Chaos and oscillations continue to capture the interest of both the scientific and public domains. Yet despite the importance of these qualitative features, most attempts at constructing mathematical models of such phenomena have taken an indirect, quantitative approach, for example, by fitting models to a finite number of data points. Here we develop a qualitative inference framework that allows us to both reverse-engineer and design systems exhibiting these and other dynamical behaviours by directly specifying the desired characteristics of the underlying dynamical attractor. This change in perspective from quantitative to qualitative dynamics, provides fundamental and new insights into the properties of dynamical systems.
Mathematical modelling requires a combination of experimentation, domain knowledge and, at times, a measure of luck. Beyond the intrinsic challenges of describing complex and complicated phenomena, the difficulty resides at a very fundamental level with the diversity of models that could explain a given set of observations. This is a manifestation of the so-called inverse problem, which is encountered whenever we aim to reconstruct a model of the process from which data have been generated. Exploring the potential space of solutions computationally can be prohibitively expensive and will generally require sophisticated numerical approaches or search heuristics, as well as expert guidance and manual interventions. Parameter estimation, model inference and model selection all address aspects of this problem.

The inverse problem also applies in a different context: the design of systems with specified or desired outputs. Here again we have a multitude of different models—or, for sufficiently complicated models, a potentially vast range of parameters—that fulfill a given set of design objectives. Therefore, system design can be fraught with the same challenges as statistical inference or reverse-engineering tasks: in the former case, we want to learn the existing structure and properties of a system that has produced certain types of data, whereas in the latter we want to design constructible systems that will reliably and robustly exhibit certain types of behaviour.

These challenges are often further exacerbated by unsuitable or insufficient encoding of the behaviour that we observe (in natural systems) or would like to see (in designed systems). For example, if we aim to estimate parameters describing an oscillating system from a series of observations, it is possible to get good and even globally optimal fits to the data, without finding a qualitatively acceptable solution. Various methods of qualitative inference have been developed to address this issue: the topology of bifurcation diagrams, local stability properties of dynamically invariant sets, symbolic sequences of chaotic systems and temporal logic constraints have variously been used to drive parameter searches, or for model checking. However, these methods are either limited in the complexity of behaviour they can detect, or by conditioning on surrogate data (for example, forcing solutions through a small number of points), they suffer in the same way as quantitative approaches. The method proposed here extends the scope of the promising, but underdeveloped, class of qualitative parameter estimation algorithms, allowing detection and control of the most complex and elusive dynamical behaviours, such as oscillations, chaos and hyperchaos.

We consider models of the general form

$$\frac{dy(t)}{dt} = f(y(t), y_0, \theta),$$  

where $y(t)$ denotes the $n$-dimensional state of the system at time $t$; $f$ is the gradient field characterized by a parameter vector; $\theta$ and $y_0 = y(0)$ are the initial conditions, which may also be unknown. Coaxing the solutions of such systems into exhibiting a desired dynamical behaviour is reliant on the ability to, first, encode the behaviour sufficiently as constraints on a set of model properties that may be conveniently evaluated, and second, to identify regions in parameter space for which these constraints are satisfied. Here we meet these challenges using a combination of statistical and dynamical systems techniques. In particular, we pose the problem within a state–space framework, where the observation function corresponds to evaluating the type of attractor exhibited by the model with given parameters and initial conditions. We then exploit the flexibility and efficiency of the unscented Kalman filter (UKF) to systematically move in parameter space until the desired or expected dynamical behaviour is exhibited. The approach, outlined in Figure 1 and developed fully in the Methods and Supplementary Information, is demonstrated below within different contexts, covering some classical dynamical model systems and electronic circuits that exhibit oscillations, chaos and hyperchaos, and a biological regulatory system that exhibits oscillatory behaviour.

**Results**

**Oscillations and chaos in electronic circuits.** The elimination of chaos from a system, or conversely its ‘chaotification’, have potential applications to biological, medical, information processing and other technological systems. Here we use a simple electric circuit (shown in Fig. 2a), to illustrate how our method can be used to tune the system parameters such that the dynamics are driven into and out of chaos. The circuit model includes a parameter $a$, representing the scaled resistance of a variable resistor, $R_v$, which we make the subject of the inference. In turn, we start the system in an oscillatory regime and tune the parameter according to the posterior distribution is calculated via the LE estimation routine L and the unscented transform. Comparing the mean LE, $\lambda_{mean}$, to the target LE, $\lambda_{target}$, the prior parameters are updated using the UKF update equations. As the filter proceeds, parameters are found that locally minimise the sum of squared error between target and estimated LEs.

