Reinforcement Learning in Modern Biostatistics: Constructing Optimal Adaptive Interventions

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Abstract. In recent years, reinforcement learning (RL) has acquired a prominent position in the space of health-related sequential decision-making, becoming an increasingly popular tool for delivering adaptive interventions (AIs). However, despite potential benefits, its real-life application is still limited, partly due to a poor synergy between the methodological and the applied communities. In this work, we provide the first unified survey on RL methods for learning AIs, using the common methodological umbrella of RL to bridge the two AI areas of dynamic treatment regimes and just-in-time adaptive interventions in mobile health. We outline similarities and differences between these two AI domains and discuss their implications for using RL. Finally, we leverage our experience in designing case studies in both areas to illustrate the tremendous collaboration opportunities between statistical, RL and healthcare researchers in the space of AIs.

Key words and phrases: Reinforcement Learning, Dynamic Treatment Regimes, Multi-Armed Bandits, Adaptive Interventions, Mobile Health.

1. INTRODUCTION

In the era of big data and digital innovation, healthcare is going through a rapid and dramatic change process, transitioning from one-size-fits-all standards to the tailored approach of precision or personalized medicine [56]. Under this framework, the “individual variability in genes, environment, and lifestyle for each person” is taken into account in an effort to improve the ways we “anticipate, prevent, diagnose, and treat” a particular disease in a particular patient [21]. This paradigm encompasses a broad range of scientific domains, ranging from genomics to advanced analytics and causal inference, all in support of a data-driven, yet patient-centric, approach for delivering personalized care.

One of the key methodological lines of research within the domain of personalized medicine is the development of adaptive interventions [AIs; 3, 23]. The fundamental goal of AIs is to operationalize sequential decision-making by tailoring interventions to individuals, offering guidance on how to adapt them to an individual’s changing status and needs. In clinical practice, a typical situation is represented by a clinician who needs to use a set of treatment rules (i.e., a treatment regime) that recommend how to assign treatments or doses to patients based on their individual characteristics. These characteristics can include both baseline information (e.g., demographic data or pretreatment clinical conditions) and evolving health status (e.g., responses to previous treatments). For example, for patients who do not improve on the first-line treatment over a prespecified period, the clinician may plan to increase the dose, according to a dose-response relationship, or change the treatment in case of a sensitive or drug-resistant patient. Due to changes in their health status, such a treatment regime is therefore dynamic within a person. To the patient, this sequence of treatments seems...
like standard treatment; to the clinician, it represents a series of prespecified decisions to make according to the patient’s evolving history; and to the statistician, it constitutes an AI, alternatively known as dynamic treatment regime or regimen [DTR; 81, 66, 17]. The distinctive feature of AIs is their data-driven, adaptive approach guided by and oriented toward individual data. Clearly, an ambitious goal in AIs, or more specifically in DTRs, is how to construct the optimal DTRs, e.g., treatment regimes that result in an optimal mean response or outcome. Such a question has a long history in statistics, and its study will occupy a central role in this work.

The traditional way of offering AIs to a patient mostly relies on rules created by experts, based on factors such as domain theory and empirical experience with similar patients. However, the recent advances and the widespread application of artificial intelligence and machine learning (ML) techniques [see e.g., 28, 100, 92], have shed light on their ability to enable clinicians to quickly, efficiently, and accurately identify the most appropriate course of action for their patients.

ML represents a hotspot in artificial intelligence, and health systems have recently tapped into its expanding potential to complement classical statistical tools and support clinical decision-making. There is no clear line between ML models and traditional statistical models [8]. However, it is well documented that sophisticated ML models [e.g., deep learning models; 43] are well-suited to learn, and automatically improve through experience, from the high-dimensional and heterogeneous data generated from modern clinical care. By matching a patient’s characteristics to a computerized clinical knowledge base, such algorithms can suggest assessments or recommendations tailored to that patient’s characteristics, even in very complex settings.

Specifically, reinforcement learning [RL; 118, 10, 117] offers a natural framework for the sequential decision-making problem encountered in the construction of AIs. In classical RL, a learning agent has to decide which of one or more actions to take when interacting with an unknown environment. Based on the feedback or reward received from the environment for the selected action(s), the agent learns how best to act to maximize cumulative reward over time. This is done by trial-and-error, that is, by observing and inferring from the environment after actions are taken. The RL framework is abstract and yet flexible enough to accommodate a variety of domains where the problem has a sequential nature [15, 44]; it does so by specifically characterizing the environment’s (or domain’s) dynamics. In AIs, RL can be applied by regarding the alternative interventions as the actions to be chosen and the outcome of the intervention (e.g., patient behavior or response) as the reward.

Within biostatistics, RL was first introduced as a data analysis tool to discover optimal DTRs in a variety of health domains including cancer [142, 40], weight loss management [38, 97], substance use [85, 15], mental health [98], and so on. More recently, there seems to be an unprecedented interest in the application of RL to the rapidly expanding mobile health [mHealth; 50, 59, 58] domain. mHealth refers to the use of mobile or wearable technologies to promote healthy behavior changes in both clinical and nonclinical populations. A high-level goal in mHealth is to deliver efficacious just-in-time adaptive interventions [JITAIs; 89] in response to the in-the-moment changes in an individual’s internal (e.g., health) and contextual (e.g., location) state [58]. The challenge in a JITAI is thus to provide ‘the right individual with the right intervention’, as well as ‘the right intervention at the right time’. Notably, despite the relatively recent development of JITAIs compared to DTRs, research interest in both methodology and applications has substantially skewed toward JITAIs (see Fig. 1).

Given the increasing number of mHealth studies, and in tandem the ongoing interest among statisticians in DTRs (as shown in Fig. 1), integrating these two areas is a worthy objective. In the current article, we combine our methodological background with our experience in designing case studies in the above two areas to extensively review the state of the art of RL in AIs.

In Section 2, we formally characterize the problem of AIs, providing a common framework for applications to DTRs and JITAIs, and explaining their similarities and differences. We then formalize the RL paradigm and its subclasses, relating it to the problems at hand, and assimilating the different existing notations and terminologies into a coherent framework (Section 3). This provides a foundation to more easily conduct research in both methodological and applied aspects of AIs, enhancing communication and synergy between them.
Section 4 offers a review of RL methods for developing AIs, expanding on DTRs with both finite- and indefinite-time horizons and JITAIs for mHealth. Section 5 grounds Section 4 by illustrating the development and application of the presented methodology to two case studies. Section 6 presents conclusions and future research directions.

To the best of our knowledge, this represents the first comprehensive survey of RL methods for developing DTRs as well as JITAIs in mHealth, informed by our experience with the challenges and successes of real-world applications. It complements and adds to the extensively surveyed DTR literature [see e.g., 15, 17, 126], which we place together with JITAIs under the same AI umbrella.

We believe that there is ample scope for important practical advances in these areas, and with this survey we aim to make it easier for theoretical and methodological researchers to join forces to assist healthcare discoveries by developing the next generation of methods for AIs in healthcare. We finally emphasize that we focus on healthcare and biostatistics due to the central role statisticians play there traditionally. Notwithstanding, the concepts we review for AIs extend far beyond: to education [87], policy making [52], and other domains such as ecology, where RL has not been contextualized yet [see e.g., 137].

2. ADAPTIVE INTERVENTIONS AND THEIR USE IN HEALTHCARE

Adaptive interventions offer a vehicle to operationalize a sequential decision-making process over the course of a program or a condition, with the aim of optimizing individual welfare or outcomes. Technically speaking, AIs are defined via explicit sequences of decision rules that pre-specify how the type, intensity, and delivery of intervention options should be adjusted over time in response to individual progresses [3, 89]. The prespecified nature of AIs increases their replicability in research and enhances the assessment of their effectiveness [87].

The existing frameworks for formalizing AIs [23, 3] are based primarily on four key components:

(i) The decision points specifying the time points at which a decision concerning intervention has to be made; here we assume a finite or countable number of times \( t = 0, 1, \ldots \);

(ii) The decisions or intervention options at each time \( t \), that may correspond to different types, dosages [duration, frequency or amount; 131], or delivery modes, as well as various tactical options (e.g., augment, switch, maintain); we denote them by \( A_t \subseteq \mathcal{A}_t \), where \( \mathcal{A}_t \) is the decision or action space, generally discrete;

(iii) The tailoring variable(s) at each time \( t \), say \( X_t \subseteq \mathcal{X}_t \), with \( \mathcal{X}_t \subseteq \mathbb{R}^p \), capturing individuals’ baseline and time-varying information for personalizing decision-making;

(iv) The decision rules \( d = \{d_t\}_{t \geq 0} \), that, at each time \( t \), link the tailoring variable(s) to specific decisions or interventions.

A common illustrative way to describe an AI is through schematics such as the one shown in Fig 2. “If-then” statements clarify how the decision rule prespecifies the intervention options under various conditions.

Since an AI adaptation aims to optimize individual outcomes, two additional components play an essential role in their definition [87]:

(v) The proximal outcome(s), say \( \{Y_{t+1}\}_{t \geq 0} \), that is, easily observable short-term outcome(s), expected to influence a longer-term outcome of interest, according to some mediation theory [76];

(vi) The distal outcome(s), i.e., the long-term outcome of interest and the ultimate goal of the overall AI.

Note that the proximal outcomes can also be used as tailoring variables to guide later-stage decisions. In Fig 2, for example, the response status at time \( t = 1 \) represents both the proximal outcome targeted by the intervention at the decision point \( t = 0 \) and the tailoring variable at the decision point \( t = 1 \).

The development of AIs is based on the selection and integration of the aforementioned six components, taking into account their relationship. Ideally, this is informed and guided by domain theories, practical considerations, empirical evidence, or some combinations thereof. Determining optimized decision rules typically involves more sophisticated data-driven statistical and ML tools, with RL recognized as a current state-of-the-art tool.

The term AI is interchangeably used with adaptive treatment strategy [82, 84], treatment policy [75, 132, 24], and dynamic treatment regime or regimen [81, 66, 15, 61], among others. However, given its more generic nature, we use the term AI to refer to a general framework for personalizing interventions sequentially based on an individual’s time-varying characteristics. This broader definition embraces a considerable number of applications, including non-healthcare [e.g., education; 87] and the two healthcare domains of DTRs and JITAIs, which we cover below.

2.1 Dynamic treatment regimes

In medical research, DTRs define a sequence of treatment rules tailored to each individual patient based on their baseline and time-varying (dynamic) state. Traditionally, treatment assignment is based on single-stage decision-making. Specifically, one observes a set of baseline or pretreatment information \( X_0 \in \mathcal{X}_0 \), based on which a treatment \( A_0 \in \mathcal{A}_0 \) is selected. The treatment rule, say \( d_0 \), is a mapping from \( \mathcal{X}_0 \) to \( \mathcal{A}_0 \). If more stages are involved, at each stage \( t \), the treatment rule \( d_t \) is again a mapping from the stage-\( t \) information set \( \mathcal{X}_t \) to a stage-\( t \)
action space $\mathcal{A}_t$. Unlike average-based single-stage protocols, DTRs explicitly incorporate the heterogeneity in treatment effect among individuals and across time within an individual; $d_t = (d_0, \ldots, d_t)$ is now regarded as a multistage regime with each $d_\tau$, $\tau = 0, \ldots, t$, a mapping from the entire evolving history $X_0 \times A_0 \times \cdots \times X_t$ to $\mathcal{A}_t$. As such, it provides an attractive framework for personalized treatments in longitudinal settings. Furthermore, by treating only those who show a need for treatment, DTRs hold the promise of reducing noncompliance due to overtreatment or undertreatment [65]. At the same time, they are attractive to public policy makers, allowing a better allocation of public and private funds [81].

Reflecting an AI framework, a DTR is defined on a set of decision points at which treatment decisions are made through a set of decision rules. Decision points generally range from two to four stages of intervention in sequentially randomized trials, while it is common to have many more decision points in longitudinal observational studies, including data from electronic health records (EHRs). At each stage $t$, a treatment $A_t \in \mathcal{A}_t$ is selected based on an individual’s covariates $X_t$, which may include an intermediate outcome assessed at stage $t$, say $Y_t$, expected to correlate with the distal outcome of interest. In some problems, there may be only a distal (end-of-study) outcome $Y$ instead of multiple intermediate outcomes [see e.g., 96]. When intermediate outcomes are considered, it is important to assess both intermediate and long-term outcomes because what appears to be optimal in the short term may not yield the best overall outcome. Beyond personalization, DTRs can identify and evaluate delayed effects, i.e., effects that do not occur immediately after treatment but may affect a person or their disease later in time.

For developing DTRs, data sources include both longitudinal observational and randomized studies, such as randomized-controlled trials (RCTs) and sequential multiple assignment randomized trials [SMARTs; 65, 82]. Although observational studies are much more common, SMARTs are the current gold standard [67]. A SMART is characterized by multiple stages of treatment, each stage corresponding to one of the critical decision points. A concrete example is provided in Fig 3, illustrating the first two stages of the weight loss management study [97]. At study entry, all individuals are uniformly randomized to one of two first-line interventions: mobile app (APP) or APP + Coaching. Participants are assessed at weeks 2, 4, 8, and those ‘responding’ to their initial treatment (i.e., losing at least 0.5 lbs. on average per week) continue receiving the same treatment. As soon as an individual is classified as a ‘nonresponder’, they are rerandomized to one of two augmentation tactics: modest augmentation (supportive text message; TXT) or vigorous augmentation (TXT + Coaching, or TXT + meal replacement (MR), depending on the first-stage treatment). Rerandomization occurs only once per participant, with the newly assigned treatment continuing through the end of the study. Because different intervention options are considered for responders (continue) and nonresponders (modest or vigorous augmentation), the response status is embedded as a tailoring variable. Such multistage restricted randomization generates several DTRs embedded in the SMART [see 15, for details on embedded regimes].

### 2.2 Just-in-time adaptive interventions in mHealth

The ubiquitous use of mobile technologies has facilitated the development of a new area of health promotion in both clinical and nonclinical populations, known as mHealth [50]. A key objective in mHealth is to deliver efficacious real-time AIs in response to rapid changes in individual circumstances, while avoiding overtreatment and its consequences on user engagement (e.g., low adherence to recommendations or discontinued usage of the mobile device). This specialized AI is termed JITAI [89].

