noting the time effort that needs to be dedicated to the collaboration (6%). Establishing a common understanding between fields is an obstacle that's common to possibly all interdisciplinary effort (Joulian et al., 2005). For instance, a recent study of CNRS researchers recruited through the *Commission Interdisciplinaire* framework and engaging in interdisciplinary work, regardless of disciplines, also highlights difficulties linked to scientific understanding and appropriation of the other's thematic field, and the need to develop a common language ("words do not have the same meaning") (Vantard et al., 2023).

This problem can be framed, in part, as a training or knowledge alignment challenge. As already noted in (Lamnabhi-Lagarrigue, 2011), while control sciences have traditionally held a strong presence in engineering and technology education, and remain integrated into bachelor's and master's degree programs, such as Bachelor's Degrees in Technology and engineering curricula at universities and engineering schools (Stoica et al., 2023), their prominence is gradually being eclipsed by the rapid expansion of AI and data-science training. AI and control sciences each bring unique strengths to the table: AI offers powerful tools for pattern recognition and adaptability, while control sciences provide robust, explainable, and trustworthy solutions with guaranteed performance.

To ensure France remains at the forefront of innovation, it is essential to cultivate a balanced approach to education, as well as a new generation of researchers with expertise in both AI and control sciences. Some universities are already embracing this approach, such as the Numerics Graduate Program at the University of Bordeaux, which allows Master's and PhD students to tailor their education by selecting modules in mathematics, computer sciences, control sciences, and engineering. Building on these initiatives, we recommend further promoting interdisciplinary training that bridges AI and control sciences, ensuring students are equipped to leverage the full spectrum of tools available for addressing complex challenges.

Recommendation 5: *Promote the teaching of control sciences in higher education, integrating them with a theoretical foundation in AI.*

Several training initiatives also aim at teaching control-related topics to a non-engineering audience. This interdisciplinary training is challenging, but crucial to simplify communication between control sciences and medical or bio-medical developments. Among these initiatives, let us cite the Averroes program of Paris Saclay University which allows students to follow in parallel both medical or pharmaceutical studies and a more engineering-oriented training, with a graduation in both fields. Such selective and ambitious interdisciplinary programs are undoubtedly a key to smooth exchanges between those fields. This double scientific culture can also be developed through devoted master programs, which specifically target interdisciplinarity. An illustrative example is the Master 2 Computational Neuroscience and Neuroengineering, which allows for students with engineering background to develop expertise in neuroscience-related topics.

A significant challenge for interdisciplinary training programs is the traditionally structured disciplinary organization of French universities. With departments often operating independently, there is limited cross-disciplinary dialogue. This structure can make it difficult for students, especially those in life sciences or health, to access foundational knowledge in other fields, such as engineering, even when they are eager to do so. Addressing this gap could unlock valuable opportunities for collaboration and innovation.

Several initiatives aim at compensating this weakness, such as i) a cross-curricular health technology teaching for undergraduate students involved in various fields of engineering, with the aim of opening up learning practices and breaking down preconceived stereotypes (Cieslak et al., 2024), and ii) double-bachelor programs, such as Math-Biology in Lyon, Nice, and Saclay or Computer Science -Biology in Paris, which offer the possibility to graduate in two scientific disciplines. In our view, such initiatives need to be intensified and should be complemented by the creation of introductory modules in which the basics of dynamical systems and control sciences are taught to a non-engineering audience.

Recommendation 6: *Intensify basic, advanced and expert training programs that combine education in control sciences and life sciences.*

8.1.4 Industrial outreach

Finally, 7% of questionnaire respondents noted that their research was also impaired by the difficulty identifying or collaborating with industrial partners. As demonstrated in the technical chapters of this volume, modeling and analysis can often be pursued independently of a specific device — such as the decades of research on neural oscillations control that preceded the first commercial closed-loop deep brain stimulation systems. However, a substantial portion of control sciences for health research depends on access to measurement and control data, frequently sourced from experimental devices still in the R&D phase and not yet integrated into routine clinical practice. Securing such data therefore necessitates close collaboration with industry partners.

To fully harness the potential of Control4Health applications, targeted measures are therefore needed to strengthen collaboration between academia and the medtech industry. As highlighted in an AEF dispatch from July 2025, the Labex program demonstrated success by funding 170 laboratories with €1.5 billion over 10 years, fostering collaborations with local industries and attracting an additional €1.5 billion in private investment. Conversely, existing tools like the *crédit impôt recherche* (CIR) tax incentive, designed to encourage private R&D, have shown limited effectiveness in bridging the gap between industry and control engineering research. While programs like the ANR's LabCom support public-private partnerships, dedicated resources are still needed to empower researchers in public laboratories to actively drive technology transfer, particularly in health-related control applications.