**Figure 1 | Encoding and inferring the desired dynamics.** (a) LEs, $\lambda_0$, ..., $\lambda_n$, characterize the contraction/expansion of an initially small perturbation, $\epsilon_0$, to the system. (b) The leading LE determines the principal dynamics and characteristics of the attractor of a dynamical system. For $\lambda_0 < 0$, the attractor will be a stable fixed point; stable oscillating solutions will be obtained, if $\lambda_0 = 0$; for $\lambda_0 > 0$ we observe chaos and the system will exhibit a so-called strange attractor; if more than one LE is positive, then we speak of hyperchaos and the attractor will exhibit behaviour with similar statistical properties to white noise. (c) Key steps in the UKF for qualitative inference. At the $k^{th}$ iteration, the current prior parameter distribution is formed by perturbing the previous posterior, $\theta_k$, with the process noise $\nu_k$. The distribution of LEs for the model $f$ induced by the prior parameter distribution is calculated via the LE estimation routine L and the unscented transform. Comparing the mean LE, $\lambda_{mean}$, to the target LE, $\lambda_{target}$, the prior parameters are updated using the UKF update equations. As the filter proceeds, parameters are found that locally minimise the sum of squared error between target and estimated LEs.
Oscillations appear in the system's attractor (Fig. 3) of a parameter set that yields oscillations. Several regions in parameter space can be identified that exhibit oscillatory behaviour. Trajectories were sampled from the prior. Data are indicated by red circles and represent fold change in Hes1 mRNA; the blue bands in the figure show the confidence intervals, which standard Gaussian noise is assumed, with maximum marginal likelihood estimates for the other hyperparameters.

\[ \delta \] is taken larger-than-the-expected error in the LE estimation procedure, as discussed in the Supplementary Information.

For systems of this size, the qualitative dynamical regimes can be explored exhaustively and in short time (finding the desired behaviour takes minutes even for moderate sized systems).

**Detecting oscillations in immune signalling.** Oscillations appear to be ubiquitous in nature, yet, for reasons noted above, they often remain elusive to quantitatively driven parameter inference techniques. Here we consider a dynamical system describing the expression levels of the transcription factor Hes1, which is involved in regulating the segmentation of vertebrate embryos. Oscillations of Hes1 expression levels have been observed in vitro in mouse cell lines, and reproduced using various modelling approaches, including continuous deterministic delay systems, as illustrated with the Lorenz system (Fig. 3a). Designing attractors is thus a necessary step for such oscillations to occur.

The first two of these applications are illustrated with the Lorenz system (Fig. 3b) which has become a canonical example of how sensitivity to initial conditions can give rise to unpredictable behaviour. The model is known to exhibit a chaotic regime with LEs, \( \Lambda = (0.906, 0.0, -14.57) \), for parameter vector \( (\sigma, \rho, \beta) = (10, 28, 8/3) \). Here we

where state variables \( M, P_1, P_2 \), and \( P_0 \), are the molecular concentrations of Hes1 mRNA, cytoplasmic and nuclear proteins, respectively. The parameter \( k_{deg} \) is the Hes1 protein degradation rate that we assume to be the same for both cytoplasmic and nuclear proteins; \( k_i \) is the rate of transport of Hes1 protein into the nucleus; \( P_0 \) is the amount of Hes1 protein in the nucleus, when the rate of transcription of Hes1 mRNA is at half its maximal value; \( \nu \) is the rate of translation of Hes1 mRNA, and \( h \) is the Hill coefficient. For the inference we take, \( \delta \) to be the experimentally determined value of 0.03 min^{-1} (ref. 19).

In Figure 2c, we show the results for the inference using our algorithm on the model shown above. Note that the value inferred for parameter \( k_i \), is significantly lower than the range of values investigated for the continuous deterministic delay model of Momiji and Monk19. Interestingly, repeating the inference with different initial parameter sets leads to similar values of \( k_i \) (\( k_i < 0.01 \)), but to a broad range of values for the other parameters, all of which result in oscillatory behaviour. Our qualitative inference thus suggests that oscillations of Hes1 protein and mRNA levels are strongly dependent on maintaining a low rate of transport of Hes1 protein into the nucleus, and that the dependence on other system parameters is less strong.