In mHealth, JITAs refer to a sequence of decision rules that use continuously collected data through mobile technologies (e.g., wearable devices, accelerometers, or smartphones) to adapt intervention components in real time to support behavior change and to promote health.
The peculiarity of JITAIs is that they deliver interventions according to the user’s in-the-moment context or needs, e.g., time, location, or current activity, including considerations of whether and when the intervention is needed. Compared to DTRs, JITAIs are more flexible in terms of location and timing of interventions delivery. Although the adaptation and delivery of a DTR usually take place at a clinical appointment and under direct guidance of a clinician, JITAIs often adapt and assign interventions as dictated by the mobile system while users go about their daily lives in their natural environments. Furthermore, unlike DTRs, the number of decision points in JITAIs can be hundreds or even thousands, and the intervention can be delivered each minute, hour, or day (as in the case of the DIAMANTE study; see Fig 4).

In JITAIs, the time between decision points is often too short to capture the (distal) outcome of interest, and they rely on a weak surrogate, i.e., the proximal outcome. This distinctive characteristic contributes to its increasing popularity in a variety of behavioral domains, ranging from physical activity [47, 36] and weight management [97] to addictive disorders [42, 39] and smoking cessation [90]. There has also been recent interest in employing JITAIs to improve public health in general [72].

Aligned with the generic definition of AIs, JITAIs are defined according to the proximal and the distal (typically clinical) outcomes. However, unlike DTRs—which target the distal outcome and may or may not have an intermediate (proximal) outcome—JITAIs, proximal outcomes represent the direct and in-the-moment target of the intervention. The distal outcome is expected to improve only based on domain knowledge about its relationship with the proximal outcome, but is not formally included in the optimization problem. A detailed comparison between DTRs and JITAIs is provided in Table 1.

Typical experimental designs for building JITAIs are represented by factorial experiments [22], or most notably, micro-randomized trials [MRTs; 54]. In MRTs, individuals are randomized hundreds or thousands of times over the course of the study, and in a typical multicompo-

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**Fig 3. Schematic of the first two stages of the weight loss SMART in [97].** Response is defined as a weight loss ≥ 0.5 lbs. on average per week.

**Fig 4. Schematic of the DIAMANTE micro-randomized trial [2]**
nent intervention study, the multiple components can be randomized concurrently, making micro-randomization a form of a sequential full factorial design. The goal of these trials is to optimize mHealth interventions while offering a basis to assess the causal effects of each intervention component and to evaluate whether the intervention effects vary with time and/or with the individual contexts.

To better understand the characteristics and value of MRTs, let us now consider the DIAMANTE study for promoting physical activity, illustrated in Fig 4. In this study, the intervention components include whether or not to send a text message, which type of message to deliver, and at which time; the proximal outcome is the change in the number of steps a participant walked today from yesterday; and the context is given by a set of variables such as health information and study day. To assess the effectiveness of the optimized JITAI, users are assigned to different study groups: A. a static (nonoptimized) group, B.

|   | DTRs | JITAI in mHealth |
|---|------|-----------------|
| Data sources | RCTs, SMARTs, longitudinal observational data including EHRs, dynamical systems models | MRTs, RCTs, factorial designs, single-case experimental designs |
| **AI component: (i) decision points** $t = 0, 1, \ldots$ | | |
| Number of decision points | In SMARTs, generally small (e.g., two to four) and fixed; in EHRs (defined over indefinite horizons) an increased number is seen | Generally very large (hundreds or even thousands for each single unit) and can be fixed or random (e.g., upon a user’s request) |
| Distance between decision points | Sufficiently long according to the expected time to capture a potential effect (including a delayed effect) of the intervention on the primary outcome of interest or a strong intermediate surrogate | Quite short according to the expected “in-the-moment” effect of the intervention on the proximal outcome (e.g., every few minutes, hours or daily) |
| **AI component: (ii) decisions or intervention options** $X_t \subset A_t, t = 0, 1, \ldots$ | | |
| Type of intervention | Mostly drugs or behavioral interventions | Generally behavioral interventions (e.g., motivational/feedback messages, coaching, reminders) with few exceptions (e.g., insulin adjustments) |
| Intervention delivery | Assigned by the care provider during an appointment or through digital devices | Assigned through digital/mobile devices according to an automatic algorithm or/and under care provider’s guidance |
| **AI component: (iii) tailoring variable(s)** $X_t \subset A_t \subset \mathbb{R}^p, t = 0, 1, \ldots$ | | |
| Type of tailoring variable | Can include the full or partial history of baseline and time-varying patients’ information. An external context can also be considered, but it has secondary relevance. | Current users’ information, and any type of variable related to their momentary context (e.g., availability, weather), which plays a major role and can be very granular |
| **AI component: (iv) decision rules** $d_t \in \{d_t\}_{t=0,1,\ldots}$ | | |
| Main strategy to optimize decision rules | • Offline methods for finite-horizon decision problems, with some exceptions (e.g., for EHRs-based DTRs an indefinite horizon may be considered) • While finite-horizon problems in general account for the full individual history over time, indefinite horizon problems assume a Markov structure. | • Online methods over indefinite-time horizons • Considering the expected “in-the-moment” effect of the intervention, typically, only the current or last observed information is accounted for, with a predominant use of Markov, partially observed Markov, or simpler structures |
| **AI component: (v)-(vi) outcomes** $Y_t \subset Y_t \subset \mathbb{R}, t = 1, 2, \ldots$ | | |
| Proximal outcome | • Optional short-term outcomes expected to impact the distal (long-term) outcome • While not being the primary target of the intervention, they may be part of the adaptation/optimization process. | • Short-term outcomes directly targeted by the intervention and expected to mediate the effect on the distal outcome • They guide the definition of just-in-time in the context of the identified problem, as well as the formulation of the adaptation strategy. |
| Distal outcome | • The outcome directly targeted by the intervention • The primary criterion that guides the adaptation/optimization of the DTR, although intermediate outcomes are often part of the optimization | • Long-term goal of a JITAI, expected to be influenced by an intervention through the mediating role of proximal outcomes (domain knowledge) • Typically, they do not guide the adaptation/optimization of the learning strategy. |

**Table 1**

*Differences between current state-of-the-art characteristics of DTRs and JITAI in terms of the key elements constituting an AI*
an adaptive group based on RL, and C. a control group (see Fig 4). In the two intervention groups, users are randomized every day to receive a combination of categories of the different intervention components, delivered within different time frames. The adaptive RL-based optimized group will be briefly discussed in Section 5, after introducing the RL framework.

3. REINFORCEMENT LEARNING FRAMEWORK

Generally speaking, RL is an area of ML concerned with determining optimal action selection policies in sequential decision-making problems [118, 10]. This framework is based on repeated interactions between a decision maker or learning agent and the environment it wants to learn about, to take better decisions or actions. Before characterizing this process and formalizing the RL problem(s), it is paramount to set out clearly the fundamental prerequisites that enable RL to solve decision-making problems such as developing AIs with rigor.

3.1 A preliminary note: causal inference and RL

While in this work our focus is primarily on RL, we note that this is neither a necessary nor generally a sufficient solution for building valid AIs. As we will mention in passing in Section 4.1.1, a variety of other traditional statistical approaches, mostly confined to the causal inference literature, exist and have a substantial relevance in the field. In fact, for developing AIs, one needs to assess the causal relationship between interventions and outcomes, thus, requiring an adequate framework for causality.

Causal inference provides a set of tools and principles that allow one to combine data and causal assumptions about the environment to reason with questions of counterfactual nature. Through considerations on study designs, estimation strategies, and certain fundamental assumptions (e.g., no unmeasured confounders), it provides the building blocks that enable researchers to draw causal conclusions based on the observed data. On a different tangent, RL is concerned with efficiently finding a policy that optimizes an objective function (e.g., the expected cumulative reward) in interactive and uncertain environments. In practice, despite being causal by nature—any system looking to advise on interventions in some way quantifies their effects—the classical RL does not conduct causal inference. We can think of at least two reasons. First, RL practitioners often consider problems in which the data are unconfounded (e.g., robotics), because these are collected through direct interactions with a relatively well-understood environment, governed by physical laws, and actions are taken by the learning agent depending only on the data available (experimental data). To illustrate, this is the case of current JITAI practices. Second, and most importantly, the fundamental problem of RL, rather than dealing with causal effects estimation, is oriented toward causal-decision making. We note that the two are not the same, and counterintuitively, accurate estimation is not essential for accurate decision-making [34]. While these two areas have evolved independently over different aspects of the same building block and with no interaction between them, disciplines such as AIs can be developed only under an integrated framework that permits causal conclusions.

Our attention in the current work is devoted to RL rather than causal inference, and we point the readers to the seminal works of Neyman and Rubin [91, 110] for the potential outcomes framework, and to Pearl [95] for the causal graphical model perspective. For a comprehensive treatment of both, we refer to [48]. Furthermore, recent attempts in the ML community have worked toward a unified framework called causal RL, which embeds the causal graphical approach within sample efficient RL algorithms [140].

For simplicity of exposition, in this work, we assume that the main assumptions of causal inference [see e.g., 17] hold, and that the conditional distributions of the observed data are the same as the conditional distributions of the potential outcomes, given the assigned treatment. It follows that RL can operate in a simplified causal inference problem (in which actions are unconfounded), and that optimal AIs may be obtained using the observed data.

3.2 Formalization of the general RL problem

Consider a discrete time space indexed by \( t \in \mathbb{N} = \{0, 1, \ldots\} \). In RL, at each decision time point or simply time \( t \), an agent faces a decision-making problem in an unknown environment. After receiving some representation of the environment’s state or context, say \( X_t \in \mathcal{X}_t \), it selects an action, denoted by \( A_t \), from a set of admissible actions \( \mathcal{A}_t \). As a result, one step later, the environment responds to the agent’s action by making a transition into a new state \( X_{t+1} \in \mathcal{X}_{t+1} \) and (typically) providing a numerical reward \( R_{t+1} \in \mathcal{Y}_{t+1} \subset \mathbb{R} \). By repeating this process over time, the result is a trajectory of states visited, actions pursued, and rewards received. In a medical context, this trajectory can be viewed as the individual history (of covariates, treatments, and responses to treatments) of a patient over time. Note that in some settings there may be only one terminal reward (or a final outcome, e.g., overall survival or school performance at the end of the study [96]); in this case, rewards at all previous time points are taken to be 0. In other settings (e.g., multiarmed bandits; Section 3.3.2), states may be ignored, thus leading to a trajectory of actions and rewards only.

Define \( X_t = (X_0, \ldots, X_t) \), \( A_t = (A_0, \ldots, A_t) \), \( Y_t = (Y_1, \ldots, Y_t) \), and similarly \( X_{t+1}, a_{t+1}, y_{t+1} \), where the upper and lowercase letters denote random variables and their particular realizations, respectively. Also, define history \( H_t \) as all the information available at time \( t \) prior
to decision $A_t$, i.e., $H_t = (A_{t-1}, X_t, Y_t)$; similarly $h_t$. The history $H_t$ at time $t$ belongs to the product set $\mathcal{H}_t = X_0 \times \prod_{r=1}^{t} X_r \times A_{r-1} \times Y_r$. Note that, by definition, $H_0 = X_0$.

We assume that each longitudinal history is sampled independently according to a distribution $P_{\pi}^{\text{Full-RL}}$ (with the superscript clarified later in Section 3.3), given by

$$P_{\pi}^{\text{Full-RL}} = p_0(x_0) \prod_{t \geq 0} \pi_t(a_t|h_t)p_{t+1}(x_{t+1}, y_{t+1}|h_t, a_t),$$

where:

- $p_0$ is the probability distribution of the initial state $X_0$.
- $\pi = \{\pi_t\}_{t \geq 0}$ represents the exploration policy that determines the sequence of actions generated throughout the decision-making process. More specifically, $\pi_t$ maps histories of length $t$, $h_t$, to a probability distribution over the action space $A_t$, i.e., $\pi_t(\cdot|h_t)$. The conditioning symbol $\cdot|h_t$ reminds us that the exploration policy defines a probability distribution over $A_t$ for each $h_t \in \mathcal{H}_t$. Sometimes, $A_t$ is uniquely determined by the history $H_t$, therefore, the policy is simply a function of the form $\pi_t(h_t) = a_t$. We call it deterministic policy, in contrast with stochastic policies that determine actions probabilistically.
- $\{p_t\}_{t \geq 1}$ are the unknown transition probability distributions and they completely characterize the dynamics of the environment. At each time $t \in \mathbb{N}$, the transition probability $p_t$ assigns to each trajectory $(x_{t-1}, a_{t-1}, y_{t-1}) = (h_{t-1}, a_{t-1})$ at time $t - 1$ a probability measure over $X_t \times \mathcal{Y}_t$, i.e., $p_t(\cdot|h_{t-1}, a_{t-1})$.

At each time $t$, the transition probability distribution $p_{t+1}(x_{t+1}, y_{t+1}|h_t, a_t)$ gives rise to:

(i) $p_{t+1}(x_{t+1}|h_t, a_t, y_{t+1})$, the state-transition probability distribution, representing the probability of moving to state $x_{t+1}$ conditioning on the observed history $h_t$, the current selected action $a_t$, and the reward received $y_{t+1}$;

(ii) $p_{t+1}(y_{t+1}|h_t, a_t, x_{t+1})$, the immediate reward distribution, specifying the reward $Y_{t+1}$ after transitioning to $x_{t+1}$ with action $a_t$.

Generally, in DTRs, the immediate reward $Y_{t+1}$ is conceptualized as a known function of the history $H_t$, the current selected action $A_t$ and the new state $X_{t+1}$; that is, conditional on $H_t$, the reward function is deterministic and $Y_{t+1}$ is uniquely determined. To give a concrete example, one can think of a dose-finding trial, where the level of toxicity is one of the state variables, among others. In this setting, at each time $t$, the immediate reward $Y_{t+1}$ of a patient with history $H_t$ and administered dose $A_t$ could be potentially defined as a binary variable assuming value $-1$ if a toxicity level ($X_{t+1}$) higher than a certain value is observed, and $0$ otherwise.

