

Multi-Timescale Adaptation and Emergent Learning in Single Bacterial Cells

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How do single-celled organisms adapt and learn to survive in unpredictable environments without the benefit of a nervous system? In this study, we provide experimental and theoretical evidence that single bacterial cells exhibit sophisticated learninglike behavior in changing environments. Using a custom microfluidic platform, we tracked individual *E. coli* cells in fluctuating nutrient conditions and found that bacteria do not merely react to the present; they integrate their environmental history to tune their future growth. We show that this adaptation process is scale-free, meaning cells possess a memory that stretches across multiple timescales, from minutes to hours. To explain this, we developed a mathematical framework based on fractional-order dynamics, demonstrating that a dynamic, power-law memory governs how cells integrate environmental history, which we validate with additional nutrient perturbation experiments. We demonstrate that this memory emerges naturally from the cell's internal machinery, specifically a heterogeneous population of ribosomes that react at different speeds. This mechanism reveals a strategic tradeoff between cellular adaptation speed and growth rate, which we confirm experimentally in pulsatile nutrient environments. By mapping the reaction-network architecture underlying bacterial physiology onto the logic of artificial recurrent neural networks, we show that even the simplest unicellular organisms implement complex computational strategies. Our findings establish a new foundation for understanding learning in non-neuronal systems, revealing how single cells use their history to navigate a changing environment.

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I. INTRODUCTION

Single-celled micro-organisms exhibit remarkable phenotypic plasticity, dynamically reshaping their intracellular composition to adapt to diverse conditions [1–4]. To do so, cells utilize environmental cues to modulate gene expression, leading to condition-dependent changes in physiology and behavior [5–8]. Remarkably, such complex responses emerge in the absence of any nervous system, yet they allow microbes to thrive under a wide range of stressors [9–14]. While the link between environmental inputs and gene expression is well-studied [15–19], the physical principles governing the integration of temporal information remain elusive. Can single cells, as nonequilibrium physical systems, process environmental history to predict future states? Addressing this question is key to understanding how adaptation, memory, and even rudimentary computation emerge from the collective dynamics of intracellular reaction networks.

Bacterial cells are known to exhibit adaptive behaviors in fluctuating environments, where prior environmental experiences can shape future responses [5,7,8,20,21]. These include

memorylike traits such as faster adaptation to repeated nutrient or antibiotic shifts [7,8]. Specifically, it has been shown that bacteria exhibit faster cellular response times in fluctuating nutrient environments, but they do so at the expense of growth [Fig. 1(a)] [7]. Such tradeoffs represent a fundamental balance between responsiveness and fitness. While theoretical models have explored how environmental stress profiles influence phenotypic switching and resource allocation strategies [4,15,16,18,22–26], they typically assume single-timescale dynamics and lack mechanisms for integrating environmental history into cellular decision-making. As a result, the physical principles by which single cells adaptively tune their growth in dynamic environments remain poorly understood.

In this study, we use *Escherichia coli* as a model organism to investigate learninglike behavior at the single-cell level. Using a high-throughput microfluidic platform, we track individual *E. coli* cells exposed to pulsatile nutrient signals and show that these cells are capable of adapting over multiple timescales, tuning their growth control strategies based on environmental patterns. Our data reveal that the timescale of adaptation decreases as the frequency of nutrient fluctuations increases, but this faster response comes at the expense of reduced growth rates. We show that this behavior stems from a power-law memory in proteome allocation, driven by heterogeneous ribosomal relaxation dynamics, providing a mechanistic model of bacterial memory and continual learning. This framework captures key features of bacterial learning and allows us to map bacterial adaptation onto the dynamics of artificial recurrent neural networks, identifying the

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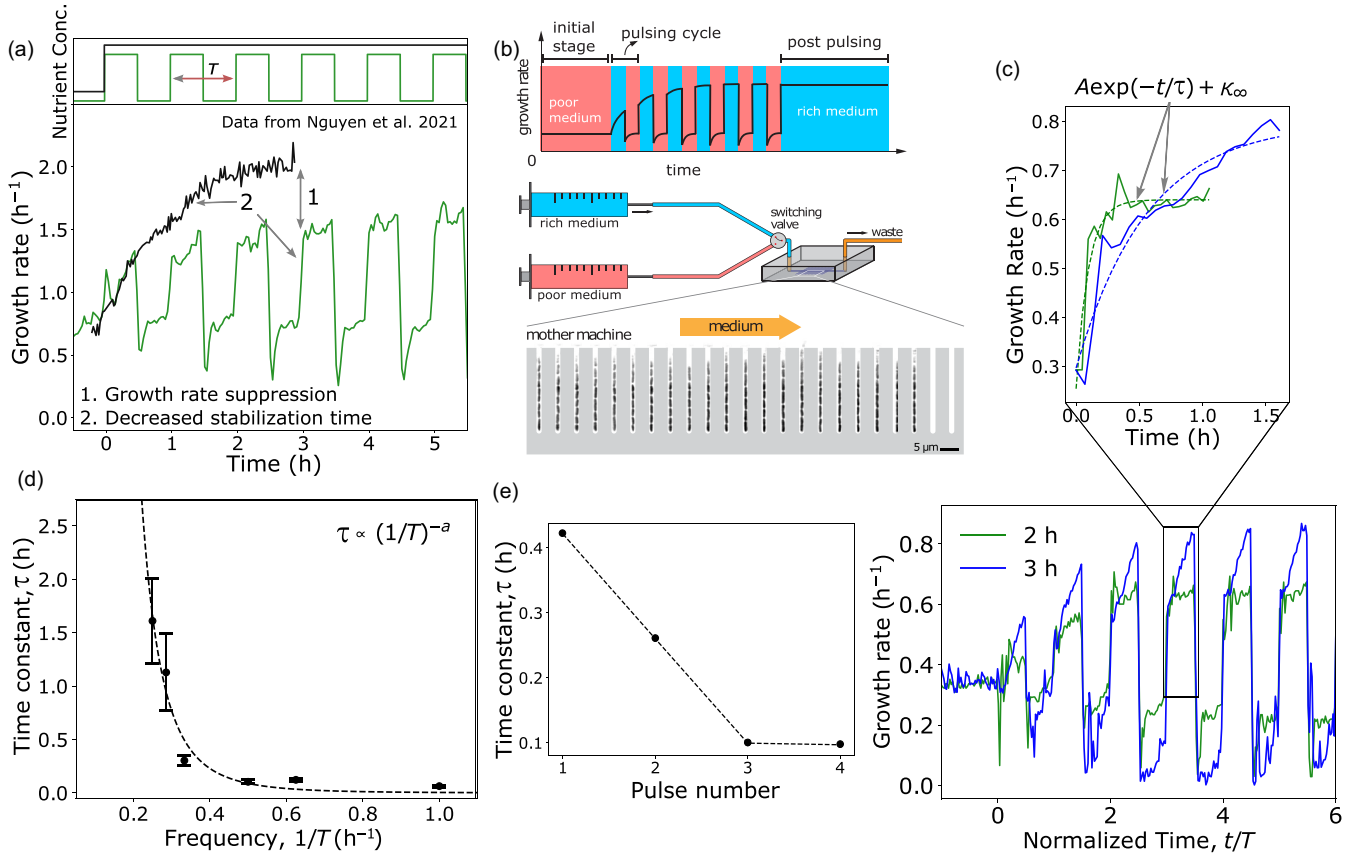


