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Why the temporal dimension matters in cellular signalling

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Temporal encoding of signalling dynamics is not just widespread; it offers a fundamental information-theoretic advantage in cellular communication. Recent advances in channel capacity measurement and decoding of second-messenger networks now provide a predictive framework linking temporal codes to differential gene regulation.

A central question in signal transduction is how cells use the same signalling molecule to elicit different responses. In mammalian cells, the transcription factor NF-κB can either oscillate in and out of the nucleus, or translocate there in a sustained manner; despite involving the same molecule, these dynamics activate distinct subsets of target genes[1]. In budding yeast, the stress-response factor Crz1 enters the nucleus in short, stochastic bursts whose frequency, rather than amplitude, is proportional to extracellular calcium concentration[2]. In the pathway mediated by the tumour suppressor p53, DNA damage triggers either repeated pulses (leading to cell-cycle arrest and repair) or a single sustained pulse (committing cells to apoptosis), depending on the nature and context of the genotoxic insult[3]. In each case, distinct signals are encoded by temporal variation in the behaviour of a single molecule (Fig. 1).

These are not isolated cases. In mammalian cells, pulsatile ERK kinase activity distinguishes proliferation from differentiation[4]. Oscillatory expression of the Notch target HES1 maintains neural progenitor pools during embryonic development[5]; while the frequency of pulsatile GnRH secretion differentially drives luteinizing hormone (LH) versus follicle-stimulating hormone (FSH) production from the same pituitary cells[6]. In *Bacillus subtilis*, the stress-response sigma factor σ^B is activated through stochastic, frequency-modulated pulses[7]. In yeast, the stress-response activator Msn2 shuttles into the nucleus in frequency-modulated bursts[2]. A broad pattern is emerging: across bacteria, fungi and animal cells, signalling molecules routinely encode information in their temporal dynamics (Fig. 1). This temporal code operates alongside, and often dominates, the classical view that information resides solely in molecular concentration. In what follows, we describe two recent quantitative advances: first, the absolute measurement of how much information dynamic signalling can carry; and second, a predictive framework explaining how oscillatory signals expand regulatory capacity beyond what static concentration control can achieve. We then discuss the outstanding challenges in extending these principles to natural multicellular contexts and explore how temporal multiplexing can serve as a practical engineering resource for synthetic biology.

Quantifying temporal encoding and decoding

That dynamic signalling carries information has been recognized for over a decade. Two recent developments, however, now place temporal encoding and decoding on a quantitative physical foundation, which, in our view, highlights a shift in the field from phenomenological description to a predictive, testable framework.

First, advances in synthetic biology, optogenetics and quantitative biology have made it possible to measure the information capacity of a temporal signalling pathway (here termed a 'channel' in the information-theoretic sense; see Box 1) for the first time. By genetically isolating the cAMP signalling pathway in *Pseudomonas aeruginosa*, we created a system in which temporal cAMP signals could be precisely 'written' through blue-light pulses and simultaneously 'read' via a fluorescent cAMP probe at single-cell resolution[8]. This experimental platform enabled the direct quantification of how much information the cAMP signalling pathway transmits as a function of input frequency. The pathway achieves approximately 40 bits per hour (see Box 1 for an introduction to information theory). To appreciate this number, consider that a single promoter reading a static transcription factor concentration can distinguish only about 1–2 bits per readout on the timescale of a bacterial cell cycle[9], which is equivalent to approximately two to four concentration levels (Box 1 and Fig. 2a). Temporal dynamics therefore increase the information throughput of the same molecular entity by more than an order of magnitude, providing capacity that is sufficient, in principle, to regulate dozens of independent downstream genes within one division cycle (Fig. 2b). Crucially, this capacity is not achieved at arbitrary signalling speeds: an optimal transmission frequency exists, set by the cAMP degradation rate in this case, and at this optimum, cells use a binary temporal code[9]. These results establish that temporal signalling parameters are physically constrained quantities that can be predicted from molecular rate constants — although the absolute capacity measured here reflects a specific engineered bacterial pathway, and whether comparable values are achieved in other organisms and signalling contexts remains an important open question.