The cumulative sum (often time-discounted) of immediate rewards is known as return, say $R_t$, and is given by

$$R_t = Y_{t+1} + \gamma Y_{t+2} + \gamma^2 Y_{t+3} + \cdots = \sum_{\tau \geq t} \gamma^{\tau-t} Y_{\tau+1},$$

for $t \in \mathbb{N}$. The discount rate $\gamma \in [0, 1]$ determines the current value of future rewards: a reward received $\tau$ time steps in the future is worth only $\gamma^\tau$ times what it would be worth if it were received immediately. If $\gamma < 1$, the potential infinite sum in Eq. (2) has a finite value as long as the reward sequence $\{Y_{\tau+1}\}_{\tau \geq t}$ is bounded. If $\gamma = 0$, the agent is myopic in being concerned only with maximizing the immediate reward, i.e. $R_t = Y_{t+1}$; this is often the case of MABs (see Section 3.3.2). If $\gamma = 1$, the return is undiscounted and it is well defined (finite) as long as the time horizon is finite, i.e., $t \in [0, T]$, with $T < \infty$ [118]. If $T$ is fixed and known in advance, e.g., in clinical trials, the agent faces a finite-horizon problem; if $T$ is not prespecified and can be arbitrarily large (the typical case of EHRs), but finite, we can call it an indefinite-horizon problem; finally we use the term infinite-horizon problem when $T = \infty$. In this case, we need $\gamma \in (0, 1)$ to ensure a well-defined return. As preliminarily outlined in Table 1, DTRs mainly deal with finite-horizon problems (exception made for EHRs), while JITAs involve indefinite-horizon problems.

Roughly, solving an RL task means learning an optimal way to choose the set of actions, or learning an optimal policy, so as to maximize the expected future return. However, in many decision problems, the target policy or estimation policy we want to learn about, say $d$, might be different from the exploration policy $\pi$ that generated the data. This may happen when we want to estimate an optimal policy without interacting with the environment but using some already collected data (e.g., observational EHR data), for which a certain exploration policy, often unknown, was used. We refer to it as offline RL, as opposed to online RL, where the agent interacts with the environment to collect the samples and iteratively improve the policy. Taking into account this potential policy change, the RL problem at any time $t$ is to find an optimal policy $d^*_t = \{d^*_t\}_{t \geq t}$ such that

$$d^*_t = \arg \max_{d_t} \mathbb{E}_d[R_t] = \arg \max_{d_t} \mathbb{E}_d \left[ \sum_{\tau \geq t} \gamma^{\tau-t} Y_{\tau+1} \right],$$

where the expectation is meant with respect to a trajectory distribution analogous to Eq. (1), say $P_d$, where the fixed exploration policy $\pi$ that generated the data is replaced by an arbitrary policy $d$ we use to learn about the data.

To estimate optimal policies, various methods have been developed so far in the RL literature (see [118] and
A traditional approach is through value functions. These define a partial ordering over policies with insightful information on the optimal ones. In fact, optimal policies share the same (optimal) value function. For this reason, efficient estimation of the value function is one of the most important components of almost all RL algorithms, and it occupies a central place in the decision-making paradigm. In DTRs, for example, evaluating the value function of a treatment regime is equivalent to evaluating the average outcome if the estimated treatment rule were to be applied to a population with the same characteristics (state or history) in the future [148]. Comparing the estimated value functions of different candidate treatment regimes offers a way to understand which regime may offer the greatest expected outcome.

There are two types of value function: i) state-value or simply value functions, representing how good it is for an agent to be in a given state, and ii) action-value functions, indicating how good it is for the agent to perform a given action in a given state. More specifically, the time-

\[ V^t_d(h_t, a_t) = \max_{a_t \in A_t} \mathbb{E}_d \left[ Y_{t+1} + \gamma V^t_d(h_{t+1}) \mid H_t = h_t, A_t = a_t \right], \]

∀t ∈ N and ∀h_t ∈ H_t. To ensure that the conditional expectation in \( V^t_d(h_t) \) is well defined, each history \( h_t \) in \( H_t \) should have a positive probability (i.e., \( \mathbb{P}(H_t = h_t) > 0 \)). Note that, by definition, at time \( t = 0, V^0_d(h_0) = V^0_d(x_0) \); while for the terminal time point, if any, the state-value function is 0.

Similarly, the time-

\[ Q^t_d(h_t, a_t) = \mathbb{E}_d \left[ Y_{t+1} \mid H_t = h_t, A_t = a_t \right], \]

∀t ∈ N, ∀h_t ∈ H_t and ∀a_t ∈ A_t. As in Eq. (4), \( H_t \) and \( A_t \) are such that \( \mathbb{P}(H_t = h_t) > 0 \) and \( \mathbb{P}(A_t = a_t) > 0 \).

At time \( t \), the optimal value function \( V^t_* \) yields the largest expected return for each history with any policy \( d \), and the optimal Q-function \( Q^t_* \) yields the largest expected return for each history-action pair with any policy \( d \), i.e.,

\[ Q^t_* (h_t, a_t) = \max_{d_t} Q^t_d (h_t, a_t), \quad \forall h_t \in H_t, \forall a_t \in A_t \]

and

\[ V^t_* (h_t) = \max_{d_t} V^t_d (h_t) = \max_{a_t \in A_t} Q^t_* (h_t, a_t), \quad \forall h_t \in H_t. \]

Because an optimal action-value function is optimal for any fixed \( h_t \in H_t \), it follows that the optimal policy at time \( t \) must satisfy

\[ d^t_* (h_t) \in \arg \max_{a_t \in A_t} Q^t_* (h_t, a_t). \]

A fundamental property of the value functions used throughout RL is that they satisfy particular recursive relationships, known as Bellman equations. For any policy \( d \), the following consistency condition, expressing the relationship between the value of a state and the values of the successor states, holds:

\[ V^t_d (h_t) = \mathbb{E}_d [Y_{t+1} + \gamma V^t_d (h_{t+1}) \mid H_t = h_t], \]

∀h_t ∈ H_t, ∀t ∈ N. Based on this property and Eqs. (6)-(7), at each time \( t \), \( V^t_d (h_t) \) is well defined, each history \( h_t \) in \( H_t \) should have a positive probability (i.e., \( \mathbb{P}(H_t = h_t) > 0 \)). Note that, by definition, at time \( t = 0, V^0_d (h_0) = V^0_d (x_0) \); while for the terminal time point, if any, the state-value function is 0.

Similarly, the time-

\[ Q^t_d (h_t, a_t) = \mathbb{E}_d [Y_{t+1} \mid H_t = h_t, A_t = a_t], \]

∀t ∈ N, ∀h_t ∈ H_t and ∀a_t ∈ A_t. As in Eq. (4), \( H_t \) and \( A_t \) are such that \( \mathbb{P}(H_t = h_t) > 0 \) and \( \mathbb{P}(A_t = a_t) > 0 \).

At time \( t \), the optimal value function \( V^t_* \) yields the largest expected return for each history with any policy \( d \), and the optimal Q-function \( Q^t_* \) yields the
3.3 Formalization of specific RL problems

The RL problem can be posed in a variety of different ways depending on the assumptions about the level of knowledge initially available to the agent. The framework is abstract yet flexible enough to be applied to many different (sequential) problems by specifically characterizing the state and action spaces, the reward function, and other general domain (or environment) aspects, such as the time horizon or the dynamics of the process. The general framework introduced in Section 3.2 does not make any simplifying assumptions on the dependency between rewards, actions, and states: by carrying over all the available history from the starting time, it considers a full dependency between them. We name this framework full reinforcement learning (full-RL).

Often, specific domains of application may have an underlying theory about the potential relationships between the key elements of an RL problem. To illustrate, consider a hospital admission scheduling problem [55], wherein the action set is represented by the number of daily admissions. To determine the optimal action, it may be necessary to know the current number of beds occupied, while all the information on the previous occupations or on the set of previous actions can be ignored. In other words, one may ignore the overall history and consider only the current state in the decision-making process. This example fits into the Markov decision process (MDP) framework discussed in Section 3.3.1.

Furthermore, in some applied problems (e.g., indefinite-horizon problems), a full-RL formalization may be infeasible and/or intractable for both optimization and inference purposes. Thus, some forms of simplification in the distribution of the longitudinal histories may be needed. For example, in JITAI, the ‘just-in-time’ nature of decision-making requires a computationally feasible estimation and application of the decision rule continuously in time.

Common examples of specific formalizations of an RL problem include Markov decision processes (MDPs) and multi-armed bandit (MAB) or contextual MAB problems. Although we discuss the MAB problem as a subclass of–or a special way of formalizing–the RL problem [as in 118], we want to point out that some key researchers in the domain [see e.g., 64] distinguish between the two. According to them, RL is mostly associated with ML, whereas MABs are with mathematics. One driver of this choice may be related to the major focus and attention to theoretical guarantees, e.g., optimal regret bounds, that MAB algorithms seek to satisfy.

In what follows, we illustrate these two specific formalizations, starting with the MDPs, the main framework in indefinite-horizon DTR problems. A graphical illustration of the different settings is given in Fig. 5.

3.3.1 Markov decision processes

An MDP is a stochastic process used to define the dynamics of an environment and to model the interaction between the agent and the environment. It provides a convenient mathematical framework for modeling decision-making in situations where the environment is deemed to evolve according to the Markov model [99]. Notably, it is the most common setting assumed in RL [129].

What distinguishes an MDP-based RL (MDP-RL) from the full-RL framework is the environment’s random memoryless characteristic. More specifically, assuming that the current state $X_t$ contains all the information of the past history $H_{t-1}$ relevant to future predictions, it allows us to ignore the past when modeling future states and rewards. This property, known as Markov property, leads to a low-dimensional representation of the past, exemplifying the trajectory distribution in Eq. (1) as follows:

$$P_{\pi}^{MDP} = p_0(x_0) \prod_{t \geq 0} \pi_t(a_t|x_t)p_{t+1}(x_{t+1},y_{t+1}|x_t, a_t)$$

$$= p_0(x_0) \prod_{t \geq 0} \pi_t(a_t|x_t)p_{t+1}(x_{t+1}|x_t, a_t)$$

$$p_{t+1}(y_{t+1}|x_t, x_{t+1}, a_t).$$

Note that under the Markov property, the agent’s decisions can be entirely determined based on the current information only, as it fully determines the environment’s transition-probability distributions, i.e., $p_{t+1}(\cdot|H_t, A_t) = p_{t+1}(\cdot|X_t, A_t), \forall t \geq 0$. When the transition probabilities $\{p_{t+1}\}_{t \geq 0}$ are also time independent, i.e., $p_{t+1} = p, \forall t \geq 0$ the process is called time-homogeneous or stationary MDP. In light of this additional assumption, states, rewards, and actions are now time independent, given the information of previous time points. In the context of DTRs as well as JITAI, time-homogeneous MDPs were proposed in indefinite-time
horizons, as they simplify the problem by working with time-independent quantities, which do not require a backward induction strategy (see Section 4.1.3).

While both full-RL and MDP-RL are typically formulated as problems with states, actions, rewards, and transition rules that depend on previous states, an exception is made for MABs, whose original formulation can be viewed as a stateless variant of RL [11]. In a typical MAB problem, either the actions and the rewards are not associated with states or they are assumed to depend only on the current state. This feature enables faster learning in settings such as JITAI where RL is continuously implemented in an online fashion. This aspect will be discussed in more detail in Section 4.3.

3.3.2 Multi-armed bandits MAB problems, often identified as a special subclass of RL [118, 11], have a long history in statistics. They were introduced in 1933 by [124] and extensively studied under the heading sequential design of experiments [101, 63].

Generally speaking, the MAB problem (also called the K-armed bandit problem) is a problem in which a limited set of resources (e.g., a group of individuals) must be allocated between competing choices in order to maximize the total expected reward over time. Each of the K choices (i.e., arms or actions) provide a different reward, whose probability distribution is specific to that choice.

If one knew the expected reward (or value) of each action, then it would be trivial to solve the bandit problem: they would always select the action with the highest value. However, as this information is only partially gained for the selected actions, at each decision time, the agent must trade-off between optimizing its decisions based on acquired knowledge up to time t (exploitation) and acquiring new knowledge about the expected rewards of the other actions (exploration).

MAB strategies were originally proposed to solve stateless problems, in which the reward depends uniquely on actions. Subsequently, a ‘stateful’ variant of MABs, named contextual MAB (C-MAB), in which actions are associated with some state, or context, was introduced. However, unlike full-RL and MDP-RL, in contextual MABs, actions do not have any effect on the next states. In addition, generally, there are no transition rules from one state to another in subsequent times. This implies that states, actions, and rewards can be treated as a set of separate events over time. The most typical assumption is that contexts \( \{X_t\}_{t \in \mathbb{N}} \) are independent and identically distributed (i.i.d.) with some fixed but unknown distribution. This means that action \( A_t \) at time \( t \) has an in-the-moment effect on the proximal reward \( Y_{t+1} \) at time \( t+1 \), but not on the distribution of future rewards \( \{Y_r\}_{r \geq t+2} \), for which the i.i.d. property holds as well. Under this assumption, one can be completely myopic and ignore the effect of an action on the distant future in searching for a good policy. This problem is better known as stochastic MAB, in contrast to adversarial MABs [64], in which no independence assumptions are made on the sequence of rewards. In stochastic contextual MABs, and further in the context-free MAB problem, the trajectory distributions are simplified as follows:

\[
P_{\pi} = p_0(x_0) \prod_{t \geq 0} \pi_t(x_t)p_{t+1}(x_{t+1}, y_{t+1} | x_t, a_t)
\]

\[
= p_0(x_0) \prod_{t \geq 0} \pi_t(x_t)p_{t+1}(x_{t+1})
\]

\[
\pi_t(x_t)p_{t+1}(y_{t+1} | x_t, a_t).
\]

Note that, since the effect of an action in the stochastic MAB is in-the-moment, the bandit problem is formally equivalent to a one-step/state MDP, wherein the states progression is not taken into account. Thus, compared to MDP-RL and full-RL, MABs provide a simplified structure of the relationships between the components of RL within time. For a graphical summary, see Fig. 5.