FIG. 1. History-dependent adaptation in bacterial growth control. (a) In contrast to bacteria experiencing a single nutrient upshift (black), bacteria subjected to pulsatile nutrient-rich pulses (green) increase growth rate following upshift significantly faster after experiencing several pulses, but growth rate stabilizes at a value well below that of cells experiencing constant nutrient-rich conditions. Experimental data are from Ref. [7] and are of *E. coli* K-12 NCM3722 ΔmotA cells switching between low (0.1%) and high (2%) concentrations of LB. Each curve represents the population-averaged instantaneous growth rate, which was calculated from single-cell volume trajectories time-averaged across 2 min interval bins. (b) To elucidate the dependence of growth rate behavior on the time-profile of nutrient fluctuations, we measured the single-cell growth rate of *E. coli* K-12 MG1655 cells subjected to nutrient shifts between MOPS sodium acetate and MOPS glucose with amino acids using a custom microfluidic device (see the Appendix) for both single shifts and for pulses over a range of time periods, T . (c) (bottom) Two example trajectories are shown for pulsing with a time period of $T = 2$ h (green) and $T = 3$ h (blue). As in (a), each curve represents the population-averaged instantaneous growth rate dynamics, calculated from single-cell volume trajectories and time-averaged across the population in 3 min interval bins (see the Appendix), resulting in $\sim 30\,000$ cells being tracked over the course of each experiment (see Table S3 [27] for a full list of experimental conditions and sample sizes). (c) (top) For each experimental condition, the effective adaptation time constant, τ , was obtained by fitting the growth rate data to the exponential $A \exp(-t/\tau) + \kappa_\infty$ (best fit shown by the dashed line for each example). (d) Adaptation time constant τ decreases with increasing pulse frequency $1/T$. The time constants were obtained by fitting the average growth rate trajectory of the first three upshifts 6 h after the onset of pulsing. Error bars indicate uncertainty in the exponential fit. The dashed line denotes the best-fit power law relating $1/T$ and τ . (e) For cells initially grown in nutrient-poor media as in (c), adaptation time constant decreases with subsequent nutrient-rich pulses before stabilizing. Time constants shown are for the first four pulses when $T = 2$ h, and were obtained by fitting the growth rate data from each upshift individually.

minimal architecture required for history-dependent behavior at the single-cell level. Together, our results establish a conceptual and quantitative foundation for understanding learning in living cells, revealing how even the simplest organisms can integrate past experience to navigate dynamic environments.

II. RESULTS

A. Bacteria exhibit multiple timescales of adaptation in fluctuating environments

To quantitatively characterize how the time-profile of nutrient fluctuations affects growth control and adaptation, we

subjected *E. coli* cells to precisely controlled nutrient shifts between a nutrient-poor medium (MOPS sodium acetate) and a nutrient-rich medium (MOPS glucose with 11 amino acids) in a mother machine [Fig. 1(b), see the Appendix for experimental details]. We measured single-cell growth rate dynamics in response to nutrient oscillations with different time periods T [Fig. 1(c), bottom]. For each frequency T^{-1} , we obtained the timescale τ of growth adaptation by fitting the average growth rate trajectory to an exponential of the form $A \exp(-t/\tau) + \kappa_\infty$ [Fig. 1(c), top]. For cells initially grown in nutrient-poor media, this timescale decreased with subsequent nutrient-rich pulses, indicative of episodic learning [Fig. 1(e)].

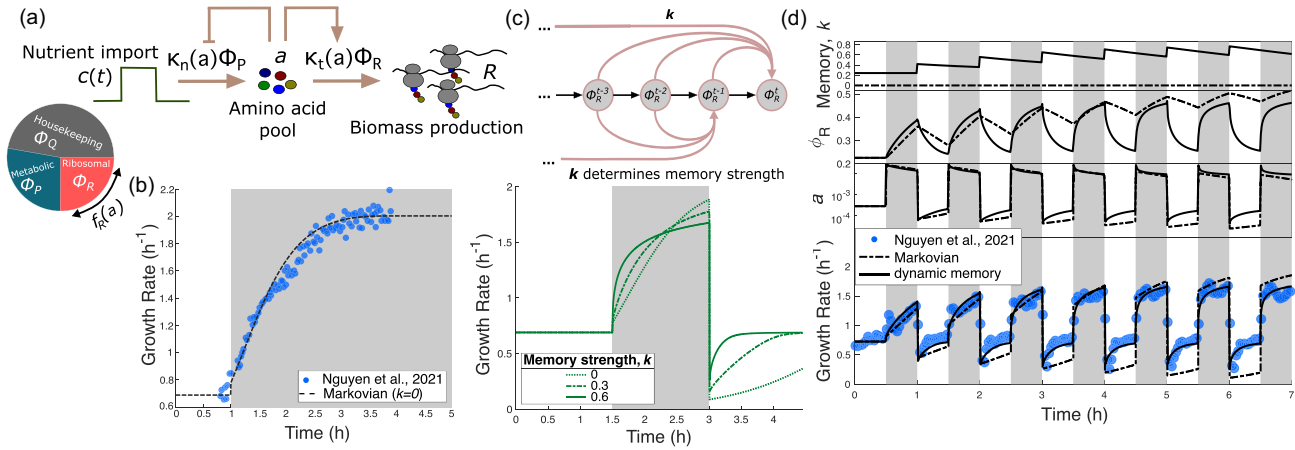


FIG. 2. Dynamic memory model of bacterial growth control. (a) Schematic of coarse-grained model of bacterial growth control. Nutrients (c) are imported by metabolic proteins (P) and converted to amino acids (a), which are then consumed by ribosomes (R) to biomass. (b) Simulation dynamics of growth rate control in response to nutrient upshift for the Markovian model, where the nutrient-rich period is denoted by gray shading. κ_t^0 , the translational efficiency rate constant, was obtained by fitting directly to growth rate data from Ref. [7] [identical to the black line in Fig. 1(a)]. See the Supplemental Material [27] for a full description of model parameters. (c) (top) Schematic depicting the time nonlocality caused by introduction of a power-law memory kernel. The ribosomal dynamics at time t are now a function of all previous values. The strength of the influence of past values on the current time is controlled by the memory strength k . (bottom) Growth rate dynamics in response to a pulse of nutrients for different constant memory strength values. Parameter values are identical to those in (b) except k . (d) Corresponding memory strength (top), ribosomal mass fraction (second from top), amino acid mass fraction (second from bottom), and growth rate (bottom) dynamics for both the Markovian (dashed) and the dynamic memory model (solid). To match with experiment, cells were initialized in poor nutrient conditions followed by nutrient-rich pulsing. While the Markovian model is unable to capture observed behavior, the dynamic memory model can be fit to agree well with experimental data from Ref. [7] [identical to the green line in Fig. 1(a)], yielding values for model parameters T_π , ρ , and π_0 . See the Appendix for a full description of iterative value estimation model parameters. For (b)–(d) nutrient-rich periods are denoted by gray shading. See Table S1 [27] for a list of all model parameters.

In addition, our data indicate that τ scales approximately as a power law with T , showing bacteria exhibit multiple timescales of adaptation and suggesting scale-free behavior [Fig. 1(d)]. These data indicate that single cells integrate environmental information over both short and long durations to facilitate rapid adaptation.

To understand the mechanisms underpinning memory and adaptation in bacterial growth, we first tested an existing model of bacterial growth control based on proteome allocation theory, which has previously been validated in dynamic environments [18,24,28]. In this framework, the environment is defined by the nutrient availability $c(t)$, which we define as the product of nutrient concentration and quality (yield). The cell imports nutrients and converts them into amino acids with mass fraction a by metabolic proteins. Amino acids are consumed by translating ribosomes, to synthesize each of the three proteome sectors defined by their mass fraction: ribosomal (ϕ_R), metabolic (ϕ_P), and “housekeeping” (ϕ_Q) [Fig. 2(a)]. The ribosomal mass fraction sets the exponential growth rate, given by

$$\kappa = M^{-1}dM/dt = \kappa_t(a)M_R/M = \kappa_t(a)\phi_R, \quad (1)$$

where M is the total protein mass of the cell, M_R is the ribosomal mass and $\kappa_t(a)$ is the translational efficiency (see [27] for details). The dynamics for the ribosomal sector can be written as

$$\frac{d\phi_R}{dt} = \kappa_t(a)f_R(a)\phi_R - \phi_R\kappa(a, \phi_R), \quad (2)$$

where $f_R(a)$ denotes the fraction of total synthesis capacity devoted to ribosomes, and is chosen to maximize translational flux at steady state, thus maximizing growth rate [16,28–30]. A significant portion of the *E. coli* proteome is invariant to environmental perturbations [2,3,6], thus we take the housekeeping sector to be constant, such that $\phi_Q = \phi_Q^{\text{const}}$ and $\phi_R + \phi_P = 1 - \phi_Q = \phi_R^{\text{max}}$. Here we neglected the mass contribution from amino acids, as $a \ll \phi_{i \in \{R, Q, P\}}$. This allows the amino acid dynamics, which are coupled to Eq. (2), to be written as

$$\frac{da}{dt} = \kappa_n(a)(\phi_R^{\text{max}} - \phi_R) - \kappa(a, \phi_R), \quad (3)$$

where $\kappa_n(a)$ is the nutritional efficiency (see [27] for details), and here we neglect the effects of growth-mediated dilution as $a \ll 1$ (Fig. S1 [27]). In this way, a acts as a read-out of flux imbalance, and so by altering proteome allocation in response to a , the cell can dynamically respond to nutrient changes.