A critical gap also exists in initiatives like the Projet Important d'Intérêt Européen (PIIEC), which allows for broad collaboration between companies in the health sector, but lacks explicit incentives for integrating public laboratories. This is particularly problematic given France's Zones of Restricted Regime (ZRR), introduced in 2013 to foster industry-laboratory collaboration. In practice, these zones often create administrative barriers rather than enabling seamless partnerships, limiting researchers' ability to contribute fully to innovation in health-focused control systems.

With the European Commission's upcoming Biotechnology Act prioritizing AI and digital tools, France must mobilize all stakeholders — large companies, SMEs, startups, and research laboratories — to avoid fragmentation and remain competitive. A unified approach would not only elevate the visibility of control engineering in health but also accelerate technology transfer, ensuring that innovations like closed-loop medical devices, adaptive control algorithms, and robust physiological models reach clinical and industrial applications faster.

Recommendation 7: *Mobilize resources and lighten administrative constraints to bring together various (public and private) digital stakeholders in the health sector, with the aim of achieving a major socio-economic impact.*

It is also critical to acknowledge that, regardless of the specific field of application, French academic researchers are generally reluctant to engage in technology transfer. This constitutes a significant barrier to translating scientific advancements into industrial innovation. The issue is systemic: French universities often prioritize traditional academic achievements, such as publications, teaching, and administrative duties, over technology transfer and industrial partnerships. For example, an associate professor investing time in technology transfer risks compromising their career progression, as such efforts rarely translate into the scientific publications required for promotion to full professor. Additionally, there is little compensation for these contributions, either through financial incentives tied to innovation profits or through reductions in teaching workload.

Recommendation 8: *Develop an incentive strategy for academic personnel willing to invest in technological transfer.*

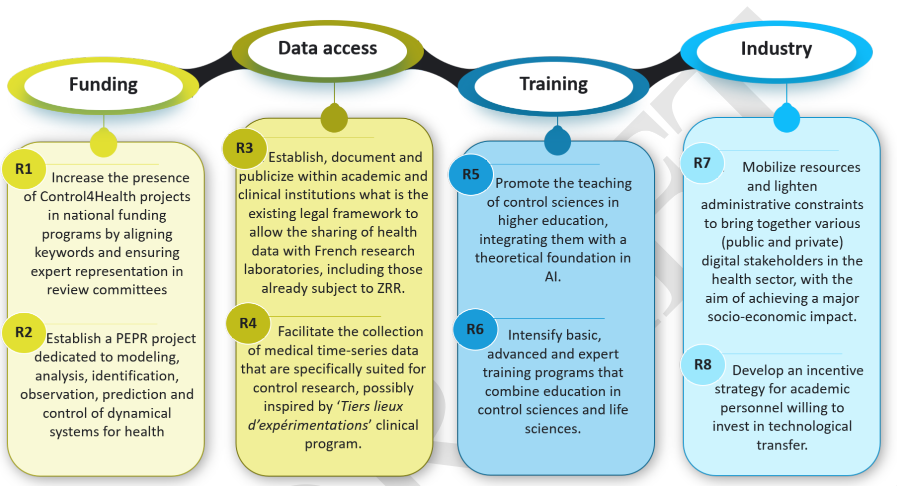

Fig. 8.2 Summary of the eight recommendations to support Control4Health community.

8.2 Concrete steps at the individual, laboratory and operating agency levels

In an effort to operationalize the above recommendations, we list here a number of concrete actions that can be taken at each level of the community: individual control researchers, laboratories, and operating institutions.

8.2.1 At the individual level

- **Consider getting biological or medical training**. To address the challenge of accessing clinical collaborators and facilitate interdisciplinary dialogue, researchers in control sciences can benefit from participating in specialized professional training programs in their clinical field of interest. In France, the *Diplôme Universitaire* (DU) format is designed as complementary training for medical professionals and is often open to non-degree auditors, including those from non-medical backgrounds. These programs are structured to accommodate full-time professionals, with intensive teaching sessions concentrated over a few weeks throughout the year. Several of such DUs are available in medical domains relevant to control engineering applications, such as the DU in clinical neurophysiology at the University of Lille, the DU on neuromodulation at University of Créteil, and the DU in diabetes management at the University of Montpellier. While participating in these programs obviously does not make one a medical practitioner, it provides access to a network of active healthcare professionals, among which potential future collaborators, and also fosters more effective communication by establishing a shared knowledge base and vocabulary.
- **Join medical science societies**. Similarly, the control community can benefit from the activities of health-related science societies by participating in their conferences or thematic days. A recent example is a seminar called *La boucle fermée : Thérapie Innovante du Diabète de type 1* organized in 2025 by the *Société Française du Diabète*. A list of French medical science societies can be found here.
- **Publish your data as an open-data benchmark, and use existing benchmarks**. To facilitate access to medical data within the control community, one simple yet impactful action researchers can take is to publish their data as open datasets or benchmarks. For instance, on Nonlinear Benchmarks, a platform dedicated to comparing nonlinear identification algorithms, there is currently only one EEG dataset (related to wrist movement). Expanding such initiatives serves multiple purposes: it mutualizes available data, increasing its accessibility and utility for the broader research community; it enhances the visibility of laboratories that invest in data collection, showcasing their contributions; and it attracts new researchers to the field (e.g. researchers analyzing an industrial robot benchmark who then notice a diabetes-related benchmark on the same platform).