As in the general RL problem, the goal of an MAB problem is to select the optimal arm at each time \( t \) so as to maximize the expected return, alternatively (and with a slightly different nuance) expressed in the bandit literature in terms of minimizing the total regret. Indeed, in (online) real-world problems, until we can identify the best (unique) arm, we need to make repeated trials by pulling the different arms. The loss that we incur during this learning phase (i.e., the time spent for learning the best arm) represents what is called regret, i.e., how much we regret not picking the best arm. Formally, denoted by

\[
A^*_t = \arg \max_{a_t \in A} E(Y_{t+1} | X_t = x_t, A_t = a_t)
\]

the optimal arm at time \( t \), we define the immediate regret \( \Delta(A_t) \) of action \( A_t \) as the difference between the expected reward of the optimal arm \( A^*_t \) and the expected reward of the ultimately chosen arm \( A_t \), i.e.,

\[
\Delta(A_t) = E(Y_{t+1} | X_t, A^*_t) - E(Y_{t+1} | X_t, A_t).
\]

Given a (random) horizon \( T \), the goal of the learner is to minimize the total regret given by \( \text{Reg}(T) = \sum_{t=0}^{T} \Delta(A_t) \). Note that the agent may not know ahead of time how many time points \( T \) are to be played. Therefore, the goal is to perform well not only at the final time point \( T \), but also during the learning phase. For example, in a dose-finding problem as the one mentioned in Section 3.3.1, the objective may not only be to minimize the sum of toxicities over time, but also to ensure that these toxicities have a proper upper limit—thus, limiting extremely harmful adverse events—uniformly over time. For this reason, as we will see later in Section 4.2, theoretical works on regret bounds occupy a central place in the bandit literature.
3.4 RL and AIs: a joint overview

So far, we have introduced the RL as a mathematical framework for sequential decision-making problems and discussed its applicability and characterization in illustrative examples of interest within the AI area. Before diving deep into the rich literature of existing RL methods for building (optimized) AIs, we provide the reader with a joint overview on the different problems, which notably share the same key elements and a common optimization objective. As such, they can be unified under a unique formal framework and solved with techniques developed under the RL paradigm.

Table 2 serves as a table of equivalence between the terminologies of reference in each setting, with a unified notation adopted from the general RL. Note that, while we report only the most common terminology employed in each setting, lexical borrowing is widely used across the different theoretical and applied domains. To illustrate, the term ‘treatment policy’, or just ‘policy’ is often used in place of ‘treatment regime’ in the DTR literature.

Also note that, in general, the terminology adopted in a specific application is guided by the RL method and framework used in that application; see e.g., the similarity between the terms used in JITAIs and MABs such as ‘contextual variables’ and ‘context’ (i.e., the state of the environment). Both contextual and tailoring variables represent the set of baseline and time-varying information that is used to personalize decision-making. Alternative terms such as covariates or features (which we use with a slightly different meaning, as we discuss in Section 4.2.1) are also common. We anticipate that most (if not all) of the methods to construct JITAIs would generally belong to the MAB class, although the applied literature commonly refers to it with the generic ‘reinforcement learning’ name [see e.g., 138, 70, 35]. In DTRs, the predominant class of methods is full-RL, followed by MDP-RL proposed specifically for indefinite-horizon (e.g., EHR-based) DTR problems. In fact, the underlying theory of DTRs—characterized by potential delayed or carried-over effects of treatment over time—and the importance of the evolving history of a patient for predicting future outcomes requires accurate consideration of information from previous time points. Generally, the meaningful relationship between the different variables of a patient’s history does not allow simplifying or ignoring the (state-)transition rules, making full-RL (and occasionally MDP-RL) the ideal option. On the other hand, the behavioral theory of a momentary effect of an intervention on the proximal outcome (underlying mHealth applications) makes MAB a more suitable framework compared to full-RL and MDP-RL in this setting. In addition, the reduced computational burden from carrying through all the historical information allows MAB strategies to be applied continuously in time, e.g., every hour, and efficiently construct JITAIs.

4. A SURVEY OF RL METHODS FOR ADAPTIVE INTERVENTIONS

Methodology for constructing optimal AIs, i.e., the ones that, if followed, would yield the most favorable (typically long-term) mean outcome, is of considerable interest within the domain of precision medicine, and comprises a large body of research within theoretical and applied sciences [15, 61, 56]. Although their relevance has been long documented within statistics and causal inference (see Section 4.1.1), recently it has generated a lot of interest within the computer science and engineering communities, due to the similarity between the mathematical formalization of AIs and the RL framework.

4.1 RL methods for dynamic treatment regimes

4.1.1 A historical overview Perhaps due to the need to identify causal relationships, the study of AIs originated in causal inference with the pioneering works of Robins [102, 105, 106] for DTRs. Over an extended period of time, the author introduced three basic approaches for finding effects of time-varying regimes in the presence of confounding variables: the parametric G-formula or G-computation [102], structural nested mean models with the associated method of G-estimation [104, 103, 105], and marginal structural models with the associated method of inverse probability of treatment weighting [IPW; 107].

Table 2

| Notation | RL | MABs | DTRs | JITAIs |
|----------|----|------|------|--------|
| $i$      | Trajectory | Trajectory | Patient | User |
| $t$      | Time point | Round, Time point | Stage, Interval, Time point | Time point |
| $X$      | State | Context | Tailoring Variables | Contextual Variables |
| $A$      | Action | Arm | Treatment, Intervention | Intervention |
| $Y$      | Reward | Reward | Intermediate, Distal Outcome | Proximal Outcome |
| $H$      | History | History, Filtration | History | History |
| $\pi, d$ | Policy | Policy | (Dynamic) Treatment Regime | Policy |
| $\pi^*, d^*$ | Optimal Policy | Optimal Policy | Optimal DTR | Optimal Policy |
A number of methods have subsequently been proposed within statistics, including both frequentist and Bayesian approaches [121, 122, 123, 65]. However, all estimate the optimal DTR based on distributional assumptions on the data-generation process via parametric models, and, as such, can easily suffer from model misspecification [144]. The first semiparametric method for estimating optimal DTRs was proposed by Murphy [81], immediately followed by Robins [108], who introduced two alternative approaches using G-estimation. These methods use approximate dynamic programming, where ‘approximate’ refers to the use of an approximation of the value or Q-function introduced in Eq. (5), or parts thereof. Thus, they can be considered as the first prototypes of RL-based approaches in the AI literature.

RL methods represent an alternative approach to estimating DTRs that have gained popularity due to their success in addressing challenging sequential decision-making problems, without the need to fully model the underlying generative distribution. The connection between statistics and RL (previously confined to the computer science and control theory literature) was bridged by Murphy [83], who proposed estimating optimal DTRs with Q-learning [136, 118]. Promptly, a large body of research has embraced the use of Q-learning, integrating various parametric, semiparametric, and nonparametric strategies [83, 15, 17, 60] to model the Q-function.

Q-learning and the semiparametric strategies of Murphy [81] and Robins [108] are considered indirect methods: optimal DTRs are indirectly obtained by first estimating an optimal objective function (e.g., the Q-function), and then getting the associated (optimal) policy. In contrast, IPW-based strategies [107, 86, 135] seek optimal policies by directly looking for the policy (within a pre-specified class of policies) that maximizes an objective function (e.g., the expected return), without postulating an outcome model [143]; they are regarded as direct methods.

In what follows, we review existing RL techniques for developing DTRs focusing on the indirect methods, while an up-to-date review including direct methods can be found in [26]. We cover both finite- and indefinite-horizon settings. We emphasize that most of the current work in DTRs deals with finite-horizon problems and offline learning procedures that assume access to a collection of observed trajectories. This opposes to the JI-TAI tradition—originated with the practical need to deliver AIs in real time—which uses an online learning approach for performing data collection and policy optimization simultaneously. Such procedures can be deployed indefinitely, conditional on practical limitations. In DTRs, the indefinite-horizon setting, particularly suitable for chronic diseases where the number of stages can be arbitrarily large, has been addressed only recently. Nevertheless, it remains relatively understudied.

4.1.2 Finite-horizon DTR problems Finite-horizon DTR problems are designed to identify optimal treatment policies \( d^* = \{d^*_t\}_{t=0,...,T} \) over a fixed and known period of time \( T < \infty \). Learning methods typically use offline RL based on finite observational data trajectories of a sample of say \( N \) patients, and causal assumptions about the data [see e.g., 26]. Each patient trajectory has the form \( \{X_0, A_0, Y_1, \ldots, X_T, A_T, Y_{T+1}\} \), with \( X_0 \) and \( X_1, \ldots, X_T \) the pretreatment and evolving information, respectively, \( A_0, \ldots, A_T \) the assigned treatments, and \( Y_1, \ldots, Y_{T+1} \) the intermediate and final outcomes. In finite-horizon problems, RL methods are mainly based on DP or approximate DP procedures. These include Q-learning [83], with the Q-function as the objective, and A-learning [108, 81], which focuses on contrasts of conditional mean outcomes. We now discuss the former, assuming throughout this section deterministic policies, that is, policies that map histories \( h \) directly into actions or decisions, i.e., \( d(h) = a \).

Q-learning with function approximation. In Section 3, we showed that optimal value functions can be obtained by iteratively solving the Bellman optimality relationship in Eq. (10) and Eq. (11). In finite-horizon DP problems, this procedure is known as backward induction. However, the iterative process may be memory and computationally intensive, especially for large state and action spaces. Furthermore, traditional DP procedures assume an underlying model for the environment, which is often unknown due to unknown transition probability distributions. Q-learning [136] offers a powerful and scalable tool to overcome the modeling requirements as well as the computational burden of traditional DP-based RL methods and constitutes the core of modern RL.

The general idea of Q-learning is that, at each new \( t \), the Q-function is updated based on a previous value and the new acquired information:

\[
Q_t^d(h_t, a_t) \leftarrow Q_t^d(h_t, a_t) + \alpha_t \left[ Y_{t+1} + \gamma \max_{a_{t+1} \in A_{t+1}} Q^d_{t+1}(h_{t+1}, a_{t+1}) - Q^d_t(h_t, a_t) \right],
\]

with \( \alpha_t \) a constant that determines to what extent the newly acquired information overrides the old information or how fast learning takes place, and \( \gamma \) a discount factor that balances immediate and future rewards (in finite-horizon problems, it is generally set to one).

The original version of this approach is known as tabular Q-learning [118]. This is based on storing the Q-function values for each possible state and action in a lookup table and choosing the one with the highest value. Since the agent selects the actions based on their maximum associated Q-function value, this is equivalent to exploiting (recall the notion of exploitation introduced in Section 3.3.2). However, the tabular approach is slow and
impractical for large state and action spaces. A powerful and scalable solution to this problem is a more recent version of Q-learning, known as Q-learning with function approximation [118, 83]. This version first assumes an approximation space for each of the Q-functions in Eq. (5), e.g., \( Q_t = \{ Q_t^d(h_t, a_t; \theta_t) : \theta_t \in \Theta_t \} \), with parameter space \( \Theta_t \) a subset of the Euclidean space, and then estimates the optimal stage-\( t \) Q-functions \( Q_t^* \) backward in time for \( T, T-1, \ldots, 0 \) [7]. According to Eq. (8), estimating an optimal regime \( \hat{d}^* = (d_0^*(x_0), d_1^*(h_1), \ldots, d_T^*(h_T)) \) is equivalent to getting estimates of the optimal Q-functions, or in this case, getting an estimate \( \hat{\theta}_t \), \( \forall t = 1, \ldots, T \), of the parameters, i.e.,

\[
\hat{d}_t^*(h_t) = \arg \max_{a_t \in A_t} \hat{Q}_t^d(h_t, a_t) = \arg \max_{a_t \in A_t} \hat{Q}_t(h_t, a_t; \hat{\theta}_t) = d_t^*(h_t; \hat{\theta}_t).
\]

Noticing, for example, that the Q-function is a conditional expectation, we can get the optimal Q-functions as:

\[
Q_t^*(h_t, a_t; \hat{\theta}_t) = \mathbb{E}[Y_t + \max_{a_{t+1} \in A_{t+1}} Q_{t+1}^*(h_{t+1}, a_{t+1}; \hat{\theta}_{t+1}) | H_t = h_t, A_t = a_t],
\]

with \( \mathbb{E} \) denoting the empirical mean over a sample of \( N \) individuals. The general procedure is illustrated in Algorithm 1, while a more specific implementation with linear regression is reported in the Supplementary Material A.2.

It is important to recognize that the estimated regime \( \hat{d}^* \) may not be a consistent estimator for the true optimal regime \( d^* \), unless all models for the Q-functions are correctly specified. A strategy that may offer robustness to Q-function misspecification is A-learning [108, 81], where ‘A’ stands for the ‘advantage’ incurred if the optimal treatment were given as opposed to what was actually given. A-learning represents a class of alternative methods to Q-learning, predicated on the fact that it is not necessary to specify the entire Q-function to estimate an optimal regime. A more in-depth discussion is provided in the Supplementary Material A.3. Schulte et al. [111] showed that A-learning outperforms Q-learning under misspecifications of Q-function models.

Given that a linear regression model may be quite simple and prone to misspecification, more sophisticated approximators can be used both in Q-learning and in A-learning. These include support vector regression [142] and deep neural networks [DNNs; 4], among others.

Deep Q-network. The tremendous success achieved in recent years by RL has been greatly enabled by the use of advanced function approximation techniques such as deep neural networks [DNNs; 51, 112, 78], giving rise to the deep Q-network algorithm [78]. Specifically, at a given time \( t \), a DNN [see 43, for an overview of existing DNN architectures] is used to fit a model for the Q-function in a supervised way and then estimate the optimal Q-function: histories \( \{H_{t,i}\}_{i=1, \ldots, N} \) are given as input, and the predicted Q-function values \( Q_t^d(H_t, a_t; W, b) \) associated with each action \( a_t \in A_t \), e.g., with \( A_t = \{a_1, \ldots, a_K\} \), are generated as output. \( W \) and \( b \) represent the unknown weight and bias parameters of a typical DNN; see e.g., the schematic of a feed-forward neural network in Fig. 6.