Second, having quantified how much information the cAMP signalling pathway (Box 1) can carry, the question becomes: how is frequency-encoded information decoded into differential gene expression? By reconstructing the downstream cAMP regulatory circuit with controllable components[10], we discovered through systematic timescale analysis that the system naturally decomposes into three temporally separated modules, which we term the frequency-to-amplitude converter (FAC): a wave converter that transforms discrete light pulses into continuous cAMP concentration oscillations; a thresholding filter that converts oscillating cAMP concentrations into promoter activation events through cooperative molecular binding; and an integrator that time-averages promoter activity into stable protein expression levels (Fig. 3a). The pronounced temporal separation between these modules enables sequential signal processing with minimal interference,

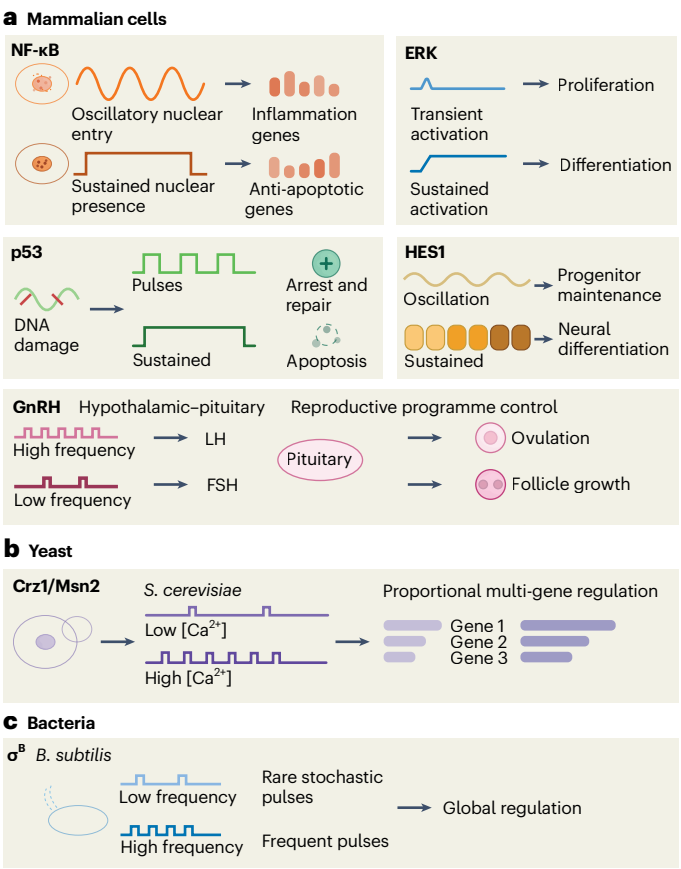

Fig. 1 | Temporal encoding of signalling across species. Signalling molecules can elicit distinct cellular outcomes depending on the temporal pattern of their activity — characterized by pulse amplitude, frequency and duration (see Box 1 for definitions). **a**, In mammalian cells, oscillatory nuclear translocation of NF-κB activates inflammatory gene programs, whereas sustained nuclear presence activates anti-apoptotic genes. Repeated pulses of p53 nuclear accumulation after DNA damage promote cell-cycle arrest and DNA repair, whereas a single sustained pulse of p53 commits cells to apoptosis. Transient versus sustained ERK kinase activation drives proliferation versus differentiation. High-frequency GnRH pulses from the hypothalamus preferentially stimulate LH secretion from pituitary gonadotrope cells, whereas low-frequency pulses favour FSH secretion. The Notch target HES1 oscillates during embryonic development to maintain neural progenitor pools; sustained HES1 expression drives differentiation. **b**, In yeast (*Saccharomyces cerevisiae*), the transcription factors Crz1 and Msn2 shuttle into the nucleus in stochastic bursts. Higher stimulus intensity increases the burst frequency without changing the amplitude of each burst. This frequency modulation ensures that several target genes with different promoter sensitivities are co-regulated in fixed proportions. **c**, In bacteria such as *B. subtilis*, the stress-response sigma factor σ^B activates in stochastic pulses whose frequency rises with increasing stress, thereby engaging a progressively larger fraction of the σ^B regulon. Together, these examples illustrate that encoding information in temporal dynamics is a conserved signalling strategy across bacteria, fungi and animal cells.

providing a physical basis for how cells convert temporal input patterns into distinct gene expression outputs.