As 1/\( k_i \), is the expected time Hes1 spends in the cytoplasm, this corresponds to the delay that had previously been posited to be necessary for such oscillations to occur7. Our approach readily identifies a parameter regime exhibiting oscillatory dynamics without explicitly requiring (discrete) time delays.

Next, we used the qualitative inference result as the basis to estimate the model parameters from the Hes1 data described below. An approximate Bayesian computation algorithm (ABC SMC20), capable of sampling from non-Gaussian and multimodal posteriors, was employed and Figure 2d shows the fits of simulated trajectories to 20 parameters drawn randomly from the resulting posterior distribution; these are in good agreement with the confidence intervals (the blue bands in Fig. 2d), which can be obtained from the time-course data via a Bayesian nonparametric method21. It is worth noting that using the UKF alone, we could in principle consider the LEs and data together to infer parameters that are both qualitatively and quantitatively acceptable. However, by splitting the inference, we take advantage of the strengths of each algorithm within the Bayesian framework; first we exploit the efficiency of the UKF to work with a sophisticated encoding of the desired behaviour that is computationally expensive to calculate; subsequently we use this qualitative information to construct suitable priors for an ABC method capable of dealing with non-Gaussian posteriors.

**Designing attractors.** Although the maximal LE alone is sufficient to encode fixed points, limit cycles and strange attractors, we may include extra target exponents to design the complete Lyapunov function, \( M = -k_{deg} M + 1/(1 + (P_2/P_0)^{1/\nu}) \), (2) \( P_1 = -k_{deg} P_1 + \nu M - k_i P_1 \), (3) \( P_2 = -k_{deg} P_2 + k_i P_1 \), (4)

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The last aspect will have particular appeal to information and communication scientists as such hyper-chaos shares important properties with white noise and potential applications in cryptography and coding theory around.

Finally, our approach can also be used to condition dynamical systems on all manner of observed or desired qualitative dynamics, such as threshold behaviour, bifurcations, robustness, temporal ordering and so on. To rule out that a mathematical model can exhibit a certain dynamical behaviour will, however, require exhaustive numerical sampling of the parameter space; but coupled to ideas from probabilistic computing, our procedure lends itself to such investigations. Both for inference and design problems, we foresee vast scope for applying this type of qualitative inference-based modelling. There is still a lack of understanding about the interplay between qualitative and quantitative features of dynamical systems; this becomes more pressing to address as the systems we are considering become more complicated and the data collected more detailed. Flexibility in parameter estimation—whether based on qualitative or quantitative system features—will be an important feature for the analysis of such systems and to test robustness of qualitative system features systematically.

Methods

Encoding dynamics through Lyapunov exponents. Consider a continuous time dynamical system—similar results hold for the discrete case—described by,

$$\frac{dy}{dt} = f(y),$$

where $f$ is an $n$-dimensional gradient field. To study the sensitivity of $y(t)$ to initial conditions, we consider the evolution of an initially orthonormal axes of $n$ vectors, $y_0$.

For the third application of driving a system into hyper-chaos, we investigate a four-dimensional system with six parameters, whose significance lies in having two very large LEs ($\lambda_e < 10.7741, 12.9798$) and $\lambda_e > 0.4145, 2.6699$) over a broad parameter range. The resulting highly complex deterministic dynamics share statistical properties with white noise, making it attractive for engineering applications such as communication encryption and random number generation. By setting large target values of $\lambda_1$ and $\lambda_5$, we use our method to obtain parameters for which the system displays LEs twice the size of any that had previously been reported.

For the second aspect of the current approach, we are able to do this reliably from random starting positions. The parameter trajectories and evolving attractor of a parameter vector $(a, b, c, d, e, f) = (49.98, 35.86, 30.5, 1.35, 36.6, 33.8)$ and corresponding LEs $(31.8, 16.8, -19.1, -71.4)$. Within a few iterations, our algorithm was able to drive the system towards an attractor characterized by LEs twice the size of any that had previously been reported.