Once Q-function estimates are obtained with the DNN, the algorithm proceeds with executing, in an emulator, an action according to an exploration scheme named \( \epsilon \)-greedy [118]. This probabilistically chooses between the optimal action so far (i.e., the one with the highest estimated Q-function value) and a random action. Specifically, \( \epsilon \) is the exploration probability for a random action. At the end of the execution sequence, first the Q-function

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**Algorithm 1: Q-learning with Function Approximation [83]**

**Input:** Time horizon \( T \), sample of \( N \) trajectories, approximation space for the Q-functions \( Q_t \doteq \{ Q_t^d(h_t, a_t; \theta_t) : \theta_t \in \Theta_t \} \), for all \( t = 0, \ldots, T \).

**Initialization:** Stage-(\( T + 1 \)) optimal Q-function; for convenience, is typically set to

\[
Q_{T+1}(h_{T+1}, a_{T+1}; \theta_{T+1}) = \mathbb{E}[Y_{T+1} | H_T = h_T, A_T = a_T] = 0.
\]

for \( t = 0, 1, 2, \ldots, T \) do

1. **Q-function parameter estimates:** get updated estimates \( \hat{\theta}_{T-t} \) backward by minimizing a loss, e.g., squared-error loss, \((\mathbb{F}_N)\) is the empirical mean over \( N \) trajectories

\[
\hat{\theta}_{T-t} \in \arg \min_{\theta_{T-t} \in \Theta_{T-t}} \mathbb{F}_N [Y_{T-t+1} + \max_{a_{T-t+1} \in A_{T-t+1}} Q_{T-t+1}^*(h_{T-t+1}, a_{T-t+1}; \hat{\theta}_{T-t+1}) - Q_{T-t}^*(h_{T-t}, a_{T-t}; \hat{\theta}_{T-t})]^2.
\]

2. **Optimal policy estimate:** get the \((T-t)\)-time optimal regime estimate as the one that maximizes the optimal \((T-t)\)-time Q-function estimate

\[
d_{T-t}^*(h_{T-t}; \hat{\theta}_{T-t}) = \arg \max_{a_{T-t} \in A_{T-t}} Q_{T-t}^*(h_{T-t}, a_{T-t}; \hat{\theta}_{T-t})
\]

end for
is re-estimated based on the observed reward, and then the DNN parameters are updated using the last Q-function estimates. The pseudo-algorithm is given in Algorithm 2. A DNN offers a more flexible and scalable approach, particularly suitable for real-life complexity, high dimensionality, and high heterogeneity. Compared to their shallow counterparts, they enable automatic feature representation and can capture complicated relationships [see e.g., an application in the graft-versus-host disease; 73].

A general limitation of indirect methods such as Q-learning, is that the optimal DTRs are estimated in a two-step procedure: first, the Q-functions are estimated using the data, and then these are optimized to infer the optimal DTR. In the presence of high-dimensional information, even with flexible nonparametric techniques such as DNNs, it is possible that these conditional functions are poorly fitted, with the derived DTR far from optimal. Furthermore, as demonstrated by [143], indirect approaches may not necessarily result in maximum long-term clinical benefit, motivating direct methods. We refer to [26, 126] for a survey of direct approaches.

Nonetheless, we emphasize that here we present indirect methods in some detail because they are somewhat similar to well-known regression methods that most readers can relate to. Furthermore, many of the methods for developing JITAIs (e.g., Thompson sampling, among the other methods discussed in Section 4.2) are also regression-based methods. Thus, by focusing on regression-type methods across apparently disjoint application domains, we help enhance the synergy between them.

4.1.3 Indefinite-horizon DTR problems While in computer science there is a vast literature on estimating optimal policies over an increasing time horizon [119, 117], that is not the case in DTRs. In fact, by adopting backward induction, most existing methods cannot extrapolate beyond the time horizon in the observed data. Nevertheless, for some chronic conditions, or those with very short time steps, including mHealth applications (see Section 2), the time horizon is not definite. Treatment decisions are made continuously throughout the life of a patient, with no fixed time point for the final treatment decision.

To the best of our knowledge, only a limited number of statistical methodologies have been developed for the indefinite-horizon setting. These include the indirect greedy gradient Q-learning method of [32], and the direct V-learning approach of [74], who proposed to search for an optimal policy over a prespecified class of policies. More recently, a minimax framework called proximal temporal consistency learning was proposed [147]. We now detail the first two approaches, while for the third, we refer the reader to the original work in [147].

Greedy gradient Q-learning. The first extension to indefinite-time horizons in DTRs was proposed in [32], under the time-homogeneous Markov assumption (see Section 3.3.1). Although not imposed by general DTR

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**Algorithm 2:** Deep Q-Network [78, 73]

**Input:** Pre-processing real data profiles \((\mathbf{H}_{0,i}, A_{0,i}), Y(\mathbf{H}_{0,i}, A_{i})\), \(i=1,\ldots,N\); \(\epsilon > 0\); \(\gamma > 0\).

**Initialization:** Experience memory \(D_0 = \{(\mathbf{H}_{0,i}, A_{0,i}), Q^d_0(\mathbf{H}_{0,i}, A_{0,i}; \mathbf{W}_0, \mathbf{b}_0)\}\), \(i=1,\ldots,N\) with \(\{Q^d_0(\mathbf{H}_{0,i}, A_{0,i}; \mathbf{W}_0, \mathbf{b}_0)\}\), \(i=1,\ldots,N\) based on random parameters \((\mathbf{W}_0, \mathbf{b}_0)\).

**Train a DNN with labeled data** \(D_0\) and get estimates \((\hat{\mathbf{W}}_0, \hat{\mathbf{b}}_0)\) for \(t = 0, 1, 2, \ldots T\) do

**\(\epsilon\)-greedy step:** select a random action \(a_t\) with probability \(\epsilon\); otherwisely \(a_t = \arg \max_{a \in A} Q_t(\mathbf{H}_t, a; \hat{\mathbf{W}}_t, \hat{\mathbf{b}}_t)\);

Execute \(a_t\) in emulator and observe state transition \(X_{t+1}\) and reward \(Y_{t+1}(\mathbf{H}_t, a_t)\);

Update the experience memory data: \(D_{t+1} = (D_t, Y_{t+1}, X_{t+1})\);

**Q-learning update:** update Q-function

\[
Q_t^d(\mathbf{H}_t, a_t; \hat{\mathbf{W}}_0, \hat{\mathbf{b}}_0) = Y_{t+1}(\mathbf{H}_t, a_t) + \gamma \max_a Q_{t+1}^d(\mathbf{H}_{t+1}, a; \hat{\mathbf{W}}_0, \hat{\mathbf{b}}_0)
\]

**DNN Update:** get updated estimates \((\hat{\mathbf{W}}_{t+1}, \hat{\mathbf{b}}_{t+1})\) that minimize the expected loss \(Q_t^d(\mathbf{H}_t, a_t; \mathbf{W}_0, \mathbf{b}_0) - Q_t(\mathbf{H}_t, a_t; \hat{\mathbf{W}}_t, \hat{\mathbf{b}}_t))^2\) based on the Q-learning update.

end for
methods, such assumption overcomes the need for backward induction, and exemplifies inference by working with time-independent Q-functions.

We adopt the notation of the previous sections and introduce an absorbing state $c$, representing, e.g., a death event. We assume that at each time $t$, covariates $X_t$ take values in a finite state space $\mathcal{X}^* = \mathcal{X} \cup \{c\}$, with $\mathcal{X} \cap \{c\} = \emptyset$. Let the action space $\mathcal{A}_x$ be finite and defined by covariate information such that $\mathcal{A}_x$ consists of 0 $< m_x \leq m$ treatments, with $m$ being the total number of treatments over the time horizon. For any $t$ such that $X_t = c$, let $A_x = \mathcal{A}_x = \{u\}$, where $u$ stands for ‘undefined’. Now, denoting a stopping time (e.g., death) by $\hat{T} = \inf \{t > 0 : X_t = c\}$, individual trajectories are of the form $(X_0, A_0, R_1, \ldots, X_{\hat{T}-1}, A_{\hat{T}-1}, R_{\hat{T}}, X_{\hat{T}})$. Note that $\mathbb{P}(\hat{T} < \infty | X_0, A_0) = 1$, regardless of $(X_0, A_0)$.

Based on these specifications, the indefinite time-$t$ Q-function for regime $\pi(t) = \pi(x_t) = \pi(x)$, for $x \in \mathcal{X}$, is given by:

$$Q_\pi(x, a) = E_{\mathcal{P}}[R_t | X_t = x_t, A_t = a_t] = E_{\mathcal{P}} \left[ \sum_{t=0}^{\infty} \gamma^{t} Y_{t+1} | X_t = x_t, A_t = a_t \right].$$

We set $Q^*(c, a) = 0$ since the return is 0 after an individual is lost to follow-up.

For estimating an optimal DTR, Q-learning is proposed. Let $Q(x, a; \theta^*)$ be a parametric model for $Q^*(x, a)$ indexed by $\theta^* \in \Theta \subseteq \mathbb{R}^q$ and postulate a linear model with interactions, i.e., $Q(x, a; \theta^*) = \theta^T \psi(x, a)$, with $\psi(x, a)$ being a known feature vector summarizing the state and treatment pair. To ensure $Q^*(c, a) = 0$, we also need $\psi(c, a) = 0$. Now, Bellman optimality suggests and motivates the following unbiased estimating function for $\theta^*$:

$$\hat{\dot{\theta}}(\theta) = \mathbb{P}_N \left\{ \sum_{t=0}^{T-1} \left( Y_{t+1} + \gamma \max_{a' \in \mathcal{A}} Q(X_{t+1}, a'; \theta^*) - Q(X_t, A_t; \theta^*) \right) \psi(X_t, A_t) \right\},$$

with $\psi(X_t, A_t) = \nabla_{\theta^*} Q(X_t, A_t; \theta^*)$.

Note that the estimating function in Eq. (16) is a nonconvex and nondifferentiable function of $\theta$, which complicates the estimation process. Under regularity conditions, the authors suggested that any solution $\theta^*$ can be equivalently defined as a minimizer of $\hat{M}(\theta^*) = \hat{D}(\theta^*)^T \hat{W}^{-1} \hat{D}(\theta^*)$, with $\hat{W} = \mathbb{P}_N \left\{ \sum_{t=0}^{T} \psi(X_t, A_t) \otimes \psi(X_t, A_t) \right\}$, and $\otimes^2 = x x^T$, for any vector $x$. If $\hat{\theta}^* = \arg \min_{\theta^*} \hat{M}(\theta^*)$ is the unique solution, then $\hat{Q}^*(x, a) = Q(x, a; \hat{\theta})$, and the corresponding optimal regime is given by $\hat{\pi}^* = \arg \max_{a \in \mathcal{A}_x} Q(x, a; \hat{\theta}^*)$.

**V-learning.** The greedy gradient Q-learning approach based on Eq. (16) involves a nonsmooth max operator that makes estimation difficult without large amounts of data [60, 71]. Motivated by an mHealth application, where policy estimation is continuously updated in real time as data accumulate (starting with small sample sizes), an alternative method is proposed in [74]. Under the same time-homogeneous MDP assumption, and provided interchange of the sum and integration is justified, the authors consider the value function

$$V_t^d(x_t) = \sum_{\tau \geq t} \mathbb{E} \left[ \gamma^{\tau-t} Y_{\tau+1} \left( \prod_{v=0}^{\tau} \frac{d(A_v | X_v)}{\pi_v(A_v | S_v)} \right) | X_t = x_t \right],$$

and follow a direct approach to directly maximize estimated values over a prespecified class of policies. In light of the Bellman equation in Eq. (9), it follows that, for any function $\psi$ defined on the state space $\mathcal{X}_t$, the following importance-weighted variant is satisfied:

$$0 = \mathbb{E} \left[ \frac{d(A_t | X_t)}{\pi_t(A_t | S_t)} \left( Y_{t+1} + \gamma V^d(X_{t+1}) - V^d(X_t) \right) \psi(X_t) \right].$$

Now, let $V^d(x; \theta)$, with $\theta \in \Theta \subseteq \mathbb{R}^q$, be a model for $V^d(x)$. Assume that $V^d(x; \theta)$ is differentiable everywhere in $\theta$ for fixed $x$ and $d$, and denote by $\psi(x) = \nabla_{\theta} V^d(x; \theta)$. Then, the proposed estimating equation is given by:

$$\hat{\dot{\lambda}}(\theta) = \mathbb{P}_N \left\{ \sum_{t=0}^{T} \frac{d(A_t | X_t)}{\pi_t(A_t | S_t)} \left( Y_{t+1} + \gamma V^d(X_{t+1}; \theta) - V^d(X_t; \theta) \right) \nabla_{\theta} V^d(X_t; \theta) \right\}.$$  

Again, $\hat{\lambda}$ can be obtained by minimizing $\hat{M}(\theta) = \hat{\lambda}(\theta)^T \hat{W}^{-1} \hat{\lambda}(\theta) + \lambda \mathcal{P}(\theta)$, with $\hat{W}$ a positive definite matrix in $\mathbb{R}^{q \times q}$, $\lambda$ a tuning parameter, and $\mathcal{P} : \mathbb{R}^q \rightarrow \mathbb{R}_+$ a penalty function. The estimated optimal regime $d^*$ is the argmax of $V^d(x; \theta)$.

Compared to greedy gradient Q-learning, V-learning requires modeling both the policy and the value function, but not the data-generating process. In addition, by directly maximizing the estimated value over a class of policies [see 74, for more details], it overcomes the issues of the nonsmooth max operator in Eq. (16). The method is applicable over indefinite horizons and is suitable for both offline and online learning, which is typical in JITAIs.