8.2.2 At the laboratory level

- **Appoint a coordinator for medical/health activities.** Although control applications to various subfields of medical science necessarily grapple with domain-specificities (one has to learn about anesthesia, or diabetes, but not necessarily both), they also share common difficulties, notably linked to accessing clinical resources. Establishing a single, dedicated point of contact for medical applications at the laboratory level can significantly enhance external communication, both incoming and outgoing. First, potential clinical or industrial partners have a clear contact for initiating collaborations, and this individual can then direct inquiries to relevant colleagues. Second, the designated person builds expertise and a network of contacts, enabling them to efficiently connect colleagues with clinical partners as needed. Finally, this structure streamlines reporting to the lab's operating institutions (*tutelles*), which may request last-minute summaries of clinical activities; having a centralized point of contact ensures comprehensive and accurate reporting. Note that the CNRS *Science Informatiques* Institute has recently encouraged the appointment of such "*correspondants santé*" in their affiliated laboratory, with the mandate to specifically facilitate such bottom-up reporting and expression of needs.

- **Establish a cross-cutting structure for medical activities**. Once a critical mass of activity is reached, some laboratories have also found it beneficial to establish a cross-cutting center or *"axe transverse"* dedicated to health research, such as the FEMTO-ST Institute's Biomax center, or LS2's *axe santé-vivant*. This center not only serves as a point of contact but can also organize events like workshops, further fostering collaboration and innovation. This organization may be particularly relevant when the laboratory is involved with medical activities across multiple domains, e.g. spanning not only control but also robotics and other fields.
- **Formalize the activity as an official team**. When a laboratory is organized in disciplinary teams (e.g. control), Control4Health activities may become invisible in the organizational chart, while they already suffer from a structural lack of visibility. Even small, formally recognized teams, with a distinct name and web presence (e.g. IMS's BioMAS team, *Biotechnologies et Modélisations Avancées pour une Santé durable*), can significantly enhance research opportunities, because teams serve as the operational unit for several important funding and evaluation mechanisms (e.g. the new PRME *Projet de recherche mono-equipe* instrument at ANR). Certain research structures also encourage the affiliation of specialized teams with external institutions. For example, the *équipe-projet INRIA* model enables the creation of computer science teams within non-INRIA laboratories, such as the INRIA ARAMIS team (*Algorithmes, modèles et méthodes pour les images et les signaux du cerveau humain sain et pathologique*) at the Paris Brain Institute, a biology lab otherwise affiliated with INSERM and CNRS. These teams benefit from INRIA's full institutional support while operating directly within a biological research environment
- **Attract and affiliate medical research personnel**. University Hospital personnel (MCU-PH, *maitre.sse.s de conférence personnel hospitalier* and PU-PH, *professeur.e.s des université personnel hospitalier*) are both clinical practitioners and academics who, as all French research personnel, are required to be affiliated to a research laboratory (besides the Hospital department in which they do their clinical service). While many of these personnel chose to affiliate by default in biology labs sometimes co-located with the hospital, nothing prevents them to affiliate to other laboratories within the same university system, including control research teams in computer science or engineering laboratories, especially when they can motivate an interest based on an existing collaboration. Conversely, incorporating clinical personnel in Control4Health teams greatly enhance research opportunities (for a particularly successful example, see for instance the Biosis team at *Centre de Recherche en Automatique de Nancy* whose roster currently includes 5 MCU-PH and 5 PU-PH).