In this model, there exists a unique proteome allocation (value of ϕ_R) which maximizes growth in a given nutrient environment (value of c). Thus, in response to an environmental change, bacteria can adapt by reshaping their proteome to increase fitness. This requires global reallocation of protein synthesis (change in f_R), as well as growth-mediated dilution of the current suboptimal proteome—a process which in this model occurs over a single timescale set by the translational efficiency κ_t . While different in quantitative formulation from other recent proteome-allocation models [18], it recovers the same qualitative transitions in ribosomal and metabolic

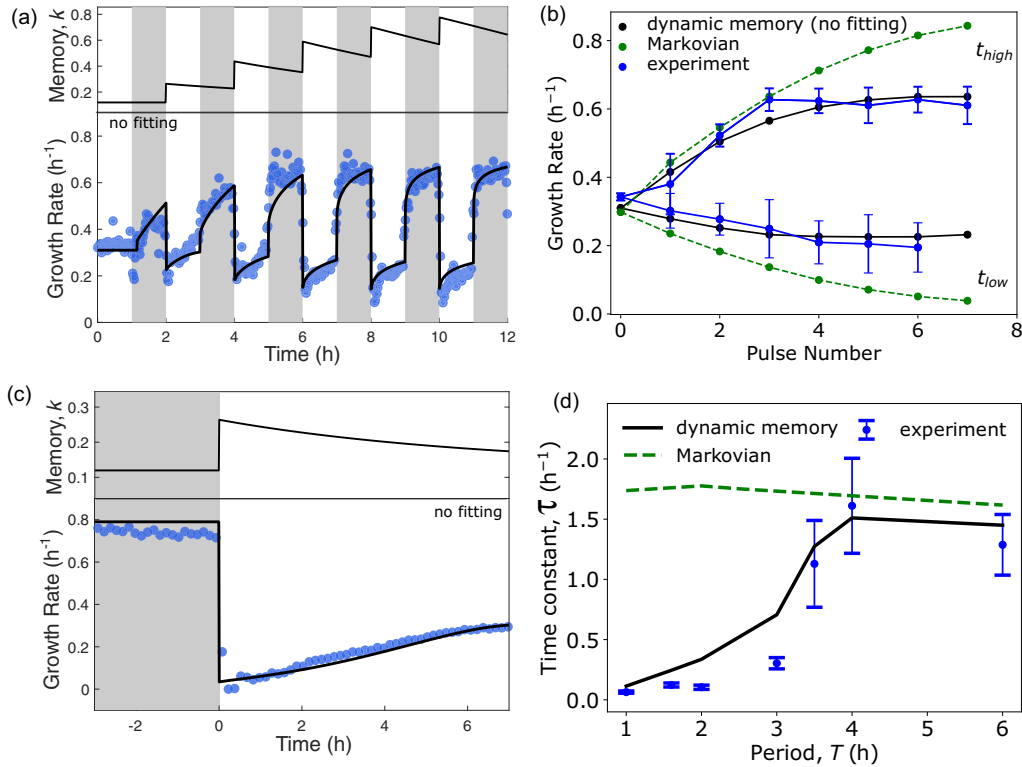


FIG. 3. Dynamic memory model captures a wide range of observed growth control behavior. (a) Predicted memory strength dynamics (top) and corresponding growth rate dynamics (bottom) for the proposed dynamic power-law memory model for cells initialized in nutrient-poor conditions followed by nutrient-rich pulsing, compared to our experimental growth rate measurements [identical to the green line in Fig. 1(c)]. (b) Average growth rate during the nutrient-rich half-periods (t_{high}) and the nutrient-poor half-periods (t_{low}) for cells initialized in poor nutrient conditions (period 0) followed by nutrient-rich pulsing for the dynamic memory model [quantification of growth rate dynamics shown in (a)] compared to the Markovian model and experimental data. Error bars represent standard deviation of the average growth rate. (c) Predicted memory strength dynamics (top) and corresponding growth rate dynamics (bottom) in response to nutrient downshift for the dynamic memory model, compared to our experimental growth rate measurements. Parameters are identical to that of (a). (d) Effective adaptation time constant, τ , as a function of time period of nutrient pulsing, T , for both the dynamic memory and Markovian models, compared to our experimental data. Model parameters were obtained by fitting to the data in (d), and then were used to make growth rate predictions for simulations in (a)–(c). Procedure for obtaining τ is identical to that described in Fig. 1(d), where error bars indicate uncertainty in the exponential fit. See Table S1 [27] for a list of parameters. For both the pulsatile (a) and single shift (c) conditions, single-cell growth rates were calculated from volume trajectories and averaged across the population through time (see the Appendix), resulting in $\sim 30\,000$ cells being tracked over the course of each experiment (see Table S3 [27] for a list of experimental conditions and sample size). For (a) and (c), nutrient-rich periods are denoted by gray shading.

sectors during nutrient shifts and has been validated for single-shift dynamics [Fig. 2(b) and Fig. S2 [27]]. However, this minimal model fails to capture experimentally observed growth control in pulsatile environments [Fig. 2(d)]. Most notably, growth rate fails to recover following each nutrient downshift, and after several pulses growth rate exceeds experimentally measured values. Furthermore, the predicted adaptation timescale shows no correlation with the time period of the nutrient pulse [Fig. 3(d)], contrary to experimental data.

B. Fractional-order dynamics capture scale-free adaptation

Our data show that the adaptation timescale τ follows an approximate power law relationship with the nutrient pulse frequency T^{-1} , which is a signature of scale-invariant dynamics. Such behavior is characteristic of systems with a

broad distribution of relaxation times, which are elegantly described by fractional-order differential equations (FDEs) [31,32]. FDEs have proven successful in modeling memory effects in neuronal systems [33], as well as in ecological [34] and physical contexts [35]. Motivated by this, we construct a model for proteome allocation where the dynamics are governed not by an ordinary, local-in-time derivative, but by a fractional derivative that introduces a nonlocal, power-law memory kernel:

$$\frac{d^\alpha \phi_R}{dt^\alpha} = F(t) = \phi_R(t)[\kappa_I(a(t))f_R(a(t)) - \kappa(t)], \quad (4)$$

where $\alpha = 1 - k$ is the fractional order of the dynamics with $k \in [0, 1)$, and $F(t)$ is the instantaneous production-dilution flux. A value of $k = 0$ ($\alpha = 1$) recovers the Markovian limit [first-order derivative given by Eq. (2)], whereas $k > 0$ describes a system whose present state depends on the entire

history of its dynamics, weighted by a power-law. We use the term “Markovian” here to describe a state-determined system, in which future evolution is fully determined by the current state and dynamics, rather than by its specific trajectory history. This serves as the baseline for comparison against our proposed fractional-order dynamics, which are inherently nonlocal. The time evolution of ϕ_R can also be written in the integral form:

$$\phi_R(t) = \int_{-\infty}^t \frac{(t-\tau)^{-k}}{\Gamma(1-k)} F(\tau) d\tau, \quad (5)$$

where $\Gamma(\cdot)$ denotes the Gamma function.

The effect of adding a memory kernel to the model can be made clear by analyzing its effect on resulting growth rate trajectories. In response to a single nutrient pulse, including a nonzero memory strength ($k > 0$) results in an initial period of rapid growth rate increase following upshift, but comes at the cost of reduced growth rate at longer timescales compared to the Markovian model ($k = 0$) [Fig. 2(c)]. Conversely, increasing memory strength aids in growth rate recovery following downshift.