### 4.2 JITAIs in mHealth

Unlike DTRs, where the number of decision points is generally small, JITAIs are defined upon a random and indefinitely large number of times. They are carried out in dynamic environments with the scope of capturing rapid changes in an individual user’s context and needs [88, 89]. Methodologies for optimizing JITAIs require the ability to
learn nearly continuously, with no definite time horizon. Furthermore, learning is performed online as data accumulate, often using trajectories defined over very short time periods. Thus, existing methods for DTRs, which mainly target a finite-time horizon problem and are implemented offline (e.g., Q-learning), are not directly applicable to JITAIAs. Furthermore, by carrying over an entire history of an individual, they may not be feasible from a computational perspective.

As discussed in Section 3, the standard approach for developing JITAIAs is given by contextual MABs [120], an intermediate solution between MABs [12, 6] and the full-RL approach used in DTRs. With a few exceptions, contextual MAB algorithms applied in mHealth rely on two fundamental bandit strategies, originally implemented in advertising: the linear Thompson sampling [LinTS; 1] and the linear upper confidence bound [LinUCB; 68, 20] and the linear Thompson sampling [LinTS; 1]. Alternative methods include the actor-critic strategy [49] and other full-RL oriented techniques [146].

4.2.1 Contextual MABs with LinUCB exploration So far, optimal AIs have typically been identified by finding the optimal Q-functions recursively with the Bellman recursion. If we assume a ridge penalized estimation strategy, with a standard linear regression model with 

$$Y_t = X_t \beta + \epsilon_t$$

where 

$$\beta = (X'X)^{-1}X'Y$$

as a generalization of the critical value. Note also that 

$$B_t^{-1}$$

and 

$$b_t$$

are analogous to the terms “($X'X)^{-1}$” and “$X'TY$”, respectively, appearing in the OLS estimator for a standard linear regression model with 

$$E[Y|X] = X\beta.$$ 

If we assume a ridge penalized estimation strategy, with penalty parameter $\lambda \geq 0$, these values are recursively computed at each time $t$ taking into account previously explored arms: 

$$B_t = \lambda I_d + \sum_{\tau=0}^{t-1} f(x_{\tau}, \bar{a}_{\tau})^T f(x_{\tau}, \bar{a}_{\tau})$$

and 

$$b_t = \sum_{\tau=0}^{t-1} f(x_{\tau}, \bar{a}_{\tau})^T Y(x_{\tau}, \bar{a}_{\tau}),$$

where \( \bar{a}_{\tau} = \arg\max_{a_\tau \in A} U_t(a_{\tau}) \) are the optimal arms estimated at previous times and \( I_d \) is the identity matrix of order $d$. Algorithm 3 provides a schematic of the LinUCB approach.

Several variations of LinUCB were proposed in the bandit literature. These include: i) the linear associative RL strategy [5], based on singular value decomposition rather than ridge regression; ii) generalized linear models, aiming to accommodate more complex models either for the reward [UCB-GLM; 37, 69] or the environment [127]; iii) nonparametric modeling of the reward function, such as Gaussian processes [GP-UCB; 114, 115], and iv) the neuralUCB method, which leverages the representation power of DNNs [145]. More recently, in addition to the (bandit) optimization goal, attention has been given to statistical objectives. To illustrate, in a similar context as ours, i.e., behavioral science, Dimakopoulou et al. [30] introduced balancing methods from the causal inference literature. Specifically, to make the algorithm less prone to bias, authors proposed to weight each observation with the estimated inverse probability of a context being observed for an arm. This algorithm helps to reduce bias, particularly in misspecified costs, at the cost of increased variance.

Successful applications of LinUCB in mHealth can be found in [94] and [38]. The former developed a LinUCB-based intervention recommender system for delivering stress management strategies (upon user’s request in a mobile app), with the goal of maximizing stress reduction. After four weeks of study, participants who received LinUCB-based recommendations demonstrated to
use more constructive coping behaviors. Similarly, in [38], a pilot study was conducted to evaluate the feasibility and acceptability of an RL-based behavioral weight loss intervention system. Participants were randomized between a nonoptimized group, an individually-optimized group (individual reward maximization), and a group-optimized (group reward maximization) group. The study showed that the LinUCB-based optimized groups have strong promise in terms of the outcome of interest, not only being feasible and acceptable for participants and coaches, but also achieving desirable results at roughly one-third the cost.

4.2.2 Contextual MABs with LinTS exploration Although Thompson sampling [124] has been introduced more than 80 years ago, it has only recently reemerged as a powerful tool for online decision-making, due to its optimal empirical and theoretical properties. Under the same linear reward assumption as in LinUCB, Agrawal [20] proposed a randomized MAB algorithm based on a generalization of TS to a contextual setting. Rooted in a Bayesian framework, the idea of TS is to select arms according to their posterior probability of being optimal, i.e., by maximizing the posterior reward distribution at each time $t$. The policy $\pi$ at each time $t$ is thus explicitly defined as:

$$\pi_t(a) = \mathbb{P}(Q^*_t(x, a) \geq Q^*_t(x, a') \land a' \neq a \mid H_t = h_t)$$

$$= \mathbb{P}(\mathbb{E}[Y_{t+1} \mid X_t = x_t, A_t = a]$$

$$\geq \mathbb{E}[Y_{t+1} \mid X_t = x_t, A_t = a'] \land a' \neq a \mid H_t = h_t),$$

where the conditioning term $H_t = h_t$ reflects the posterior nature of this probability and should not be confused with the conditioning terms of the Q-function. The TS policy is shown to be asymptotically optimal, meaning that it matches the asymptotic lower bound of the regret introduced by Lai and Robbins [63].

The typical way to implement TS is iterative and involves a posterior sampling procedure [see e.g., 18]. For example, in the common case of a Gaussian reward model with variance $\nu^2$, i.e., $Y_t \mid \mu, f(x_t, A_t) \sim N(f(x_t, A_t) \mu, \nu^2)$, considering a Gaussian prior for the regression coefficients vector $\mu$, e.g., $\mu \sim N(0_d, \sigma^2_{\mu} I_d)$, at each time $t$, the optimal arm is the one that maximizes the posterior estimated expected reward, or $f(x_t, A_t)^T \hat{\mu}_t$. The posterior nature is reflected in $\hat{\mu}_t$, which represents a sample from the estimated posterior distribution, given by $N(\hat{\mu}_t, \nu^2 B_t^{-1})$; here $\hat{\mu}_t = B_t^{-1} b_t$ is the posterior mean, with $B_t$ and $b_t$ defined in the same way as for LinUCB. The iterative LinTS procedure is given in Algorithm 4.

Given the history up to time $t$, and $f(x_t, A_t)$, LinUCB is deterministic and allows exploration through the uncertainty term $s_t(a_t)$, while LinTS is randomized and exploration is dictated by the random draws from the posterior distribution. Note that the standard deviation of LinUCB and LinTS is of the same order. In fact, in LinTS $Y_t \mid \mu_t, f(x_t, a_t) \sim N(f(x_t, a_t) \mu_t, \nu^2 f(x_t, a_t)^T B_t^{-1} f(x_t, a_t))$, and by definition $f(x_t, a_t)^T B_t^{-1} f(x_t, a_t) = s_t(a_t)$.

Similar to LinUCB, many extensions have been considered. In the mHealth literature, specifically addressing complex likelihood functions, Eckles and Kaptein [31] formulated a Bootstrap TS version to replace the posterior by an online bootstrap distribution of the point estimate $\hat{\mu}_t$ at each time $t$. The approach offers improved robustness to model misspecifications (due to the robustness of the bootstrap approach), and it can be easily adapted to dependent observations, a common feature of behavioral sciences.
Tackling a different issue, namely sparse and noisy data, Tomkins et al. [125] introduced Intelligent Pooling, a generalized version of LinTS with a Gaussian mixed-effects linear model for the reward. By explicitly modeling heterogeneity between individuals and within an individual over time, the method demonstrates a better promise of personalization, even in small groups of users.

Action-centered TS. Motivated by the potential nonstationary nature of mHealth problems, Greenewald et al. [45] extended the stationary linear model of LinTS to a nonstationary and nonlinear version composed of two parts: a baseline reward (associated with a “do nothing” or control arm, say 0) and a treatment or action effect. At each time $t$, the expected reward model is formalized as:

$$E(Y_{t+1} | X_t = x_t, A_t = a_t) = f(x_t, a_t) \mu I(a_t \neq 0) + g_t(x_t),$$

with $f(x_t, a_t) \in \mathbb{R}^d$ a fixed context-action feature (with context $X_t$ chosen by an adversary based on history up to time $t$), $\mu \in \mathbb{R}^d$ the parameter vector, and $g_t(x_t)$ a time-varying component that can vary in a way that depends on the past, but not on current action (thus, allowing for nonstationarity). The term adversarial in contextual MABs refers to the context and reward generation mechanism: when both contexts and actions are allowed to be chosen arbitrarily by an adversary, no assumptions on the generating process are made (see also Section 3.3.2). The indicator function $I(a_t \neq 0)$ in Eq. (17) specifies the additional component of the expected reward given by the noncontrol arms.

To estimate the unknown parameter $\mu$, due to the arbitrarily complex baseline reward, the authors propose to work on the differential reward, defined as $Y_{t+1}(X_t, A_t) - Y_{t+1}(X_t, 0) = f(X_t, A_t)^T \mu I(A_t > 0) + \epsilon_{t+1}$, and involve the so-called action-centering trick to eliminate the component $g_t(x_t)$ and derive an unbiased estimator. Furthermore, to avoid sending too few or too many interventions and to prevent the algorithm from converging to an ineffective deterministic policy, a stochastic chance constraint on the size of the probabilities of delivering the noncontrol arm is considered. Formally, for a noncontrol arm $a \neq 0$,

$$\pi_t(a) = \max \left( \pi_{\min}, \min(\pi_{\max}, \mathbb{P}(f(x_t, a)^T \tilde{\mu} > 0)) \right),$$

with $\tilde{\mu}$ being a draw from the posterior distribution, and $\pi_{\min}$ and $\pi_{\max}$ fixed probability constraints in $[0, 1]$.

The proposed strategy, named action-centered TS, can be viewed as a two-step hierarchical procedure, where the first step is to estimate the arm that maximizes the reward in Eq. (17) and the second step is to randomly select between a control and noncontrol arm $A_t \neq 0$.

The algorithm was empirically evaluated in an mHealth physical activity study, HeartSteps [70, 54], which has been of great interest both in biostatistics and in the RL / bandit literature. In this context, Liao et al. [70], for example, incorporated in the differential reward model an “availability” variable, stating whether the user is available to receive an intervention or not.

The authors showed that the action-centered TS achieves performance guarantees similar to LinTS, while allowing for nonlinearities in the baseline reward. Additional theoretical improvements are given in [57] and [53]. Here, a relaxation of the action-independent assumption of the component $g_t(x_t)$ in Eq. (17) is considered, making the reward model entirely nonparametric.

4.3 Insights on current methodological differences and their drivers

So far, a broad literature documented and demonstrated the premise of RL in both types of AIs. However, the practical methodological realities of the two remain apparently disjoint or with little commonalities. Why does Q-learning, a popular algorithm for estimating DTRs, have

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**Algorithm 4: LinTS [1]**

**Input:** $\sigma_\mu \in \mathbb{R}, \nu \in \mathbb{R}, T \in \mathbb{N}, d \in \mathbb{N}, \lambda \in \mathbb{R}_+$

**Initialization:** $B_0 = \lambda dl, b_0 = 0_d$

**for** $t = 0, 1, 2, \ldots T$ **do**

1. Estimate the regression coefficient $\hat{\mu}_t = B_t^{-1} b_t$.
2. Get posterior samples $\hat{\mu}_t \sim N(\hat{\mu}_t, \nu^2 B_t^{-1})$

**for** $a_t \in A$ **do**

1. Observe feature $f(X_t = x_t, A_t = a_t)$ and compute the ‘a-posteriori’ estimated reward, i.e., $f(X_t = x_t, A_t = a_t) \hat{\mu}_t$

**end for**

2. Select arm $\hat{a}_t = \arg \max a_t \in A f(X_t = x_t, A_t = a_t) \hat{\mu}_t$ and get the associated reward $Y_{t+1}(X_t = x_t, A_t = \hat{a}_t)$;
3. Update $B_{t+1}$ and $b_{t+1}$ according to the best arm $\hat{a}_t$:

   $$B_{t+1} = B_t + f(X_t = x_t, A_t = \hat{a}_t)^T f(X_t = x_t, A_t = \hat{a}_t);$$

   $$b_{t+1} = b_t + f(X_t = x_t, A_t = \hat{a}_t)^T Y_{t+1}(X_t = x_t, A_t = \hat{a}_t).$$

**end for**

---
no practical use in JITAIs, where simplified frameworks are used? Is it reasonable to adopt simplified RL formulations given the nature of mHealth applications? Can we expect Thompson sampling, largely employed in JITAIs, to dictate the next generation of DTRs? Or ultimately, should we expect a convergence, dictated, e.g., by a greater synergy between the two areas, or should we regard them as unrelated?

Although these questions were partially covered throughout the previous sections, here, we offer a systematic synthesis of the main differences and their drivers. We propose a number of insights that may guide the thinking about the future of the two areas and their potential relationship (or lack thereof), convergence or complementarity.

 Offline vs online learning: a different primary objective. One of the main differences between the DTR and JITAIs settings is the relationship between RL and the data collection process in the learning phase. In DTRs, RL is typically (we will mention a few exceptions shortly) implemented in an offline manner: we assume data have already been collected, and RL serves for estimating an optimal regime according to a batch of N i.i.d. data trajectories. Thus, RL has no role in the data collection process. Data are typically generated according to a randomized study—where interventions are assigned with e.g., fixed and equal probability at each stage—or based on routine clinical practice according to clinicians’ beliefs that lead to large EHRs. On the contrary, in JITAIs, RL is the main determinant of data collection: its scope is to determine and deliver, based on accumulating data, the right interventions in real time so as to benefit the most of the study participants. Clearly, the accumulated data depend on the interventions automatically assigned by the algorithm.