Crucially, whether a given promoter acts as a low-pass or high-pass filter is quantitatively predicted by a single dimensionless threshold parameter, λ, determined by the ratio of transcription factor abundance to promoter binding affinity (Fig. 3a). This framework yields a testable prediction: when n genes with different λ values are co-regulated, the number of distinguishable multi-gene expression states under amplitude modulation scales as $H \propto 0.8 \cdot \log_2(n)$, whereas adding frequency modulation yields $H \propto 2.0 \cdot \log_2(n)$ (Box 1 and Fig. 3b, c). In a three-gene system — the scale at which the prediction was experimentally validated[10] — this provides approximately two additional bits of information entropy (from approximately 4.75 to 6.57 bits), corresponding to approximately a 4-fold expansion in the number of distinguishable regulatory states — from 27 states under amplitude modulation alone to 95 states when frequency modulation is included.

From single genes to network-level control

The encoding, decoding and scaling principles described above were established in engineered bacterial circuits. This inevitably raises the question of whether they exist in natural signalling systems. Several lines of evidence suggest they do. In yeast, the transcription factor Crz1 enters the nucleus in frequency-modulated bursts, and this frequency modulation — rather than changes in the amplitude of each burst — ensures proportional co-regulation of several target genes with different promoter affinities[2]. The combinatorial pulse timing of the activator Msn2 and its repressor Mig1 enables gene-specific regulation in yeast that neither factor could achieve through concentration changes alone[11]. In mammalian cells, computational analyses of NF-κB dynamics suggest that oscillation frequency encodes stimulus identity by multiplexing information to diverse target gene programmes[12]. In each case, a shared regulatory molecule controls several targets with different response kinetics, and temporal dynamics provide the additional degrees of freedom needed for differential regulation — precisely the scenario, in which our quantitative framework predicts frequency modulation to outperform amplitude modulation (Box 1).

Why might this temporal strategy be so widespread? We suggest that the answer connects to a fundamental constraint at the single-gene level. Individual promoters are imprecise receivers: stochastic transcription factor binding, chromatin fluctuations, and low numbers of molecules limit information transmission to approximately 1–2 bits per promoter[9,13] (Fig. 2a), sufficient to produce only about two to four discernible expression outputs (Box 1). Under amplitude modulation, this constraint has a compounding effect at the network level: changing transcription factor concentration shifts all target genes in the same direction along their respective dose–response curves, producing correlated expression patterns that limit the accessible regulatory state space. Frequency modulation breaks this correlation. Because promoters with different biochemical properties, parameterized by λ (ref. 10), respond preferentially to different frequency ranges, modulating oscillation frequency can increase the expression of one gene while decreasing that of another (Figs. 2b and 3a). This differential selectivity expands the repertoire of achievable multi-gene states far beyond what amplitude variation alone permits (Fig. 3b,c), offering a physical explanation for why temporal encoding has been independently adopted across bacteria, fungi and animal cells.

Outstanding challenges

Despite the insights highlighted here, several important questions remain (Fig. 4a).

How do promoters physically decode dynamic signals? Different genes respond differently to the same oscillatory transcription factor, indicating that promoter architecture acts as a molecular frequency filter. Some promoters behave as low-pass filters (responding

BOX 1

A primer of information theory in cell signalling

Information theory, developed by Claude Shannon in 1948, provides a mathematical framework for quantifying how reliably a message can be transmitted through a noisy channel. Its concepts have proven valuable for understanding cellular signalling.