While the power-law model with a constant memory strength captures growth rate repression and rapid adaptation behavior of cells stabilized in a pulsatile nutrient environment, it does not capture the result that adaptation rate increases with successive periods of nutrient pulse and the episodic increase in growth seen by cells which are first grown in nutrient-poor media before being exposed to pulsatile conditions (Figs. S3 and S4 [27]). This suggested that in fluctuating conditions, instead of optimizing for growth rate, bacteria maintain a memory of past environments which allows for increased adaptation speed to changing environments. This motivated us to consider a dynamic memory model of growth control, in which k is a function of time through its dependence on the environment, $k(t) = k(c(t))$, as cells which can tune their memory strength to match the environmental fluctuations are able to thrive in diverse conditions.

To model this cellular decision-making process, we introduced a biologically-plausible iterative value estimation approach (see the Appendix) in which a cell dynamically updates its estimate of the expected cost of the environment based on previous nutrient signals. Specifically, the cell incurs a cost if the nutrient quality decreases, as it causes growth rate to reduce. This is equivalent to tracking the exponential moving average $\pi(t)$ of the magnitude of nutrient downshifts $c(t)$:

$$\pi(t) = \rho \int_{-\infty}^t e^{-\rho(t-t')} c(t') dt', \quad (6)$$

where ρ is the learning rate (see the Appendix). Interestingly, in two-state environments like the one tested experimentally, this is equivalent to a Bayesian inference scheme in which the cell estimates the likelihood of receiving a nutrient downshift signal (see the Supplemental Material [27]). Although nutrient downshifts may not seem like an interpretable signal for the cell to track, recent experiments [36] have shown that the concentration of ppGpp, a small molecule known to be important in regulating cellular growth rate [36,37], increases abruptly and then slowly decays following downshifts, the

dynamics of which are captured well by Eq. (6) (Fig. S5 [27]), suggesting that ppGpp directly computes the expected cost of the environment.

In this framing, $\pi(t)$ serves as the cell’s internal representation of the environment which takes into account historical context, enabling it to accurately discriminate between different environmental time profiles. In costly environments [when $\pi(t)$ is high], the timescale of growth rate adaptation, and thus proteome reallocation, should be minimized to allow for rapid adaptation to costly nutrient downshifts. Thus we relate the memory strength $k(t)$ to $\pi(t)$ through a simple sigmoid relation, yielding: $k(t) = 1/[1 + e^{-[\pi(t)-\pi_0]/T_\pi}]$, such that k increases in fluctuating environments. Together, π_0 and T_π encode a bias for the cell to expect nutrient crashes (see the Appendix for more details).

Using this framework, we can simulate the full dynamic memory model to make predictions for bacterial growth control in fluctuating environments with arbitrary pulsing time profile (see the Appendix for numerical simulation details). As seen in Figs. 2(d) and 3(a), our proposed model is able to successfully capture experimentally observed *E. coli* growth rate dynamics for cells experiencing a transition from constant to pulsatile nutrient environments with different pulsing frequencies and nutrient types, highlighting the generality of our model and the robustness of the observed growth control phenomena.

Furthermore, for cells initialized in poor nutrients which then experience the onset of rich nutrient pulses, the dynamic memory model predicts an increase in average growth rate in rich nutrients for several pulses before stabilizing at a value well below the steady-state growth rate, matching trends seen in our experimental data [Fig. 3(b)]. In contrast, growth rate converges to the steady-state value in the Markovian model. Additionally, during nutrient-poor half-periods, growth rate in the Markovian model falls to zero, whereas average growth rate in the dynamic memory model stabilizes well above zero, indicative of the quick growth rate recovery caused by the maintenance of a nonzero memory [Figs. 2(d) and 3(a)].

Critically, our model can simultaneously capture single-shift growth rate dynamics with no change in parameter values due to the decay of memory in constant environments [Fig. 3(c) and Fig. S6 [27]], underscoring the importance of the dynamic memory formulation. Furthermore, our model captures the observed increase in adaptation timescale with the time period of nutrient oscillation [Fig. 3(d)], suggesting that the learning traits seen in experiment are a consequence of bacterial regulatory strategies which tune ribosomal adaptation dynamics to match the time-profile of nutrient fluctuations.

To give further support to our proposed fractional-order model, we examined whether simpler memory architectures could explain the data. We find that three plausible alternative models—those with either constant or tunable exponential memory kernels, and one with power-law memory in amino acid dynamics—all fail to capture the experimentally observed growth control (see the Supplemental Material and Figs. S7–S9 [27]). This result suggests that the emergent, multi-timescale memory must reside specifically within the ribosomal dynamics to accurately describe bacterial adaptation in fluctuating nutrient environments.

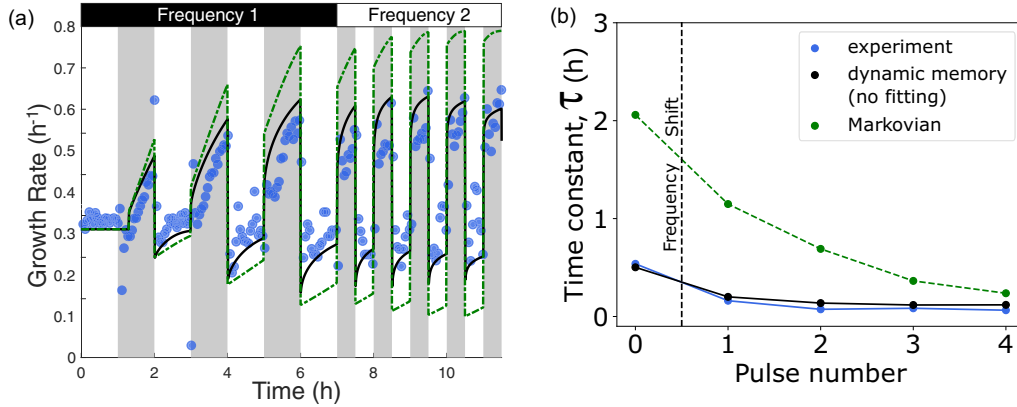


FIG. 4. Dynamic memory enables rapid readaptation to environmental frequency perturbations. (a) Predicted growth rate dynamics for the proposed dynamic memory model (black solid line) for cells which initially receive three periods of nutrient-rich pulsing at a frequency of 0.5 h^{-1} , followed by an immediate switch to 1 h^{-1} , compared to our experimental growth rate measurements (blue dots), as well as the prediction from the Markovian model (green dashed line). To directly test the predictive power of both models, parameter values obtained in Fig. 3 were reused here (no further fitting was done). Thus, slight discrepancies between the dynamic memory model and experimental values are visible, but as all qualitative features are captured well, this experiment gives strong support to the validity of the dynamic memory model. Parameter values are given in Table S1 [27]. Single-cell growth rates were calculated from volume trajectories and averaged across the population through time (see the Appendix). Nutrient-rich periods are denoted by gray shading. (b) Effective adaptation time constant, τ , as a function of pulse number since the start of the frequency shift, for both the dynamic memory and Markovian models, compared to our experimental data. Without any direct fit to this data, the dynamic memory model quantitatively predicts the rapid re-adaptation behavior observed experimentally, showing that bacteria utilize a nonlocal memory of the temporal pattern of past environmental conditions to discriminate between different time profiles and set cellular response times.

C. Dynamic memory enables rapid readaptation to frequency perturbations

To test the predictive power of our dynamic memory model and probe how environmental history shapes future growth control, we challenged *E. coli* cells with abrupt frequency perturbations. Cells were initially trained through three cycles of pulsing at a 2-h period before being immediately switched to a faster (1-h) frequency [Fig. 4(a)]. Experimentally, the adaptation timescale τ adjusted rapidly, within two pulses, to match the new environmental statistics. Remarkably, the dynamic memory model captures this transition using the original parameter set from Fig. 3, requiring no additional fitting [Fig. 4(b)].

In contrast, the Markovian baseline model fails to replicate the observed growth rate dynamics [Fig. 4(a)]. Specifically, the Markovian model's adaptation time constant τ requires significantly more pulses to stabilize following the perturbation [Fig. 4(b)]. These frequency shift tests provide strong independent validation for our hypothesis that bacteria utilize a nonlocal memory of the temporal pattern of past environmental conditions to discriminate between different time profiles and optimize cellular response times in nonstationary environments.