This difference is mainly due to the definition of the primary objective in each AI area. For DTRs, even in the case of SMARTs, the purpose of the trial that generates the data is generally to evaluate and compare treatments; only in subsequent analyses/phases, the goal embraces identifying and assigning the optimal regime. In JITAIs, optimization is the primary goal, with optimal estimated AIs delivered directly during the trial. In Section 5, case studies documenting this aspect will be illustrated.

There are some exceptions, and these may indicate a potential convergence. For example, in the context of infectious diseases, the application of a fixed randomization strategy for a prolonged period is neither ethical nor feasible. To this end, the use of TS has been proposed to learn and assign an optimal treatment strategy online [62]. Notably, the MAB choice in this setting addresses some challenges that cannot be directly addressed with offline methods such as Q-learning, including: (i) scarcity of data at the onset of an epidemic, (ii) high dimensionality and scalability with respect to state and action spaces, and (iii) a long and indefinite time horizon. Similarly, there have been theoretical works [see e.g., 19, 134] that tried to incorporate online adaptations within a SMART to skew the randomization probabilities toward the most promising treatments.

Simplifying assumptions and domain aspects. Delivery of JITAIs in mHealth is carried out primarily through the simplified RL framework of contextual MABs. This simplification is essentially dictated by the strong assumption that actions $A_t$ have a momentary effect on rewards $Y_{t+1}$, but do not affect the distribution of the next states $\{X_{t+1}\}_{t \geq t+1}$. Essentially, one sets the discount parameter $\gamma$ to 0, and looks for the optimal in-the-moment action. Domain knowledge envisions that such an assumption is reasonable in many mHealth applications, where information such as weather, time of the day, and GPS location, among others, is momentary, as is also its effect. However, one may certainly question the validity of such a choice or whether we should use a larger $\gamma$, full- or MDP-RL, or other strategies. In clinical conditions, this is often unrealistic: the effect of a treatment may be observed at different times, and may be affected by delayed or carryover effects. In mHealth, the study of phenomena such as habituation and delayed rewards is becoming increasingly common. Incorporating these considerations, in addition to allowing for nonstationarities (as in the action-centered TS [45]), may favor the RL methods used in DTRs and advance knowledge discovery. For example, in Zhou et al. [146], historical data as well as individual goals are included in the model and a full RL strategy is used.

Learning efficiency. Clearly, solving a full-RL or an MDP-RL problem is much more computationally demanding than solving a contextual MAB problem. The discount rate $\gamma$ is strongly related to computational expense: the larger the $\gamma$, or the farther we look ahead, the higher is the computational burden. By choosing small values of $\gamma$, one trades off the optimality of the learned policy for computational efficiency, which is a critical aspect in high-dimensional problems. Notably, contextual data in many mHealth applications is highly private. For this reason, much of the computation has to be done locally on mobile devices, with the risk of severely impacting battery life.

Inference and real-time inference. A key aspect that has been extensively studied in DTRs is the problem of inference [see 26, 126, for a recent overview]. This aspect has been neglected in JITAIs, where the primary goal is oriented toward reward optimization, or alternatively, participants’ benefit. Learning about intervention regimes and drawing generalized conclusions is often beyond the scope of their delivery. However, even when the focus is on the ongoing study itself, how can we support the development of high-quality JITAIs without adequately assessing the effectiveness of the sequence of interventions delivered by the mobile device? Clearly, compared
to (mostly behavioral) JITAIAs, delivering DTRs involves a higher risk, as each intervention (often a drug) can have a substantial impact on patients’ lives. Thus, among other critical points, including e.g., cost, this ethical aspect has long limited the learning and delivery of DTRs online.

We emphasize that adaptive data-collection settings driven by RL present major challenges for statistical inference due to e.g., potential strong imbalances in arms allocations and the underlying sequential nature of the data. The problem is nowadays well documented [27, 46], and recent solutions have borrowed tools from causal inference [141].

While this discussion is motivated by the apparent differences between the DTR and JITAI methods, we have shown that there are exceptions, and that the use of a specific RL method should be driven by the applied problem at hand and its peculiarities (population, disease or condition, underlying domain characteristics, ethical concerns). We acknowledge that computational costs (memory and time), as well as technological limitations, still play a dominant role in JITAIAs; whereas in DTRs, the main drivers relate to ethical aspects and the costs associated with running high-quality intervention studies such as SMARTs.

Going beyond methodology, we conclude this section by suggesting that, despite the fact that DTRs and JITAIAs originated and developed within two different domains while following a similar—if not the same—goal, they could often have a complementary role. In fact, if construction of an optimized DTR is part of the objectives of an experimental study (even if secondary), JITAIAs could be utilized to deliver behavioral interventions to enhance both adherence to treatment and engagement with the health study, all in support of high-quality data collection, with limited deviations from study protocol.

5. REINFORCEMENT LEARNING IN REAL LIFE

This section complements the methodological framework introduced so far with its real-world implementation. Guided by two case studies we conducted in the space of DTRs and mHealth, respectively, we: (i) illustrate the applicability of RL as well as the main challenges researchers face in applying these methods in practice; and (ii) provide a concrete illustration of the main divergence between RL methods in the two areas. We start with a brief introduction of the two studies, before summarizing and comparing their main characteristics side by side (this is done in TABLE 3).

RL for DTRs: PROJECT QUIT – FOREVER FREE

Based on a two-stage SMART design, this study aimed to develop/compar internet-based behavioral interventions for smoking cessation and for relapse prevention. The primary objective, based on the 6-month-long first stage of the study, i.e., the PROJECT QUIT, was to find an optimal multifactor behavioral intervention to help adult smokers quit smoking [see 116, for more details]. The second stage, known as FOREVER FREE, was a 6-month-long follow-on study to help PROJECT QUIT participants who quit smoking stay nonsmoking, and offer a second chance to those who failed to give up smoking at the previous stage. These two stages were then considered together with the goal of finding an optimal DTR over a 12-month study period; this was a secondary objective of the main study. RL was not used in the design phase; in other words, this was not an instance of online learning. The RL-type learning happened offline on completion of the data collection. Detailed results from this secondary analysis can be found in [13, 16].

RL in mHealth: DIAMANTE Study A preliminary illustration of this MRT was given earlier in Section 2. The primary objective of the study was to evaluate the effectiveness of an RL-based text-messaging system for developing JITAIAs to encourage individuals to become more physically active. In this case, RL was implemented online, with interventions continuously optimized according to users’ individual characteristics and time-varying outcomes. To evaluate the optimized JITAI, we used to different study groups (see Fig 4), including a static (nonoptimized) group and the experimental RL-based adaptive group. For further details, we refer to [2, 35].

6. CONCLUSIONS AND FUTURE DIRECTIONS

In this work, under a unified framework that brings together DTRs and JITAIAs in mHealth under the area of adaptive interventions, we showed how these problems can be formalized as RL problems. With a sincere hope to enhance synergy between the methodological and applied communities, we provided a comprehensive state-of-the-art survey on RL strategies for AIIs, augmenting the methodological framework with real examples and challenges. Then, we discussed the main methodological divergences in the two AI domains.

Notably, while the two areas are ideally sharing the same problem of finding optimal policies (in line with the RL framework), their priorities are not always aligned due to historical links or domain restrictions. DTRs are mainly focused on offline estimation and identification of causal nexuses, while JITAIAs are mainly engaged in online regret performances, neglecting the problem of inference. Only recently, a small body of literature started to examine the possibility of inferential goals in JITAIAs, questioning the validity of traditional statistics in adaptively-collected data [141, 46, 27]. The ML community has led the way in addressing such issues, often borrowing tools from causal
### TABLE 3  
Summary of two case studies, in DTRs and JITAs in mHealth, respectively, that used RL for constructing AIs

| Study Design | DTR: PROJECT QUIT – FOREVER FREE | JITA: DIAMANTE |
|--------------|---------------------------------|----------------|
| Primary objective | To find an optimal internet-based behavioral intervention for smoking cessation and relapse prevention | To develop and evaluate the effectiveness of a JITA system for enhancing physical activity, by means of an RL-based text-messages |
| Secondary objective | To find an optimal DTR | To assess the effectiveness of the JITA system on the distal outcomes (i.e., depression) |
| Role of RL in the analysis | Secondary, used for post-data collection analysis | Primary, used in the design (data-collection) phase |
| Number and frequency of decision points | Two, corresponding to the two 6-month-long stages of the trial | Daily, for a 6-month follow-up length (i.e., around 180 decision points) |
| Model choice: interventions and tailoring variables | A parsimonious model with the statistically significant elements of the primary regression analyses:  
• stage-1 model included two intervention factors (each at two levels) and three covariates;  
• stage-2 model included two intervention arms, the three stage-1 covariates and an additional covariate represented by the intermediate outcome (quit status at the end of stage-1);  
• interactions between interventions and covariates were included as well. | A high-dimensional model including:  
• all baseline variables shown to be relevant in the literature and other time-varying covariates;  
• an action space given by the combinations of the $4 \times 5 \times 4$ factor levels;  
• action-action and action-contextual interactions were also included. |
| Choice of the RL strategy for optimizing interventions | Offline learning based on:  
• Q-learning with a linear model, chosen for its simplicity and interpretability;  
• a soft-thresholding estimator (within the Q-learning framework) to address the vexing problem of nonregularity | Online learning based on:  
• the computationally efficient and randomized TS algorithm to mitigate bias and to enable causal inference [109];  
• self-regularization (implemented within TS) to deal with the high dimensionality and avoid overfitting;  
• an initial uniform random “burn-in” period or, more appropriately, an “internal pilot” to acquire some prior data to feed into the main algorithm and speed up learning |
| Primary outcome, i.e., the reward variable directly targeted by the intervention | A final distal outcome related to smoking cessation and defined as the seven-day point prevalence of smoking (i.e., whether or not the participant smoked even a single cigarette in the last seven days prior to the end of the study) | A proximal outcome related to physical activity and defined as the steps change from one day to another, starting the steps count from the time an intervention message is sent |
| Handling of missing data in the reward variable | • Descriptive checks, revealing a more or less uniform dropout across the different intervention arms, and  
• complete case analysis [16], as well as sensitivity analysis of multiply-imputed data [13], to avoid sub-optimal policies due to potentially different patterns across different interventions | • Online imputation with the last observation carried forward, and  
• multiple imputation as a sensitivity analysis, to provide reliable final estimates and avoid harmful impacts (due e.g., to technical errors in collecting observations) on online decision making |
| Other study challenges | Inference, high-dimensionality, feature extraction, sample size considerations and power analysis [see also 26, 61] | Inference, non-stationarity and delayed reward, model misspecification and noisy data, users’ disengagement, sample size considerations and power analysis [see also 35, 70] |

Inference well studied in the DTR literature. For example, the “stabilizing policy” approach of Zhang et al. [141] is analogous to the “stabilized weights” of the causal inference literature [107]. Similarly, the adaptively-weighted IPW estimator in Hadad et al. [46] is inspired by the IPW estimator in [107]. Furthermore, an increased attention is paid to real-time or online inference to evaluate the effectiveness of JITAs online [see e.g., 30, 29].

Despite the insufficiently mature field of mHealth, with a relatively small number of methodological studies for a rigorous evaluation of RL methods for JITAs, their popularity in real life has grown remarkably (see Fig. 1). In contrast, in DTRs, the use of RL has been extensively evaluated in theoretical works, but its application in the real world is still very limited. Most existing DTR studies use real data only as motivational or illustrative examples. The few clinical studies focus mainly on offline learning.
based on observational data (e.g., EHRs) and deep learning methodologies, which limits interpretability. The explanatory drivers may be related to: 1) the lack of existing guidelines for developing optimal, yet statistically valid, DTRs; 2) the clinical setting itself, characterized by high costs, ethical concerns, and inherent complexities, which makes experimentation hard; 3) the lack of definition of AI components and the RL dynamics for the specific disease. When defining the reward function, for instance, one may need to account for multiple objectives and the presence of unstructured data, among other prior knowledge. Even from an implementation perspective, while several software packages exist for DTRs, these are often suitable only under simplified settings, e.g., continuous and positive rewards. We recognize that the area of mHealth, mostly related to behavioral aspects rather than clinical, may have fewer concerns in terms of treatment costs and risks.

We notice that our focus in this work has been mainly devoted to the development of optimized AIs and, more specifically, to the use of RL for solving this optimization problem. Several other aspects are crucial for rigorously, validly, and ethically operating in the space of AIs. First, an adequate framework for causal inference is necessary. In this work, we only mentioned it in passing (see Section 3.1) and assumed that this foundational block and the underlying assumptions (such as unconfounding) hold. Although RL practitioners often consider problems in which the data are unconfounded, different RL methods, especially in online decision-making, may have a different impact on drawing causal conclusions.

To illustrate, online RL algorithms such as LinUCB (see Section 4.2.1) are in principle deterministic, but randomization plays a fundamental role for inference [109]. In this regard, the DTR literature offers a rich base of statistical challenges and solutions that can enhance research in the JITAI area. Second, if on one side the increasing technological and computational sophistication has led to new biomedical data sources (e.g., data from mobile devices and EHRs) and new algorithmic solutions (e.g., RL), on the other side it has posed some unique new challenges in a statistically justifiable way. For example, by using the rich resources on inference made available by the DTR literature, the JITAIs literature may extend its goal beyond within-trial optimization. Similarly, if SMARTs were to be used in practice more often, in addition to collecting high-quality experimental data, decisions could also be optimized online, benefiting trial participants as well [see e.g., 19, 62], as done in JITAIs.

We also hope that our contribution may incentivize greater synergy and cooperation between the statistical and ML communities to support applied domains in the conduct of high-quality real-world studies. We recognize that this cooperation is very timely to support both the development of real-world DTR studies and to assist the spread of mHealth applications with reliable and reproducible workflows.

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SUPPLEMENTARY MATERIAL

A.1 Google Scholar Search (Fig. 1)

The volume of literature on DTRs and JITAIs was identified on Google Scholar with the following keywords, respectively:

- “dynamic treatment regime” OR “dynamic treatment regimes” OR “dynamic treatment regimen” OR “dynamic treatment regimes”;
- “just in time adaptive intervention” OR “just in time adaptive interventions”.