Encoding and decoding. In signal transduction, 'encoding' refers to how an upstream signal is converted into a specific temporal pattern of molecular activity, and 'decoding' describes how downstream molecular machinery (such as gene promoters or effector proteins) interprets that pattern to produce a cellular response. The fidelity of this encoding–decoding process determines how much information a signalling pathway can transmit.

Pulses and their parameters. A 'pulse' refers to a transient episode of increased signalling activity. In eukaryotic cells, this typically manifests as the temporary accumulation of a transcription factor in the nucleus, followed by its return to the cytoplasm (as for NF-κB, Crz1, and Msn2). In bacterial systems, a pulse may instead correspond to a transient rise in second-messenger concentration (as for cAMP) or a burst of sigma factor activity (as for σ^B). Regardless of the mechanism, pulsatile signals are characterized by several key attributes: amplitude (peak activity level), duration (how long each pulse lasts), the time interval between consecutive pulses, and frequency (how often pulses recur). Constant signals primarily regulate responses through amplitude modulation, in which output is determined solely by signal strength. Pulsatile signals add additional layers of modulation through these temporal attributes, collectively enabling frequency modulation. The duty cycle — the fraction of each period during which the signal is active — provides a further control parameter.

Bits. The fundamental unit of information is the bit. One bit distinguishes two equally likely alternatives; two bits distinguish four; three bits distinguish eight (2^n alternatives for n bits). Importantly, bits measure information as a continuous quantity — fractional values (such as 1.5 bits) are meaningful and common. When we say a promoter transmits approximately 1–2 bits, we are describing the precision of the entire input–output mapping: how reliably differences in the upstream signal (such as the transcription factor concentration) are converted into distinguishable differences in gene expression output. At the input end, this means the promoter can effectively discriminate only about two to four levels of the upstream signal; at the output end, it means the promoter produces only about two to four reliably distinguishable expression levels. The two are equivalent — limited discrimination of the input necessarily limits the repertoire of distinguishable outputs. Why so few? Although an individual promoter switches between ON and OFF states at any instant, the biologically relevant output is the time-averaged expression level, determined by the fraction of time the promoter spends in the ON state. This time-average is, in principle, a continuously graded, analogue quantity — much like how a light flickering rapidly between on and off appears to glow at an intermediate brightness. However, molecular noise (stochastic transcription factor binding, nucleosome dynamics, and low molecule copy numbers) introduces variability in this time-average from cell to cell and from moment to moment, limiting how many graded levels the cell can reliably set and read. The result is that, despite the continuous nature of the underlying biochemistry, the effective information resolution of a single promoter is coarse—on the order of 1–2 bits.

Information entropy and state space. Shannon entropy (H) quantifies the total number of distinguishable states a system can access, expressed in bits. In gene regulation, it measures how many distinct multi-gene expression patterns a cell can reliably produce and discriminate under noise. Higher entropy means a larger 'state space' — that is, a greater repertoire of distinguishable regulatory programs available to the cell, whereas lower entropy indicates fewer accessible states and more limited regulatory capacity.

The signalling channel. By analogy with a communications channel, we define the signalling channel as the mapping from a set of dynamic input parameters — the temporal pattern of the activity of a signalling molecule (oscillation frequency, duty cycle and amplitude) — to downstream readouts. These readouts may be second-messenger concentrations (as measured in the cAMP channel capacity experiments[8]) or the resulting expression levels of target genes (as measured in the entropy scaling-experiments[10]), depending on the level of analysis. Channel capacity is the maximum rate at which information can flow reliably through this mapping.

Channel capacity and gene regulation. The measured cAMP channel capacity of approximately 40 bits per hour[8] describes the maximum rate at which information can be reliably transmitted, not the number of genes controlled at any instant. To illustrate what this rate indicates: if each downstream gene is simplified as having two states (on or off), specifying the state of n genes requires n bits. At 40 bits per hour, the channel could in principle transmit enough information to independently specify the on/off states of up to 40 genes within one hour — comparable to a typical bacterial division cycle. In practice, this upper bound will be reduced by noise, redundancy and the need for error correction, but it nonetheless demonstrates that second-messenger channels possess far greater information-carrying potential than simple binary switches.