D. Emergence of multi-timescale memory from heterogeneous ribosome dynamics

A central question in the physics of living systems is how macroscopic, nontrivial dynamics emerges from underlying molecular processes. We propose a minimal mechanistic model where the observed multi-timescale memory originates from the heterogeneous regulation of the cell's ribosome population. This hypothesis is grounded in extensive biological

evidence showing that ribosome activity is controlled by distinct feedback mechanisms that act across a wide spectrum of timescales [36,38–40]. For instance, on short timescales ($\sim$ minutes), translation is inhibited by ppGpp, while on longer timescales ($\sim$ hours), subsets of ribosomes are inactivated by hibernation factors or removed by active degradation [37,41–45]. Our model serves to unify these disparate observations into a coherent mathematical framework that explains their collective, emergent effect.

To formalize how this distribution of regulatory timescales gives rise to emergent memory, we model the total ribosome mass fraction, ϕ_R , as being partitioned into m functional subsectors, which together set the overall cell growth rate. These subsectors may reflect differences in the types of mRNAs being translated, initiation efficiencies, or other regulatory features affecting activity. Each sub-sector possesses a characteristic relaxation timescale λ_m [Fig. 5(a)], yielding the dynamics:

$$\frac{d\phi_R^m}{dt} = \kappa_i(a)\phi_R f_R^m(t) - \phi_R^m \kappa(a, \phi_R) - \lambda_m^{-1} \phi_R^m, \quad (7)$$

where $\phi_R = \sum_m \phi_R^m$ and where $f_R^m(t)$ denotes the fraction of total synthesis capacity devoted to ribosomal subsector m . As before, these m equations are coupled to the dynamics of $a(t)$ [Eq. (3)], yielding a system of $m + 1$ coupled ODEs. The first term of Eq. (7) denotes the ribosomal production rate, the second captures dilution due to growth, and the third represents additional negative feedback control, with rate λ_m^{-1} . Importantly, in Eq. (7) when $\lambda_m \gg 0$, then the third term vanishes and $\kappa_i(a)$ controls the timescale of adaptation for that sector, as in Eq. (2). In contrast, if λ_m is small such that $\lambda_m^{-1} \gg \kappa$, dilution due to growth no longer dominates, and inactivation (third term) dictates the relaxation dynamics.

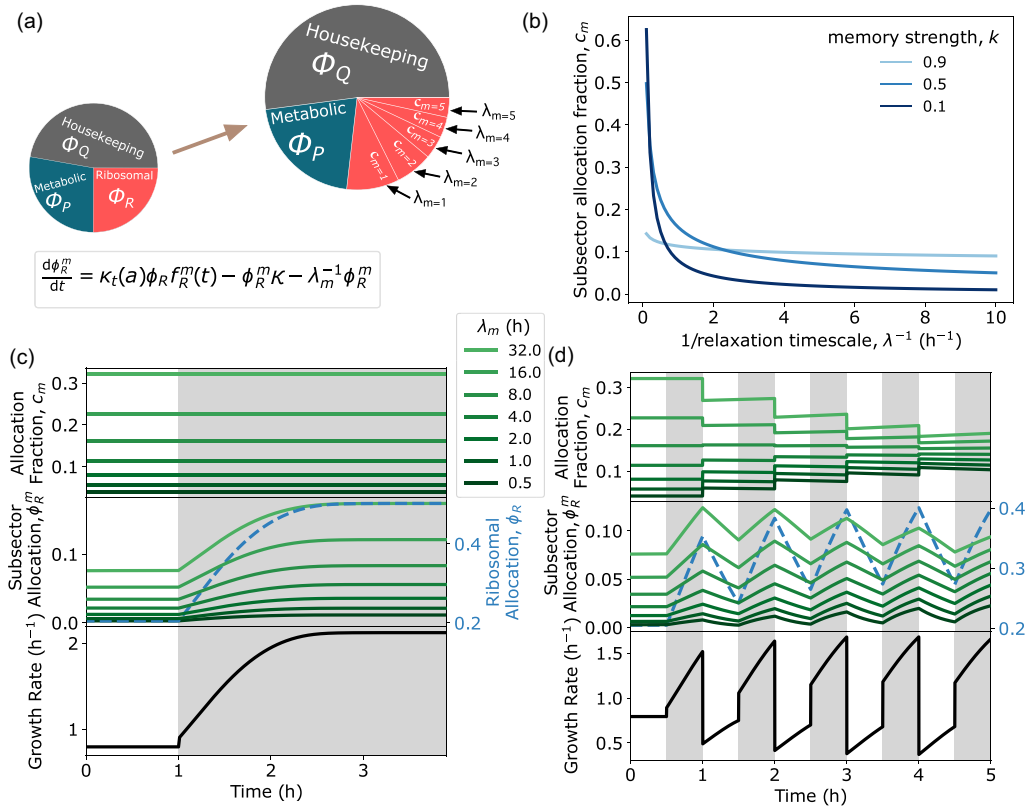


FIG. 5. Emergence of a fractional-order model of growth control from heterogeneous ribosomal adaptation dynamics. (a) To reflect the heterogeneous adaptation dynamics present in real bacterial cells, we can modify our original three-sector model to include multiple ribosomal subsectors, each with relative flux allocation c_m and characteristic relaxation timescale λ_m . (b) Subsector flux allocation follows a power law with respect to relaxation timescale, specifically $c_m(k) \sim \lambda_m^{1-k}$, where the exponent k is the memory strength. Increases in memory correspond to increases in allocation to subsectors with faster relaxation timescales. (c), (d) Example simulations of ribosomal subsector allocation fraction, $c_m(k)$, overall subsector allocation, ϕ_R^m , and resulting growth rate, κ , for a seven subsector model initialized in poor nutrients and then subjected to single nutrient upshift (c) or nutrient-rich pulsing (d), where gray shading denotes nutrient-rich environment. The environmental estimate used to determine k is computed using our iterative value estimation approach [Eq. (6)]. See Table S2 [27] for a list of parameters.

Simulating this model for a limited number of subsectors shows clearly how λ_m affects subsector dynamics, $\phi_R^m(t)$, in dynamic nutrient environments. Subsectors with larger values of λ_m respond slower to nutrient perturbations than those with smaller values (Fig. S10 [27]).

To describe how the cell dynamically regulates each subsector based on environmental context, we introduce $c_m(t)$, the fraction of the total translational flux allocated to subsector m , such that $f_R^m = c_m f_R$. We relate this allocation to the subsector's relaxation timescale λ_m and the cell's internal estimate of the environmental cost (memory), $k(t)$, using the relation: $c_m(t) = \lambda_m^{1-k(t)} / B(k(t), \lambda_i)$, where $B(k(t), \lambda_i) = \sum_i \lambda_i^{1-k(t)}$ is a normalization constant to ensure $\sum_m c_m(t) = 1$ (see the Supplemental Material [27] for detailed derivation). Thus, as the cell updates its internal representation of the environment through changes in $k(t)$, it alters the relative weights $c_m(t)$, thereby re-allocating translation capacity across subsectors with different relaxation timescales [Fig. 5(b)].

Using our value estimation scheme and Eq. (7) along with our expression for $c_m(t)$, we can simulate the effect of different environments on subsector allocation. In response to

a single upshift, subsector allocation remains constant, with greater resources devoted to subsectors with slower relaxation dynamics, indicative of the cell preventing negative feedback control to maximize growth [Fig. 5(c)]. In contrast, allocation to faster subsectors increases in fluctuating environments at the expense of subsectors with slow relaxation dynamics, enabling rapid ribosomal, and thus growth rate adaptation [Fig. 5(d)].