Figure 3 | Designing attractive models. (a) Inferring a complete spectrum. After only 22 iterations, the characteristic ‘butterfly’ strange attractor emerges. The final parameters and LEs are $\sigma = 10.2, \rho = 29.2, \beta = 2.45$ and $(0.899, 2.74 \times 10^{-4}, -14.6)$. (b) A function of the LEs, the Kaplan–Yorke fractal dimension may also be used to specify the desired attractor. Here parameters for a target dimension of 1 are found for the Lorenz system within 20 iterations, giving rise to a limit cycle as required by the theory. (c) Three-dimensional projections of the hyperchaotic system with parameter vector $(a, b, c, d, e, f) = (49.98, 35.86, 30.5, 1.35, 36.6, 33.8)$ and corresponding LEs $(31.8, 16.8, -19.1, -71.4)$. Within a few iterations, our algorithm was able to drive the system towards an attractor characterized by LEs twice the size of any that had previously been reported.
\[ \frac{d\hat{x}_k}{dt} = Df(\hat{y}_k) \cdot \hat{e}_k, \]  
\[ \text{(6)} \]

where \( Df(\cdot) \) is the Jacobian of \( f \) evaluated along the orbit \( y_k \). Equations (5) and (6) describe the expansion/contraction of an \( n \)-dimensional ellipsoid in the tangent space at \( y_k \), and we denote the average exponential rate of growth over all \( t \) of the \( \ell \)th principal axis of the ellipsoid as \( \lambda_{\ell} \). The quantities, \( \lambda_1 \geq \lambda_2 \geq \ldots \geq \lambda_n \), are called the global LEs of \( f \). In particular, the sign of the maximal LE, \( \lambda_1 \), determines the fate of almost all small perturbations to the system's state, and consequently, the nature of the underlying dynamical attractor. For \( \lambda_1 \leq 0 \), all small perturbations die out and trajectories that start sufficiently close to each other converge to the same stable fixed point in state-space; for \( \lambda_1 = 0 \), initially close orbits remain close but distinct, corresponding to oscillatory dynamics on a limit-cycle or torus (for torus, at least one other exponent must be zero); and finally for \( \lambda_1 > 0 \), small perturbations grow exponentially, and the system evolves chaotically within the folded space of a so-called 'strange attractor' (for two or more positive definite LEs, we speak of 'hyperchaos').

In general, nonlinear system equations and the asymptotic nature of the LEs preclude analytic evolution. Instead, various methods of numerical approximation of these quantities, both directly from ODE models and from time-series data\textsuperscript{34-36}, have been developed. In this paper, Lyapunov spectra are calculated using a Python implementation of a method proposed by Benettin et al.\textsuperscript{15} and Shimada and Nagashima\textsuperscript{16} (outlined in the Supplementary Information) for inference of LEs when the differential equations are known.

**Lyapunov spectrum spectrum driven parameter estimation.** Unlike in the case for linear systems, where identifying suitable parameters that produce observed or desired dynamics is trivial, inference for highly nonlinear systems is far from straightforward. Indeed, exact inferences are prohibitively expensive for even small systems, and so a host of different approximation methods have been proposed\textsuperscript{37-39}. In our case, two further complications arise from using LEs to encode the desired behaviour. First, the form of the mapping between model parameters and LEs is not closed, making methods that rely on an approximation of the estimation routine or its derivatives, such as the extended Kalman filter, difficult to apply. Second, LEs are significantly more expensive to compute than more traditional cost functions, ruling out the use of approaches such as particle filtering or sequential Monte-Carlo methods that require extensive sampling of regions of parameter space and calculation of the corresponding LEs at each iteration.