- **Co-supervise PhD theses of medical doctors**. Another effective way to strengthen ties with medical professionals is to position the laboratory as a potential host for physicians pursuing a research-focused Ph.D. — referred to in the medical field as a *thèse de science*, as opposed to the *thèse d'exercice* (M.D.) that concludes medical training. These individuals, who often aspire to *médico-universitaire* career paths (e.g., MCU-PH or PU-PH), require laboratory affiliation and may find co-supervision with a non-medical thesis advisor particularly attractive. While their technical contributions may differ from those of computer science or engineering graduates, medical Ph.D. candidates bring invaluable clinical expertise and access to patient data or cohorts, significantly enriching applied research projects. In some instances, such students also come with their own funding, e.g. provided on a part-time basis by the hospital in complement to a reduced clinical service. In the long-term, these students who are encultured in Control4Health research will also evolve to become clinical collaborators.
- **Formalize an institutional link with a partner hospital**. Another effective strategy for laboratories to expand clinical connections is to establish formal or informal partnerships with hospitals, many of which host cross-specialty clinical research units—such as INSERM's *Centres d'Investigation Clinique* (CIC). These centers often serve as gateways to broader hospital networks and possess expertise in the administrative and legal aspects of clinical trials. Moreover, they are inherently motivated to collaborate with external laboratories. Such partnerships can take various forms: informal arrangements (e.g., two personnel from CIC INSERM 1431 in Besançon maintain part-time offices at the FEMTO-ST Institute for convenience) or formal agreements. At the individual level, this might include joint appointments, such as a CNRS *Directeur de Recherche* from FEMTO-ST serving as an engineering consultant for a CIC under the *cumul d'activité* framework. At the laboratory level, collaborations can also be formalized by including CIC as a partner in joint projects, such as those funded by ANR.

8.2.3 At the university level

- **Facilitate personalized student training paths to promote control sciences.** This can take the form of i) control sciences teaching for medicine / life science students, or ii) the development of project-based learning applied to a health-related issue, see for instance the DU *Technologies au service de la santé* at Bordeaux Institute of Technology.
- **Develop double-bachelor degrees.** The prospect of obtaining a double degree has the potential to attract high-caliber students with an interest in interdisciplinarity. Examples of existing interdisciplinary training programs include M2 CNN of Paris Saclay or Mention healthcare and biomedical of CentraleSupelec. Graduate programs for joint medicine-engineering studies should be promoted, such as Averroes.
- **Encourage the deployment of transversal departments between life sciences and engineering**. For instance, H-CODE is an "Interdisciplinary object" that aims

to coordinate control sciences in Paris Saclay at the interface with Life science (Neuro), Economics, Movement Science, and Mathematics.

- **Create incentives for technological transfer** by reduced teaching load, better consideration in careers evaluation, or a financial feedback to the researcher on the profits generated by the innovative product.

8.2.4 At the research agency level

- **Establish a working group to clarify the legal framework governing the use of clinical data in non-medical laboratories.** This group would develop and publish recommendations for the research community, providing validated legal guidance and practical information to streamline procedures; publish these recommendations under the auspices of a recognized institution (e.g., the *Conseil Scientifique d'Institut* CNRS *Sciences Informatiques*), lending authority and credibility to the guidance. This would assist researchers and laboratories in their discussions with hospital institutions, which may be unfamiliar with the specific needs and practices of computer science and engineering research labs; and investigate whether a laboratory's existing *Zone à Régime Restrictif* (ZRR) status could simplify or expedite the process of accessing and using clinical data.
- **Intensify the recruitment of researchers from interdisciplinary committees, and ensure that control expertise is well-represented**. As of 2026, the *Commissions Interdisciplinaires* (e.g., CID51) at CNRS offer approximately 5–6 research positions annually, with roughly one position expected to be allocated to the broad field of computer science. While the disciplinary sections, such as Section 03 (Computer Science) which offers 6–8 positions yearly, do not formally exclude hiring in Control4Health research, these roles typically prioritize candidates with core-domain expertise. Expanding the number of positions available through the CID framework would send a strong and encouraging signal to the research community: it would demonstrate that pursuing interdisciplinary training does not limit career prospects or risk unemployment for early-career researchers. Another key step to improve prospects for Control4Health research is to ensure balanced representation of control science experts within CNU and CoNRS evaluation committees. This could be achieved by leveraging organizations like the GdR MACS to issue calls for elected members (*membres élu·e·s*), or by appointing qualified individuals through discretionary institute nominations (*membres nommé·e·s*). Finally, the specific structure of existing CIDs and sections also raise concern for members of the control engineering community that are working in laboratories not affiliated with CNRS *Sciences Informatiques* (e.g. CNRS *Ingénierie* laboratories with no or only secondary affiliation to *Sciences Informatiques*) and may not be eligible for computer science funding instruments.
- **Pursue national initiatives to raise the visibility of control sciences for health**. The CNRS, in collaboration with the Ministry of National Education and the Ministry of Higher Education, Research, and Space (MESRE), organizes an annual national scientific outreach program focused on a key theme. For the 2026-2027 academic

year, the theme will be "*l'année de la santé*". In this context, Control4Health research offers a compelling case study to highlight the impact of the broader field of computer science and engineering for the general public. These activities may also be relayed by community structures and societies such as GdR MACS and SAGIP.

- **Create a PEPR dedicated to control sciences for health**. As already discussed, while some existing PEPR address the broad field of digital health or mathematical modeling for biology, none of the existing initiatives address physiology and health as a dynamical system, leaving a large gap in the research community concerned not only with control science, but also e.g. computational neuroscience and applied mathematics.

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