In this formulation, the dynamics of the entire ribosomal sector can be approximated as (see the Supplemental Material [27]):

$$\phi_R(t) \approx \int_{-\infty}^t (t - \tau)^{-k(\tau)} A(\tau) F(\tau) d\tau, \quad (8)$$

where $A(\tau) = k(\tau) b^{-k(\tau)} \Gamma(k(\tau))$ and b is the maximum ribosomal inactivation rate. Eq. (8) shows that a system of many first-order relaxation processes with a power-law distribution of rates can, in the continuum limit, give rise to a single, effective dynamic equation of a fractional order. This demonstrates how complex, nonlocal memory can emerge from the collective behavior of simpler, local components. While

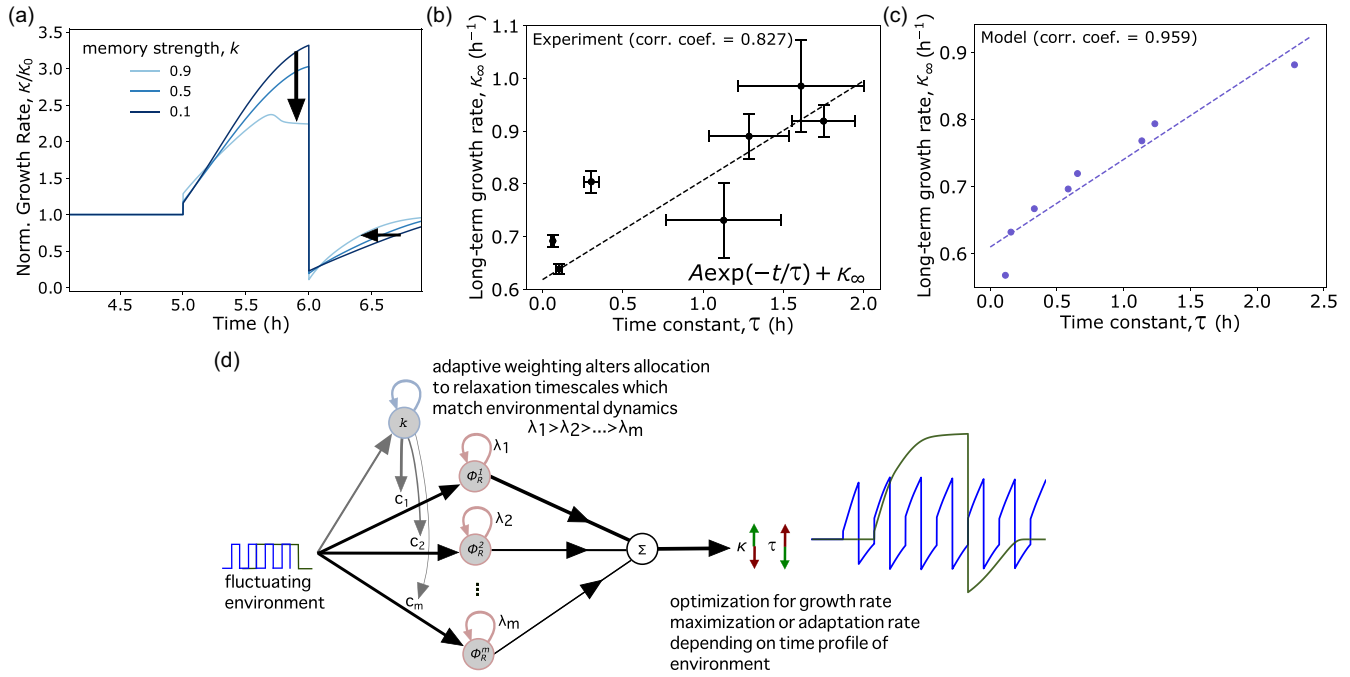


FIG. 6. Tradeoff between growth rate maximization and adaptation speed. (a) Example simulation of ribosomal subsector model with three subsectors with constant allocation for different memory strengths in response to a pulse of nutrients between hours 5 and 6. Increasing memory reduces growth rate, but increases adaptation time. (b), (c) Long-term growth rate, κ_∞ , exhibits a strong positive correlation with effective adaptation time constant, τ , in both experiment (b) and dynamic power-law memory model simulations (c), where error bars indicate uncertainty in the exponential fit. As with Fig. 1, τ and κ_∞ were obtained by fitting the average growth rate trajectory of the first three upshifts 6 h after the onset of pulsing for different time periods to the exponential $A \exp(-t/\tau) + \kappa_\infty$. (d) Cells navigate the tradeoff between growth rate and adaptation by tuning subsector allocation in response to the time profile of nutrient fluctuations. See Table S1 [27] for a list of parameters.

direct experimental validation of these subsectors is a target for future work, this model provides a compelling physical explanation for the origin of the power-law memory kernel governing adaptation dynamics.

Critically, simulating this model for different nutrient pulse frequencies predicts an increase in effective adaptation rate with time period (Fig. S11 [27]). Furthermore, this result allows us to use our mechanistic description to interpret the phenomenological power-law memory model [Eq. (5)]. Specifically, the memory strength k can now be interpreted as a parameter describing the distribution of ribosomal relaxation timescales. Therefore, the increase in memory k in fluctuating environments [Fig. 3(a)] can be interpreted to arise from an increase in allocation to ribosomal processes (subsectors) with faster relaxation timescales, as the distribution becomes more uniform [Fig. 5(b)]. We emphasize that memory in this context means the presence of non-Markovian dynamics. Thus, memory increases not because a single degradation/inactivation process is present, but rather *multiple* inactivation processes with *different* relaxation timescales are operating simultaneously.

E. Tradeoff between growth rate maximization and adaptation speed

Introducing ribosomal subsectors has important consequences to the overall cellular growth rate, as inactivated ribosomes cannot contribute to growth. As a result, the total

cellular growth rate is now given by $\kappa = \bar{\kappa}_i \phi_R$, where

$$\bar{\kappa}_i = \kappa_i(a) - b \frac{k}{k+1}, \quad (9)$$

(see the Supplemental Material [27]). Here we see that $\bar{\kappa}_i$ is the effective net translational efficiency, given by the weighted average of the translational efficiencies of each subsector. In the absence of inactivation ($b = 0$), we recover our original model for growth control with a single relaxation timescale [Eq. (1)]. However, when negative feedback control is present, it is clear from Eq. (9) that increasing the proportion of ribosomes with fast relaxation dynamics (increasing k) *necessarily reduces* the overall growth rate of the cell [Fig. 6(a)]. Thus Eq. (9) identifies an inherent tradeoff that cells must navigate between maximizing growth rate in the current environment (reducing k), and preserving the ability to adapt quickly to future changes in the environment (increasing k).

To test this prediction experimentally, we compared the relationship between the adaptation timescale, τ , and the long-term growth rate, κ_∞ , for different time periods of nutrient pulsing in both experiment and model simulations. Remarkably, we find a strong positive correlation between adaptation timescale and long-term growth rate for both cases [Figs. 6(b) and 6(c)], suggesting that growth is indeed limited by this constraint. This predicted tradeoff has been observed experimentally in various organisms and settings [46–48], suggesting that this is a universal constraint governing growth in fluctuating environments, one which bacteria navigate through utilization of history-dependent resource allocation

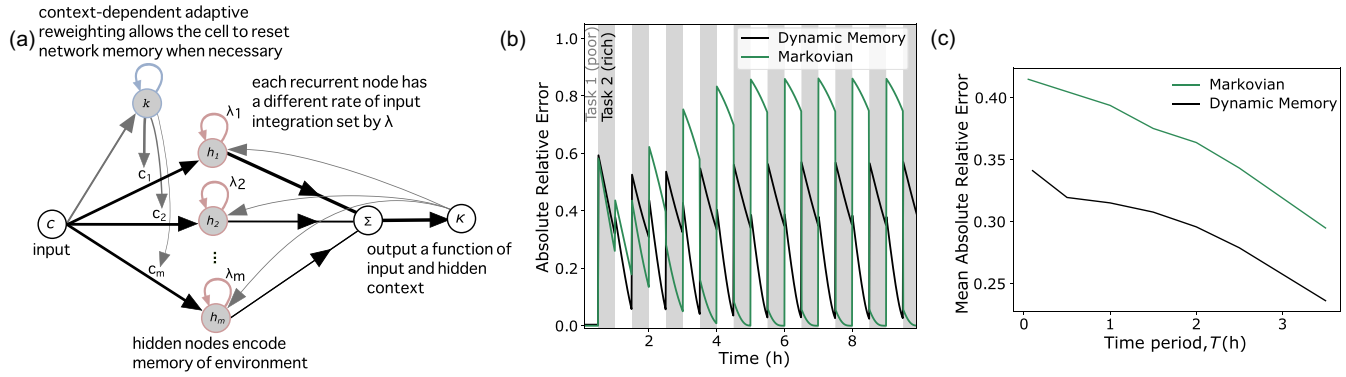


FIG. 7. Recurrent reaction networks enable efficient continual learning in fluctuating environments. (a) The features enabling efficient task switching in the mechanistic (dynamic memory) model can be understood when viewing the reaction network as an RNN. (b) “Test error,” defined as the absolute relative difference between the current growth rate and the steady-state maximum, as a function of time for cells initialized in poor nutrients (trained for task 1) which then subsequently experience nutrient rich pulsing (switching between task 1 and task 2), for both the Markovian and dynamic memory models. (c) Quantification of the average test error for the setup described in (b) for different time periods of “task switching,” simulated for 24 h. The dynamic memory model outperforms the Markovian model for all time periods, indicative of its ability to efficiently “task switch,” when the environmental input changes. See Table S2 [27] for a list of parameters.