Returned items contain both published articles and grey literature (e.g., preprints). Citations and patents were excluded from the literature search. A minimum screening was performed to evaluate the consistency of the identified items in relation to the searched term and the respective online publication date. Items that were incorrectly returned in correspondence with a certain date were removed from that date group.

A.2 Q-learning with Function Approximation

Several Q-learning function approximators have been proposed in the literature, including linear regression, decision trees, or neural networks. As Q-functions are conditional expectations, the first natural approach to model them is through linear regression models. Following the notation introduced in the main paper, and letting $\theta_t = (\beta_t, \psi_t)$, Chakraborty and colleagues [15] proposed to parametrize the stage-specific optimal Q-functions as

$$Q_t^*(H_t, A_t; \beta_t, \psi_t) = \beta_t^T H_{t0} + (\psi_t^T H_{t1}) A_t, \quad t \in [0,T],$$

where $H_{t0}$ and $H_{t1}$ are two (possibly different) vector summaries of the history $H_t$, with $H_{t0}$ denoting the “main effect of history” and $H_{t1}$ denoting the “treatment effect of history”. The collections of variables $H_{t0}$ are often termed predictive, while $H_{t1}$ are called prescriptive or tailoring variables. Parameter estimates $\hat{\theta}_t = (\hat{\beta}_t, \hat{\psi}_t)$ are obtained by solving suitable estimating equations such as ordinary least squares (OLS) or weighted least squares (WLS). Given a sample $\{X_{t0i}, A_{0i}, Y_{1i}, \ldots, X_{Ti}, A_{Ti}, Y_{(T+1)i}, X_{(T+1)i}\}_{i=1}^N$ of i.i.d. trajectories, the WLS estimator–whose choice might be dictated by heteroscedastic errors–derives $\hat{\theta}_t$ by solving

$$0 = \sum_{i=1}^N \frac{\partial Q_t^*(H_{ti}, A_{ti}; \theta_t)}{\partial \theta_t} \Sigma^{-1}_t(H_{ti}, A_{ti})$$

$$\times \left[Y_{(t+1)i} + \max_{a(t+1)i \in A(t+1)i} Q_{t+1}^*(H_{(t+1)i}, a(t+1)i; \hat{\psi}_{t+1}) - Q_t^*(H_{ti}, A_{ti}; \hat{\theta}_t)\right],$$

where $\Sigma_t$ is a working variance-covariance matrix. Taking $\Sigma_t$ as a constant yields the OLS estimator.

As noticed first by [108] for G-estimation, and then by [16] for Q-learning, the treatment effect parameters at any stage prior to the last can be nonregular under certain longitudinal distributions of the data. Q-learning, for instance, involves modeling nonsmooth, nonmonotone functions of the data, which complicates both the regression function and the associated inference. In the specific modeling assumption of Eq. (18), due to the argmax operator involved in Q-learning, $\hat{\psi}_t$ is a nonregular estimator, and inferential problems arise when $\hat{\psi}_t^T H_{t1}$ is close to zero, leading to nondifferentiability at that point. In DTRs, this can occur, for example, when two or more treatments produce (nearly) the same mean optimal outcome. To solve this problem, adapting previous work in the context of G-estimation [79], [16] proposed two alternative ways to shrink or threshold values of $\hat{\psi}_t^T H_{t1}$ close to zero. In a similar spirit, [113] and [41] proposed minimizing a penalized version of the objective in the first step of Q-learning, where the penalty is given by a function $p_\lambda(\hat{\psi}_t^T H_{t1})$ with the tuning parameter $\lambda$, while [33] introduced the smoothed Q-learning dictated by the use of a modified version of $\hat{\psi}_t^T H_{t1}$ in Eq. (18), given by $(\hat{\psi}_t^T H_{t1}) K_\alpha(\hat{\psi}_t^T H_{t1})$. Here, $K_\alpha(x) \equiv K(x/\alpha)$, with $\alpha > 0$ a smoothing parameter and $K(\cdot)$ a kernel function that admits a probability density function. Another proposal to conduct inferences for the estimated Q-function parameters arose in [14], where a general method for bootstrapping under nonregularity, i.e., $m$-out-of-$n$ bootstrap was presented. Subsequently, [60] derived a new interactive Q-learning method, where the maximization step is delayed, by adding an additional step between the Eqs. (14) and (15) of the main paper. This enables all modeling to be performed before the nonsmooth and nonmonotone transformation.

A.3 A-learning with Function Approximation

A-learning, where ‘A’ stands for the ‘advantage’ incurred if the optimal treatment were given as opposed to what was actually given, is used to describe a class of alternative methods to Q-learning, predicated on the fact that it is not necessary to specify the entire Q-function to estimate an optimal regime. Models can be posited only for parts of the expectation involving contrasts among treatments, rather than modeling the conditional expectation itself, as in Q-learning. Recalling that $d^* \equiv \{d^*_t\}_{t=0,...,T}$ denotes the optimal DTR and, denoting by $d_{\tau}^* \equiv \{d^*_t\}_{t=\tau,...,T}$ the optimal policy from time $\tau$ onward, by $d_{\tau}^{\text{ref}} \equiv \{d^*_t\}_{t=\tau,...,T}$ a reference regime with which we want to make comparisons, and by $0$ the standard or placebo treatment, examples of contrast include:

$$E[Y_{t+1|a_t, d_{\tau}^{\text{ref}}}|H_t = h_t] - E[Y_{t+1|a_t, d^*_{\tau}}|H_t = h_t],$$
E[ Y_{t+1}^{a_{t+1},0} | \mathcal{H}_t = \mathbf{h}_t] - E[ Y_{t+1}^{a_{t+1},1} | \mathcal{H}_t = \mathbf{h}_t],
E[ Y_{t+1}^{a_{t+1},0} | \mathcal{H}_t = \mathbf{h}_t] - E[ Y_{t+1}^{a_{t+1},1,0} | \mathcal{H}_t = \mathbf{h}_t],
\]
with \( Y^a \) the potential outcome associated with policy \( a \).

Optimal blip-to-reference (first expression) and optimal blip-to-zero (second expression) evaluate the removal of a unit (‘blip’) of the treatment effect at stage \( t \) on the subsequent mean outcome, when the optimal DTR \( d^*_t \) is followed from \( t + 1 \) onward: the blips are represented by the reference treatment \( d_t^r \) and the 0 treatment, respectively.

The last expression evaluates the increase in the expected potential outcome we forego by selecting \( a_t \) rather than the optimal action \( d^*_t \) at time \( t \). This is called regret, and is analogous to the notion of regret in MABs (see Section 3.3.2 of the main paper).

While [108] advocates optimal blip functions and [81] regrets, [80] demonstrated that they are mathematically equivalent. In addition, both proposed a structural nested mean model for each of the \( t \) conditional intermediate causal effects, or contrasts. However, the two authors proposed different estimation techniques: [108] uses backward recursive G-estimation, while [81] uses a technique known as iterative minimization of regrets. Thus, we distinguish the two approaches as contrast-based A-learning and regret-based A-learning and discuss them below.

Comparing A-learning with Q-learning, [111] showed that Q-learning is more efficient when all models are correctly specified and the propensity model required in A-learning is misspecified. If the Q-function is misspecified, A-learning outperforms Q-learning. Finally, with both propensity and Q-learning models misspecified, there is no general trend in efficiency of estimation across parameters that might recommend one method over the other.

Contrast-based A-learning. We define the optimal contrast or the optimal \( C \)-function \( C_t^* (\mathcal{H}_t, A_t) \) at time \( t \) as the expected difference in potential outcomes when using a reference regime \( d_t^r \) instead of \( a_t \) at time \( t \), and subsequently receive the optimal regime \( d^*_{t+1} = \{d_t^r \}_{t=t+1,...,T} \). It is basically the optimal blip-to-reference given in Section 4.1.2 (main paper) with \( g \) the identity function, i.e.,
\[
C_t^* (\mathcal{H}_t, A_t) = E( Y(A_{t-1}, A_t, d_t^r) - Y(A_{t-1}, a_t, d_t^r (d_t^r, d^*_{t+1})) | \mathcal{H}_t).
\]

For simplicity, here we consider only the case of two treatment options coded as 0 and 1, i.e., \( A_t = \{0, 1\} \) for all \( t \in [0, T] \), and let the standard or placebo “zero-treatment” be the reference treatment, i.e., \( d_t^r = 0 \), leading to an equivalence between blip-to-reference and blip-to-zero expressions. To determine an optimal DTR, we begin by defining an approximation space for the contrast functions, e.g., \( \mathcal{C}_t = \{C_t(\mathcal{H}_t, a_t; \psi_t) : \psi_t \in \Psi_t\} \), with \( \psi_t \in \Psi_t \), a subset of the Euclidean space. Then, in a backward fashion, starting from \( t = T \), and denoting the propensity to receive treatment \( A_T = 1 \) in the observed data with \( \pi_T( A_T | \mathcal{H}_T ) = P( A_T = 1 | \mathcal{H}_T = \mathbf{h}_T) \), we obtain a consistent and asymptotically normal estimator for \( \psi_T \) by G-estimation [108], i.e., by solving estimating equations of the form:
\[
0 = \sum_{i=1}^N \lambda_T (\mathcal{H}_{T_1}, A_{T_1}) \left[ A_{T_i} - \pi_T( A_{T_i} | \mathcal{H}_{T_1}) \right] [Y(T+1)_i - A_{T_i} C_{T_1}(\mathcal{H}_{T_1}, A_{T_1}; \psi_T) - \theta(\mathcal{H}_{T_1}, A_{T_1})],
\]
for arbitrary functions \( \lambda_T (\mathcal{H}_T, A_{T_1}) \) of the same dimension as \( \psi_T \) and arbitrary functions \( \theta_T(\mathcal{H}_T, A_{T_1}) \).

To implement the estimation of \( \psi_T \), one may adopt parametric models for all the unknown functions, including \( \pi_T( A_T | \mathcal{H}_T) \) if the randomization probabilities are not known, i.e., in observational studies. Under certain conditions, [111] report that an optimal choice for \( \lambda_T (\mathcal{H}_T, A_{T_1}; \psi_T) \) is given by \( \partial / \partial \psi T C_T^* (\mathcal{H}_{T_1}, A_{T_1}; \psi_T) \). Once we get estimates \( \hat{\psi}_T \), the contrast-based A-learning algorithm iteratively proceeds by estimating \( \hat{\psi}_{T-1}, \hat{\psi}_{T-2}, \ldots, \hat{\psi}_0 \). Finally, in this two-treatment setting, the optimal DTR (assuming it is unique) is given by the one that leads to a positive \( C \)-function, i.e.,
\[
\hat{d}_t^r (\mathcal{H}_t) = \hat{d}_t^r (\mathcal{H}_t; \hat{\psi}_t) = \{ C_t^* (\mathcal{H}_t, A_t; \hat{\psi}_t) > 0 \}, \quad \forall t \in [0, T].
\]
Notice that, as the additional models specified in Eq. (19) are only adjuncts to estimating \( \hat{\psi}_T \), as long as at least one of these models is correctly specified, Eq. (19) will provide a consistent estimator for \( \psi_T \) (this property is called double robustness property). In contrast, Q-learning requires correct specification of all Q-functions. An intermediate approach between G-estimation and Q-learning, which provides double-robustness to model misspecification and requires fewer computational resources compared to the former, was later introduced by [133] as the dynamic weighted ordinary least squares (dWOLS).

Regret-based A-learning. Rather than modeling a contrast defined as the expected difference in outcome when using a reference regime \( d_t^r \) instead of \( a_t \) at time \( t \), [81] proposed to model the regret. Denoting it by \( \mu_t^* \), it is defined as \( \mu_t^* (\mathcal{H}_t, A_t) = E( Y(A_{t-1}, A_t, d_t^r) - Y(A_{t-1}, a_t, d_t^r) | \mathcal{H}_t) \), for \( t \in [0, T] \). Here, the advantage/regret is the gain/loss in performance obtained by following action \( A_t \) at time \( t \) and thereafter the optimal regime \( d^*_{t+1} \) as compared to following the optimal regime \( d_t^* \) from time \( t \) on. Again, to estimate the optimal treatment regime, we model the regrets by defining an approximation space for the \( t \)-th advantage \( \mu \)-function, e.g., \( \mathcal{M}_t = \{ \mu_t (\mathcal{H}_t, a_t; \psi) : \psi \in \Psi_t \} \), with \( \psi \in \Psi_t \), a subset of
the Euclidean space. As with Q-learning and in contrast-based A-learning, we use approximate dynamic programming and permit the estimator to have different parameters for each time $t$. However, in this case, an estimation strategy known as *iterative minimization for optimal regimes* [81] is adopted. Specifically, [81] proposed to simultaneously estimate the regret model parameter $\psi$ plus a parameter $c$ used to improve the stability of the algorithm, searching for $(\hat{\psi}, \hat{c})$ that satisfy

\begin{equation}
\sum_{t=0}^{T} P_N \left[ Y + \hat{c} + \sum_{\tau=0}^{T} \mu_{\tau}(H_{\tau}, A_{\tau}; \hat{\psi}) \right. \\
\left. - \sum_{a} \mu_{t}(H_{t}, a; \hat{\psi}) \pi_{t}(a|H_{t}; \hat{\alpha}) \right]^2 \\
\leq \sum_{t=0}^{T} P_N \left[ Y + c + \sum_{\tau \neq t} \mu_{\tau}(H_{\tau}, A_{\tau}; \hat{\psi}) \\
+ \mu_{t}(H_{t}, A_{t}; \psi) \sum_{a} \mu_{t}(H_{t}, a; \psi) \pi_{t}(a|H_{t}; \alpha) \right]^2,
\end{equation}

for all $\psi$ and $c$, with $P_N$ denoting the empirical mean of a sample of $N$ patients. The technique proposed to find solutions to Eq. (20) is an iterative search algorithm until convergence. It has been shown that IMOR is a special case of G-estimation under the null hypothesis of no treatment effect and modeling by a constant [80]. We point to the original work of [81] and [80] for readers interested in this technique and its relationship with G-estimation.