How frequency modulation expands regulatory capacity. When one transcription factor regulates several genes, each promoter can act as a frequency filter: some respond to slow pulses (low-pass), others to fast pulses (high-pass), and others to intermediate frequencies (band-pass). Changing pulse frequency differentially tunes the expression of each gene, expanding the repertoire of achievable expression patterns compared with amplitude control alone. An everyday analogy is the AM radio, which encodes sound in the height of the wave, whereas a FM radio encodes it in the frequency of the wave.

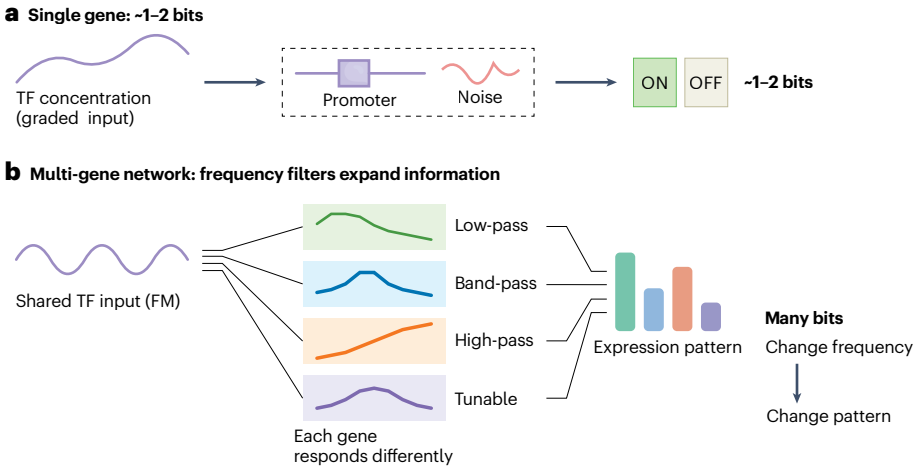

Fig. 2 | Quantifying temporal encoding and decoding. a, At the level of a single gene, several sources of molecular noise — stochastic nucleosome remodelling, random transcription factor (TF) binding and unbinding, and low regulatory molecule copy numbers — limit information transmission to approximately 1–2 bits per promoter, sufficient to produce only about two to four discernible expression outputs (Box 1). **b**, In a multi-gene network, a single shared TF encodes information in its oscillation frequency. Because different promoters have distinct biochemical properties (nucleosome turnover rates, TF-binding affinities or chromatin remodelling kinetics), each responds preferentially to a different frequency range, enabling the cell to generate different multi-gene expression patterns from one shared input.

preferentially to slow, sustained signals), whereas others function as band-pass or high-pass filters (selectively responding to specific frequency ranges)[10,14,15]. The mechanistic basis of such filtering is beginning to emerge: promoters with slow nucleosome turnover and cooperative transcription factor binding act as integrators that smooth out fast fluctuations, whereas promoters with rapid transcription factor exchange and low cooperativity can track fast oscillations[12]. In our reconstructed cAMP system, the dimensionless threshold parameter λ quantitatively predicts the transition between low-pass and high-pass filtering regimes[10]. However, a full mechanistic understanding connecting specific chromatin states and transcription factor binding kinetics to filter characteristics at the single-locus level remains a major experimental frontier, requiring integration of single-molecule transcription factor tracking with real-time nascent RNA imaging in living cells.

What happens when signals are transient? Most studies have focused on periodic, steady-state stimulation, yet natural signals are often brief and irregular. How cells extract reliable information from transient, non-stationary inputs — and whether early transient responses carry disproportionate weight in irreversible cell-fate decisions — is largely unexplored. Time-limited signals present a particular challenge: the cell may not experience enough oscillation cycles to reliably estimate frequency, potentially requiring fundamentally different decoding strategies such as reliance on signal derivatives or adaptive thresholding.