[Fig. 6(d)]. Furthermore, recent evidence [37] shows that increasing exogenous ppGpp concentration increases adaptation to nutrient downshift at the expense of growth, directly supporting our hypothesis that ppGpp acts as the cell’s internal representation of the environment which relates memory to subsector allocation.

F. Growth regulation as a recurrent neural network

The structure of our mechanistic model reveals a striking parallel with architectures used in machine learning, suggesting that evolution and engineering may have converged on similar principles for temporal information processing. The dynamical system governing bacterial growth can be rigorously mapped onto a continuous-time recurrent neural network (RNN) [49] [Fig. 7(a)].

In this framework, the nutrient signal $c(t)$ is the *input*, the sub-sector mass fractions $\mathbf{h}(t)$ constitute the *hidden state vector*, and the growth rate $\kappa(t)$ is the *output*. Critically, this growth rate output is not only a function of $c(t)$, but also of the hidden state vector comprised of subsector mass fractions $\mathbf{h}(t) = [h_1(t), h_2(t), \dots, h_m(t)]$. Abstracting away the specific biological details, the evolution of each internal state can then generically be written as

$$\frac{dh_m}{dt} = -\lambda_m^{-1}h_m + c_m(\lambda_m, \pi(c))R(\mathbf{h}, c, \kappa), \quad (10)$$

where $R(\cdot)$ denotes the recurrent input, which is a function not only of the hidden states $\mathbf{h}(t)$ but also the input $c(t)$ and output feedback $\kappa(t)$, and $c_m(\cdot)$ denotes the subsector allocation.

Analogous to neurons with different intrinsic timescales, each hidden state (h_m) possesses a unique relaxation time (λ_m) that governs its rate of input integration; together with output feedback from the growth rate (κ), this architecture encodes a complex environmental memory that enables rapid adaptation. However, a network that maintains a strong memory of past inputs and cannot be reset when needed, such that its output remains stable regardless of changes to the input, is not

very useful. This tradeoff between maintaining a memory of previous information and learning to adapt to new information has been identified in many contexts in both the machine learning and neuroscience literature [49–52]. One way this tradeoff can be navigated by RNNs is by the inclusion of various gating mechanisms [49,51], which allow for flexible updating or erasure of memory in a context-dependent manner. Remarkably, the control of subsector allocation, $c_m(\cdot)$, by the cell’s internal representation of the environment, $\pi(c)$, can be identified as an input gating mechanism which exactly serves this purpose. This simple gating mechanism exhibits functions similar to the input, forget, and output gates found in Long Short-Term Memory RNNs [51]. Specifically, environment-dependent dynamic reweighting of the input signal to the different subsectors allows the cell to regulate the effect of each subsector on setting the overall output, thus allowing the cell to maintain a flexible memory of previous environmental context which can easily be “forgotten” if this context is no longer relevant.

The advantage of this network structure can be clearly seen if growth rate adaptation is viewed as a “continual learning” problem, a classic machine learning paradigm in which models are trained on multiple tasks sequentially instead of simultaneously [52]. In this framework, the “task” can be viewed as maximizing growth rate in a given nutrient environment. Thus in fluctuating environments, a cell must constantly deal with task switching, where the objective periodically changes. In this setting, the dynamic memory model is able to outperform the Markovian model over a wide range of time periods by maintaining a low average error across both tasks [Figs. 7(b) and 7(c)]. In contrast, the Markovian model is unable to efficiently task switch due to its lack of adaptive memory.

Together, this work demonstrates that despite their relative simplicity, single-celled organisms can exhibit complex learning behavior driven by adaptive memory encoded in intracellular reaction-networks. This learning behavior is critical in ensuring robust adaptation to stress in fluctuating environments.

III. CONCLUSIONS

In this work, we combine high-resolution single-cell experiments with theoretical modeling to uncover the physical principles governing how bacteria learn from and adapt to fluctuating environments. Our central discovery is that bacterial growth control is not a Markovian process, but is instead governed by nonlocal, fractional-order dynamics. This scale-free memory allows cells to tune their adaptation timescale to match the statistical features of their environment, a behavior we frame as a form of emergent learning.

We demonstrate that these macroscopic fractional dynamics can emerge from a minimal mechanistic model of heterogeneous ribosome populations, each with distinct relaxation timescales. This finding connects the abstract mathematical framework to plausible biophysical processes and reveals a fundamental tradeoff between adaptation speed and growth rate, a constraint we experimentally verify. The success of these nontrivial predictions, which are validated by our experiments, lends strong indirect support to the core assumptions of the underlying model.

While direct experimental confirmation of these subsector dynamics remains a fascinating avenue for future work, by mapping this intracellular reaction network onto a continuous-time recurrent neural network (RNN), we reveal that evolution has converged on a sophisticated computational architecture. The cell's resource allocation strategy functions as an adaptive gating mechanism, analogous to those in advanced RNNs, which optimally balances memory retention and plasticity.

Together, these results establish a new framework for understanding cellular adaptation, recasting it as a problem of physical computation. This perspective, bridging nonequilibrium statistical physics with machine learning concepts, suggests that even the simplest forms of life can implement complex, history-dependent strategies to survive, paving the way for quantitative investigations into the physical basis of intelligence in living systems.

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J.C.K. and S.B. designed and developed the theory. H.W. and F.S. designed the experiments. J.C.K. performed the model simulations and analyzed the data. H.W. performed the experiments and image analysis. J.C.K. and S.B. drafted the paper. J.C.K., H.W., F.S., and S.B. edited the paper.

DATA AVAILABILITY

The data that support the findings of this article are openly available [53,54].

APPENDIX: METHODS

1. Experimental data acquisition and image analysis

Experimental setup. With time-lapse microscopy, microfluidic mother machine devices [55,56] allow accurate

measurements for transient growth rates of single cells in pre-programmed microenvironments. PDMS devices were fabricated as described by Wang *et al.* [55]. For each main trench on a PDMS device, two inlet holes were drilled to facilitate medium switching and oscillating. The PDMS device is then bound to a WillCo-dish (HBST-5040) glass bottom. Before use, machine devices are preprocessed in a plasma cleaner (Harrick Plasma PDC-32G) for 10 min at 0.8 Torr, baking at 80 °C for 10 min and primed with 0.5 mg/mL bovine serum albumin fraction V (BSA, Roche Diagnostics, CAS-No. 9048-46-8) for 10 min. Each main trench on the mother machine microfluidics contains 4000 individual channels. After cells were injected into the main trench, cells were loaded into channels by centrifuging the device. The sample size represents the number of single-cell division cycles measured from each mother machine experiment. Figure 1(b) illustrates the configuration of the mother machine and syringe pump.

Fresh media was infused through the microfluidic device by a syringe pump after the cell loading. Syringe pumps (NewEra pump systems, SKU:4000) were programmed to pump sodium acetate (slow growth) medium for an initial 5 h, and then pulse the slow growth medium and fast growth medium (glucose + 11 a.a.) with the set period of 1, 2, 3, 4, and 6 h cycle time. The syringe pulsing program for our experiments can be found in Table S3 [27].

Cell preparation. Cells from *E. coli* strain K-12 MG1655 background (FS003) [57] were used in this study. Prior to each time-lapse imaging experiment, cells were picked from glycerol stock in −80 °C and spread on an agar plate. After overnight culture at 30 °C, cells were inoculated into 1 ml LB medium (MP Biomedicals, LLC, SKU: 113002122-CF). The cultures were then shaken for 12–18 h at 30 °C in a water bath shaker. Cell cultures were diluted into 2 mL of MOPS medium with sodium acetate, and shaken in the water bath at 37 °C for 24 h. The cultures were then concentrated 10- to 100-fold and injected into the microfluidic mother machine device. Fresh media was infused with a syringe pump through the duration of the experiment. See Tables S4, S5, and S6 [27] for a full media description and details.