To overcome these challenges, we exploit the efficiency and flexibility of the UKF\textsuperscript{24-26}, seeking here to infer the posterior distribution over parameters that give rise to the desired LEs. Typically, the UKF is applied for parameter estimation of a nonlinear mapping \( g(\cdot) \) from a sequence of noisy measurements, \( y_k \), of the true states, \( x_k \), at discrete times \( k = 1, \ldots, T \). A dynamical state-space model is defined,

\[ \hat{\theta}_k = \hat{\theta}_{k-1} + v_k \]  
\[ \hat{x}_k = g(x_k, \hat{\theta}_k) + w_k \]  
\[ \text{(7)} \]

where \( \sim N(0, Q) \) represents the measurement noise, \( v_\ell \sim N(0, R) \) is the artificial process noise driving the system, and \( g(\cdot) \) is the mapping for which parameters \( \theta \) are to be inferred. The UKF (described in full below) is then characterized by the iterative application of a two-step, 'predict' and 'update', procedure. In the 'prediction step' the current parameter estimate \( \hat{\theta}_k \) is perturbed by the driving process noise \( v_k \) forming a priori estimates (which are conditional on all but the current observation) for the parameter mean and covariance. We denote these as \( \hat{\theta}_k^p \) and \( \hat{P}_k^p \), respectively. The 'update step' then updates the a priori statistics using the further measurement, \( y_k \), to form a posteriori estimates, \( \hat{\theta}_k^w \) and \( \hat{P}_k^w \). After all observations have been processed, we arrive at the final parameter estimate, \( \hat{\theta}_T^w \) (with covariance \( \hat{P}_T^w \)).

A crucial step in the algorithm is the propagation of the prior parameter distribution statistics through the model, \( g(\cdot) \). Assuming linearity of this transformation, a closed form optimal filter may be derived (known as the Kalman filter). However, this assumption would make the algorithm inappropriate for use with the highly nonlinear systems and the choice of \( g(\cdot) \) considered here. It is how the UKF copes with this challenge, namely its use of the 'unscented transform', which makes it particularly suitable for our method of qualitative feature-driven parameter estimation.

The unscented transform is motivated by the idea that probability distributions are easier to approximate than highly nonlinear functions\textsuperscript{8}. In contrast to the Extended Kalman filter where nonlinear state transition and observation functions are approximated by their linearized forms, the UKF defines a set, \( \Theta_0 \), of 'sigma points' — deterministically sampled particles from the current posterior parameter distribution (given by \( \hat{\theta}_k^p \) and \( \hat{P}_k^p \)), that along with corresponding weights, \( \{\omega_0^p, \omega_0^w, \omega_0^k\} \), completely capture its mean and covariance. The sigma points can be propagated individually through the nonlinear observation function, and recomputed to estimate the mean and covariance of the predicted observation, \( y_k \), to third-order accuracy in the Taylor expansion, using the equations given below. Under the approximate assumption of Gaussian prior and posterior distributions (higher order moments may be captured if desired at the cost of computational efficiency), the deterministic and minimal sampling scheme at the heart of the filter requires relatively few LE evaluations at each iteration (\( 2n_r + 1 \), where \( n_r \) is the number of parameters to be inferred). Further, the function that is the subject of the inference may be highly-nonlinear and can take any parametric form, such as a feed-forward neural network\textsuperscript{40}, or as in our case, a routine for estimating the LEs of a model with a given parameter set.

With \( [x] \), denoting the \( \ell \)th column of the matrix \( X \), the UKF algorithm for parameter estimation is given by,

\begin{align*}
\text{Initialize:} & \quad \hat{\theta}_0^w = \hat{E}(\theta), \quad P_0^w = \hat{E}(\hat{\theta}_0^w - \theta) (\hat{\theta}_0^w - \theta)^T
\end{align*}

For each time point \( k = t_s, \ldots, t_e \):

\begin{align*}
\text{Prediction step:} & \quad \hat{\theta}_k^w = \hat{E}(\theta | y_k < a_k) \quad = \hat{\theta}_{k-1}^w \\
& \quad \hat{P}_k^w = P_{k-1}^w - R_{k-1}
\end{align*}

\begin{align*}
\text{Update step:} & \quad \hat{\theta}_k^w = \hat{\theta}_k^w + K_k (y_k - \hat{y}_k) \\
& \quad \hat{P}_k^w = \hat{P}_k^w - K_k P_{k-1}^w K_k^T + Q_k
\end{align*}

where

\[ Y_k = g(x_k, \Theta_k) \]  
\[ \hat{y}_k = \sum_{i=0}^{2} \omega_0^p_i [Y_i] \]  
\[ P_{k0}^w = \sum_{i=0}^{2} \omega_0^p_i ([Y_i] - \hat{y}_k)^T ([Y_i] - \hat{y}_k) + Q_k \]  
\[ K_k = P_{k0}^{-1} \sum_{i=0}^{2} \omega_0^w_i ([Y_i] - \theta_0^w)^T ([Y_i] - \hat{y}_k) \]  
\[ \lambda_k = \lambda_k^{\text{LE}} (L + k\lambda_k - L) \]  
\[ \text{(8)} \]

\[
\begin{align*}
0 &= \frac{\lambda}{L + \lambda}i = 0 \\
0 &= \frac{\lambda}{L + \lambda} + (1 - \alpha^2 + \beta) i = 0 \\
0 &= \frac{L - \lambda}{2(L + A)}i = 1, \ldots, 2L \quad \text{(10)}
\end{align*}