How does temporal encoding operate in multicellular contexts? In tissues, cells do not signal in isolation. Paracrine communication, mechanical coupling and shared extracellular environments mean that the temporal patterns one cell experiences are influenced by its neighbours. How temporal and spatial encoding interact — and whether spatial averaging among neighbouring cells provides additional noise suppression complementing temporal multiplexing — remains a major open question for developmental and tissue biology.

Time as an engineering resource

The three challenges above concern how natural cells decode temporal signals. But the principles uncovered so far already open practical opportunities for synthetic biology that directly address a longstanding engineering bottleneck (Fig. 4b). Controlling *n* target genes independently has traditionally required *n* orthogonal transcription factor–promoter pairs; as circuit complexity grows, the required parts quickly exceed available options, and the accumulation of exogenous proteins imposes unsustainable metabolic burden. Temporal multiplexing offers an alternative: a single shared regulatory circuit encodes distinct commands in successive time windows by varying pulse frequency or duty cycle (Fig. 4b). Because different promoters act as frequency filters with distinct pass-band characteristics, each target gene responds preferentially to a specific temporal pattern, enabling differential multi-gene control from one shared input. The dimensionless threshold parameter λ that predicts filtering behaviour in natural cAMP circuits[10] could thus serve as a quantitative design rule for tuning synthetic promoter responses to desired frequency ranges.

Recent work demonstrates this is not merely theoretical. Pulsatile regulation has been shown to reduce cell-to-cell variability and enable graded multi-gene regulation at fixed expression ratios, replacing laborious optimization of genetic parts[14]. In a follow-up, the authors constructed synthetic signal demultiplexers and pulsatile signal decoders using transcription factors with differing response kinetics, and applied dynamic multiplexing to precisely regulate flux through a heterologous mevalonate pathway[15]. Furthermore, temporal strategies allow competing metabolic pathways to be driven in alternating, out-of-phase pulses, so that they never simultaneously drain shared precursors — a biological analogue of time-division multiplexing in telecommunications (Fig. 4c). Together with the quantitative framework from studies of natural frequency-decoding systems[11,12], these advances demonstrate that temporal signal processing is transitioning from a biological observation to an actionable engineering principle.