Image acquisition. We performed phase-contrast imaging on a Nikon ECLIPSE Ti2 inverted microscope with 100× oil immersion objective (PH3, numerical aperture = 1.45), and ORCA-Fusion BT Digital CMOS camera (C15440-20UP). The syringe pump programs controlled medium pulsing with a pump rate of 0.8 mL/h for all experiments. Exposure time for phase-contrast imaging was set to 40 ms, and images were captured every 2 min.

Image processing and data analysis. Image processing followed a previously developed MM3 software pipeline [58]. The MM3 image analysis pipeline includes channel compilation and designation, background subtraction, cell segmentation, cell tracking through lineages, and data output and analysis. Single-cell physical properties, such as length, width, and growth rates were calculated throughout the entire timecourse of the experiments. To calculate the instantaneous growth rate, κ , we considered single-cell growth an exponential process and fit an exponential to a sliding window of three data points. The resulting growth rates were then binned in 0.05 h intervals and averaged across the population.

2. Updating memory strength through environmental value estimation

Here we show that a cell which tracks the moving average of the magnitude of nutrient downshifts can equivalently be cast as estimating the expected cost of the environment. The proper resource allocation scheme between growth and adaptability depends on the statistics of the environment. If a cell is likely to encounter frequent or big downshifts in nutrient quality, it is advantageous for the cell to increase memory strength and thus adaptability. In contrast, when downshifts are unlikely, it is better to maximize growth. Thus, to choose how to allocate resources, a cell must make an estimate of the quality of the environment. If we consider each downshift in the environment to be a cost incurred by the cell, we can estimate the expected cost of the environment, $V \doteq \mathbb{E}[C_t]$, where C_t is the cost of the environment at time t , as measured by the magnitude of the downshift. A natural way to estimate this is by averaging the costs actually incurred in the past:

$$V_t \doteq \frac{1}{t} \sum_{i=0}^{t-1} C_i. \quad (\text{A1})$$

This value can be efficiently updated with each new observation without storing all previous costs. The update rule is given by

$$V_{t+1} = V_t + \frac{1}{t} [C_t - V_t], \quad (\text{A2})$$

where $1/t$ can be thought of as a dynamic learning rate or step-size.

In reality, the environments which cells inhabit are highly nonstationary. As such, computing the sample average over all time will quickly become a poor estimate of the true value of the current environment. A straightforward way to modify the update rule to enable continuous adaptation to nonstationary environments is to choose a fixed learning rate. The update rule in nonstationary environments is then

$$V_{t+1} \doteq V_t + \alpha (C_t - V_t), \quad (\text{A3})$$

where α is the (constant) learning rate. This small change results in computing the exponential moving average, in which the estimate will vary in response to the most recently incurred costs. The finite-difference method can be used to convert this discrete expression to a continuous one, yielding

$$\pi(t) = \rho \int_{-\infty}^t e^{-\rho(t-\tau)} c(\tau) d\tau, \quad (\text{A4})$$

where $\pi(t)$ is the continuous time estimate of expected cost, $c(t)$ is the instantaneous cost at time t , and $\rho = \alpha/\Delta t$ is the leak rate, which is analogous to the discrete time learning rate. Although at first glance this may seem like a hard quantity for the cell to track, recent experiments [36] have shown that the concentration of the small molecule ppGpp increases abruptly and then slowly decays following downshifts, which is captured well by the dynamics of $\pi(t)$ (Fig. S5 [27]), suggesting that ppGpp directly computes the expected cost of the environment. Although recent works [36,59] have proposed models that also capture these dynamics, our framework provides a novel interpretation of ppGpp's observed behavior by

identifying its role in systems-level information processing and cellular decision-making.

Memory strength $k(t)$, and thus adaptability, should increase in environments where the expected cost is high. A simple way to connect the two is by using a sigmoid function, which is ubiquitous in bacterial gene regulation [60], yielding

$$k(t) = \frac{e^{\pi(t)/T_\pi}}{e^{\pi(t)/T_\pi} + e^{\pi_0/T_\pi}}, \quad (\text{A5})$$

or equivalently

$$k(t) = \frac{1}{1 + e^{-(\pi(t) - \pi_0)/T_\pi}}, \quad (\text{A6})$$

here with parameters T_π and π_0 , which together encode a bias for the cell to expect nutrient crashes (as when $\pi(t) = 0$, then $k(t) = 1/[1 + e^{\pi_0/T_\pi}]$), as well as scale the estimated value input in relation to the output of memory strength. We can interpret $\pi(t)$ then as the cell's preference for increasing memory relative to some baseline expected cost π_0 (similar to an action preference in reinforcement learning [61]).

Remarkably, increases in ppGpp concentration are known to induce a diverse array of negative feedback controls over ribosome activity which occur over different timescales [37,41–45], which we show in Sec. II D can lead collectively to an alteration in memory strength. However, further experimental work probing ppGpp dynamics in fluctuating environments is needed to directly test this mechanistic interpretation.

3. Numerical simulations

Numerically integrating FDEs are more complex than their ODE counterparts due to the time nonlocality present in the dynamics. To simulate the variable, multiorder system of FDEs which define our model [Eqs. (3) and (5)], we extended a previously developed predictor-corrector method for constant-order FDEs based on Adams formulas [62,63] to the variable-order case. Our fractional model can be expressed as an initial value problem,

$$\mathbf{X}(t) = \mathbf{X}_0 + \int_{t_0}^t \frac{(t - \tau)^{-\mathbf{k}(\tau)}}{\Gamma(1 - \mathbf{k}(\tau))} \mathbf{F}(\tau, \mathbf{X}(\tau)) d\tau, \quad (\text{A7})$$

where $\mathbf{X}(t) = [\phi_R(t), a(t)]$, $\mathbf{k}(t) = [k(t), 0]$, and $\mathbf{F}(t) = [F(t), J(t)]$, where $J(t) = \kappa_n(a)(\phi_R^{\max} - \phi_R) - \kappa$. To solve Eq. (A7), we employed a product integration technique [63]. Briefly, for grid nodes t_j (where $j = 0, \dots, m$) with constant step size h , first the explicit product rectangle rule gives a prediction for Eq. (A7) at t_j :

$$\mathbf{X}_m = \mathbf{X}_0 + \sum_{j=0}^{m-1} h^{1-\mathbf{k}_j} \mathbf{b}_{m-j-1,j} \mathbf{F}_j, \quad (\text{A8})$$

$$\mathbf{b}_{m-j-1,j} = \frac{(m-j)^{1-\mathbf{k}_j} - (m-j-1)^{1-\mathbf{k}_j}}{\Gamma(2 - \mathbf{k}_j)}, \quad (\text{A9})$$

where $\mathbf{F}_j = \mathbf{F}(t_j, \mathbf{X}_j)$, and $\mathbf{X}_j$ denotes the numerical approximation to $\mathbf{X}(t_j)$. Second, the implicit product trapezoidal rule

provides a corrector estimate of Eq. (A7):

$$\mathbf{X}_m = \mathbf{X}_0 + h^{1-k_0} \mathbf{c}_m \mathbf{F}_0 + \sum_{j=1}^m h^{1-k_j} \mathbf{d}_{m-j,j} \mathbf{F}_j, \quad (\text{A10})$$

$$\mathbf{c}_m = \frac{(m-1)^{2-k_0} - m^{1-k_0}(m-2+k_0)}{\Gamma(3-k_0)}, \quad (\text{A11})$$

$$\mathbf{d}_{m-j,j} = \begin{cases} \frac{1}{\Gamma(3-k_j)} & \text{if } m-j=0, \\ \frac{(m-j-1)^{2-k_j} - 2(m-j)^{2-k_j} + (m-j+1)^{2-k_j}}{\Gamma(3-k_j)} & \text{if } m-j=1, 2, \dots \end{cases} \quad (\text{A12})$$

The last term of Eq. (A10), $\mathbf{F}_m = \mathbf{F}(t_m, \mathbf{X}_m)$, is calculated using the value for $\mathbf{X}_m$ obtained using Eq. (A8). Computing this algorithm is costly, as evaluation of the solution on the entire grid $t_0, t_1, \dots, t_N$ is proportional to $O(N^2)$ [63].

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