Various schemes for sigma-point selection exist including those for minimal set size, higher than third-order accuracy and (as defined and used in this study) guaranteed positive-definiteness of the parameter covariance matrices\textsuperscript{41-42}, which is necessary for the square roots obtained by Cholesky decomposition when calculating the sigma points. The scaled sigma-point scheme thus proceeds as,

\[ \Theta_k \]  
\[ \hat{\theta}_k^w = \hat{E}(\theta | y_k < a_k) \quad = \hat{\theta}_{k-1}^w + v_k \]  
\[ \hat{x}_k = g(x_k, \hat{\theta}_k^w) + w_k \]  
\[ \text{(9)} \]

\[ \lambda_{\text{target}} = L(\theta_0, \tau_0, \gamma_0) + \lambda_k \]  
\[ \text{(11)} \]

where \( L(\cdot) \) maps parameters to the encoding of the dynamical behaviour (here a numerical routine to calculate the Lyapunov spectrum), \( \lambda_{\text{target}} \) is a constant target vector of LEs, \( y_k \) denotes the initial conditions, and \( g(\cdot) \) is the dynamical system under investigation (with unknown parameter vector \( \theta_0 \) considered as a hidden state of the system and not subject to temporal dynamics). To see how equations (9) and (10) fit the state-space model format for UKF parameter estimation, it is helpful to consider the time series \( \lambda_{\text{target}}, \lambda_{\text{target}} - \lambda_{\text{target}}, \ldots \) as the ‘observed’ data from which we learn the parameters of the nonlinear mapping \( L(\cdot) \). Our use of the UKF is characterized by a repeated comparison of the simulated dynamics for each sigma point to the same (as specified) desired dynamical behaviour. In this respect, we use the UKF as a smoother; there is no temporal ordering of the data supplied to the filter because all information about the observed (target) dynamics is given at each iteration. From an optimization viewpoint, the filter aims to minimize the prediction-error function,

\[ E(\theta) = \sum_{i=1}^{n} [g(\theta, y_0; f) - \lambda_{\text{target}}]^T [g(\theta, y_0; f) - \lambda_{\text{target}}] \]  
\[ \text{(11)} \]
thus moving the parameters towards a set for which the system exhibits the desired dynamic regime.

**Hes 1 quantitative real-time PCR.** Dendritic cells were differentiated from bone marrow, as described previously. Rat IgGl/human IgG fusion protein (R&D Systems) or human IgG1 (Sigma Aldrich) (control samples) were immobilized onto tissue culture plates (10 µg/ml in PBS) overnight at 4°C. Dendritic cells were spun onto the plate and cells were collected at the appropriate time. Total RNA was isolated using the Absolutely RNA micro prep kit (Stratagene). Complementary DNA was generated from 125 ng of total RNA using an archive kit (Applied Biosystems). 1 µl of cDNA was used with PCR Mastermix and TaqMan primer and probe (Applied Biosystems) and analysed on an Applied Biosystems 7500 PCR system. Cycle thresholds were normalized to 18S and calibrated to a PBS-treated control sample for relative quantification.

**Computational implementation.** All routines were implemented in Python using LSODE for integrating differential equations. ABC inference was performed using the ABC-SysBio package. Code is available from the authors on request.

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**Author contributions**

D.S., A.R., M.J.D. and M.P.H.S. designed the research; D.S., P.D.W.K., C.B., T.T., A.R. and S.M. carried out the research; D.S., A.R. and M.P.H.S. wrote the manuscript. All authors have read and approved the final version of the manuscript.

**Additional information**

*Supplementary Information* accompanies this paper at http://www.nature.com/naturecommunications

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