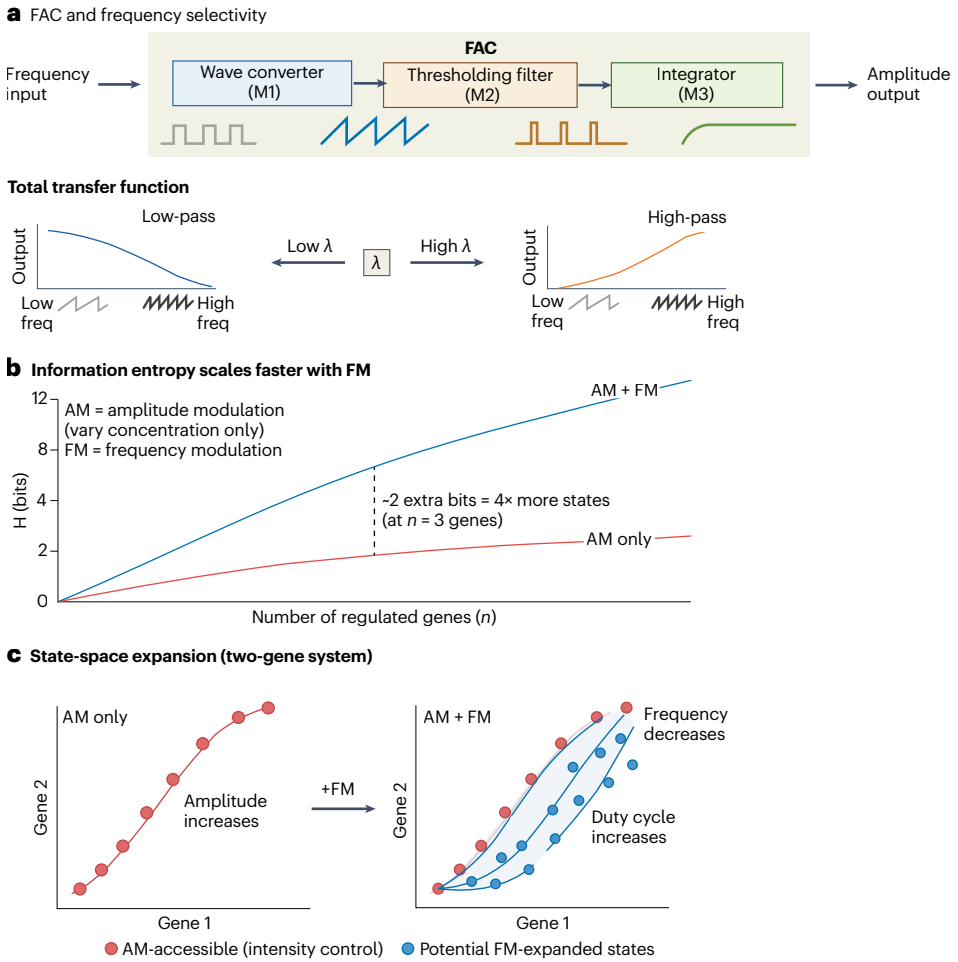

Fig. 3 | Frequency-to-amplitude conversion and information entropy scaling. **a**, Schematic of the frequency-to-amplitude converter (FAC) architecture, comprising three temporally separated modules (wave converter M1, thresholding filter M2, and integrator M3). The dimensionless threshold parameter λ determines the filtering regime of each promoter: high-λ promoters preferentially pass high-frequency signals; low-λ promoters preferentially pass low-frequency signals. See main text for mechanistic details. **b**, Information entropy (H, in bits; Box 1) plotted against the number of co-regulated genes (n), comparing amplitude modulation alone (red; $H \propto 0.8 \cdot \log_2(n)$) with combined amplitude and frequency modulation (blue; $H \propto 2.0 \cdot \log_2(n)$). Both scaling relationships were derived from theoretical and experimental analysis in ref. 10. At $n = 3$, frequency modulation provides approximately two additional bits of information entropy, corresponding to a fourfold expansion ($2^2 = 4$) in the number of distinguishable regulatory states (from 27 to 95). **c**, State-space representation of a two-gene system illustrating the concept in **b**. Each dot represents one experimentally distinguishable combination of expression levels for gene 1 (x axis) and gene 2 (y axis). Red denotes states accessible under amplitude control alone; blue denotes additional states unlocked when frequency modulation is introduced, which activates the two promoters in ratios unachievable by concentration changes alone.

Conclusions

The accumulated evidence clearly suggests that cells encode and decode crucial information in the temporal patterns of signalling molecules. However, much of cell biology continues to rely on experimental approaches — such as population-averaged western blots, bulk RNA sequencing and fixed-cell immunofluorescence — that are inherently blind to these dynamics. To address this, the field must adopt live-cell, single-cell, and time-resolved measurements as default rather than specialized methods. In particular, automated microfluidic platforms that deliver precisely timed chemical or optogenetic stimuli to living cells[8,10] will be essential for moving beyond correlative observation to establishing causal links between specific temporal codes and cellular fates.

The therapeutic implications also deserve attention. Several diseases are characterized by disrupted signalling dynamics rather than by the loss or gain of a molecular component. For instance, an abnormally accelerated GnRH pulse frequency is a hallmark of polycystic ovary syndrome, leading to a pathological shift in the LH-to-FSH ratio[6]; altered p53 pulse dynamics are linked to variable DNA damage responses across tumour types[3]; and disrupted NF-κB oscillations can shift inflammatory gene programs toward chronic inflammation[1]. In each case, the molecular components remain intact — it is their temporal behaviour that is disrupted. A deeper understanding of how cells decode these temporal patterns may therefore inform therapeutic strategies aimed at restoring physiological signalling dynamics — for example, by pharmacologically tuning oscillation frequency or duty cycle, rather than broadly inhibiting or activating entire pathways.

Deciphering the temporal code calls for an integration of molecular biology, information theory and quantitative engineering.

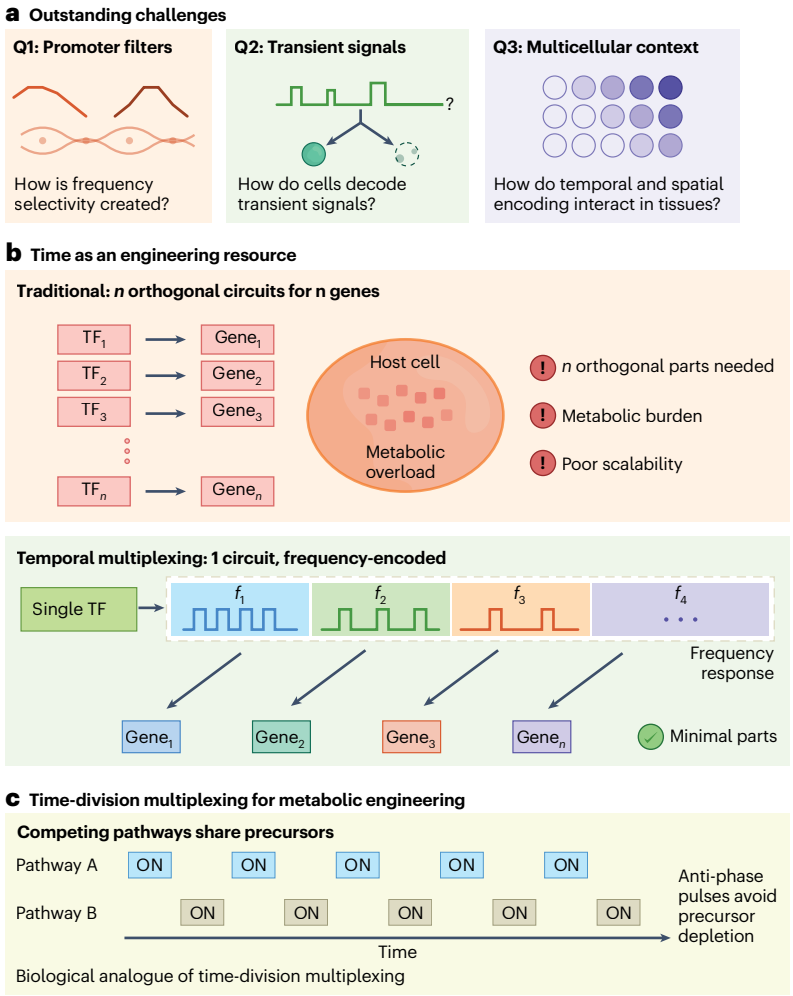

Fig. 4 | Outstanding challenges and temporal multiplexing as an engineering resource. a, Three key open questions at the frontier of temporal signalling research. Question 1 (Q1): how do the biochemical properties of promoters — nucleosome dynamics, TF binding kinetics, chromatin remodelling — create frequency selectivity? Q2: how do cells decode brief, irregular signals that do not persist long enough for many oscillation cycles, yet still make irreversible fate decisions? Q3: in multicellular tissues where cells communicate via shared extracellular signals, how do temporal and spatial encoding interact? **b**, Engineering comparison. In the traditional synthetic biology paradigm (red), controlling *n* target genes independently requires *n* separate, orthogonal transcription factor–promoter pairs, each consuming cellular resources and imposing metabolic burden that limits circuit complexity. In the temporal multiplexing paradigm (green), a single regulatory circuit produces pulses at different frequencies (f_1,f_2,f_3…f_n) in successive time windows. The promoter of each target gene is tuned through its biochemical properties (as described in **a**, Q1), to respond preferentially to a specific frequency, enabling differential regulation from one shared input without additional molecular parts. **c**, Furthermore, competing metabolic pathways (A and B) that draw on shared precursors can be driven in alternating, out-of-phase pulses — so that they never simultaneously deplete the same resources — a biological analogue of time-division multiplexing in telecommunications.

By learning to read and write this dynamic language, we stand to gain not only a deeper understanding of cellular decision-making, but also powerful new tools for both engineering and medicine.

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Competing interests
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