Lineage correlations of single cell division time as a probe of cell–cycle dynamics

Oded Sandler1*, Sivan Pearl Mizrahi1,2*, Noga Weiss2, Oded Agam2, Itamar Simon1§ & Nathalie Q. Balaban2§

Stochastic processes in cells are associated with fluctuations in mRNA1, protein production and degradation2–5, noisy partition of cellular components at division6, and other cell processes. Variability within a clonal population of cells originates from such stochastic processes, which may be amplified or reduced by deterministic factors7. Cell-to-cell variability, such as that seen in the heterogeneous response of bacteria to antibiotics, or of cancer cells to treatment, is understood as the inevitable consequence of stochasticity. Variability in cell-cycle duration was observed long ago; however, its sources are still unknown. A central question is whether the variance of the observed distribution originates from stochastic processes, or whether it arises mostly from a deterministic process that only appears to be random. A surprising feature of cell-cycle-duration inheritance is that it seems to be lost within one generation but to still present in the next generation, generating poor correlation between mother and daughter cells but high correlation between cousin cells8. This observation suggests the existence of underlying deterministic factors that determine the main part of cell-to-cell variability. We developed an experimental system that precisely measures the cell-cycle duration of thousands of mammalian cells along several generations and a mathematical framework that allows discrimination between stochastic and deterministic processes in lineages of cells. We show that the inter- and intra-generation correlations reveal complex inheritance of the cell-cycle duration. Finally, we build a deterministic nonlinear model for cell-cycle inheritance that reproduces the main features of our data. Our approach constitutes a general method to identify deterministic variability in lineages of cells or organisms, which may help to predict and, eventually, reduce cell-to-cell heterogeneity in various systems, such as cancer cells under treatment.

The cell division process has been extensively studied in many systems8,10. Models of cell-cycle durations are based on deterministic equations8. In order to account for cell-to-cell variability, the models typically take stochasticity into account, even in the ‘deterministic growth control model’8. Alternatively, cell-to-cell variability may be due to a few underlying nonlinear dynamic factors, to which noise contribution is small and could, therefore, eventually be controlled. An unresolved central question is whether the observed variability originates mainly from stochasticity, or whether it stems from a deterministic process that only appears to be random, as illustrated in Fig. 1 (ref. 10). Our goal was to measure the variability in cell-cycle durations among thousands of single mammalian cells and to determine whether experiments can distinguish between stochastic processes10 and deterministic nonlinear components12,13.

To characterize the variability in cell-cycle progression at the single-cell level, we used time-lapse microscopy to monitor the total cell-cycle duration of single L1210 lymphoblasts with an accuracy of ±1%. Stably transfected lines with Fucci markers9 also allowed us to monitor G1 and S/G2/M durations. (Fig. 2a). The cells were observed under the microscope for several days (Supplementary Video 1 and Fig. 2b, c), while maintaining constant conditions (Extended Data Fig. 1). The recorded videos were analysed by lineages to derive the total cell-cycle duration ($T^{tot}$), G1 duration ($T^{G1}$) and S/G2/M duration ($T^{G2/M}$) (Fig. 2c and Methods). This analysis resulted, for each lineage, in a series of cell-cycle durations ($T_1, T_2, T_3, \ldots$), with $T_1$ the cell-cycle duration of the mother, $T_2$ of its daughter, $T_3$ of its granddaughter, and so on.

In line with previous studies10,16, we observed a strong correlation of $T^{tot}$ between sister cells ($\rho_{s-s} = 0.71 \pm 0.07, P < 0.002$), whereas the correlation of $T^{tot}$ between mother and daughter cells was close to zero and non-significant ($\rho_{m-d} = 0.04 \pm 0.08, P > 0.2$) (Fig. 2f). We found that $T^{G1}$ and $T^{G2/M}$ had a similar pattern of correlation to $T^{tot}$, namely, sister cells were strongly correlated but mother–daughter cells were not (Fig. 2g). These results initially suggested that a factor inherited at birth determines the cell-cycle duration and that this factor is reset during each division, implying that the inheritance of cell-cycle duration is governed by stochastic processes10. When we extended our analysis to subsequent generations, we found that cousin cells were significantly correlated (Fig. 2f) ($\rho_{c-c} = 0.58 \pm 0.07, P < 0.002$). In particular, we observe that $\rho_{c-c} > |\rho_{m-d}|$, which we call the ‘cousin–mother inequality’, contrary to the expected behaviour $\rho_{c-c} = (\rho_{m-d})^2 \times \rho_{s-s}$ from simple inheritance rules17. A similar unexplained correlation in cell-cycle duration between cousins has been reported in several organisms8,15,16,19.

We performed additional measurements, using different clones and microfluidic devices, in order to rule out the possibility that experimental factors were responsible for the surprisingly high correlation between cousins. In all cases, the cousin–mother inequality was observed (Extended Data Figs 2 and 3a). Additional extensive analysis of the recordings ruled out the possibility that an external experimental factor affected the microenvironment and generated artificial correlations (Fig 3a, b and Extended Data Fig. 3b, c).

We wondered how cousin cells can remain correlated when mothers and daughters are not. High correlation in cell-cycle durations between cousins is an indication of deterministic inheritance and suggests that the initial interpretation of the low mother–daughter correlation as indicating inheritance dominated by simple noise needs to be revised.

We set out to address whether the series of cell-cycle durations along a lineage ($T_1, T_2, T_3, \ldots$) is closer to a stochastic process, or whether it is mainly consistent with a deterministic process. This question has been addressed in the context of dynamical systems, which enable the detection of deterministic tendencies by evaluation of the effective number of factors that underlie the variability (Fig. 1). A small number of effective variables would be the signature of a deterministic process, and a very large number would signify a stochastic process.

The evaluation of the effective number of factors that govern the variability of a time series can be estimated using the Grassberger–Procaccia algorithm19 (Fig. 1 and Supplementary Information). This algorithm has been applied to the analysis of time series in various systems10,21. The effective number of variables is estimated by the

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in Fig. 1) (Figs 1b and 3c). The Grassberger–Procaccia algorithm is shown in Fig. 1g, h on the trivial example of white noise, but the correlation dimension can identify stochasticity also for the more general case of coloured noise, as long as the correlation time is finite (Supplementary Information). In order to further illustrate the power of the Grassberger–Procaccia algorithm on an experimental system known to be governed by stochasticity, we analysed the published data of constitutive fluorescent gene expression in Escherichia coli. Similarly to the random data, the effective number of variables is found to be above 10 (Fig. 3c), as expected from a noisy process with short-range correlations (Supplementary Information).

Applying this algorithm to the series of cell-cycle durations extracted from the time-lapse recording of L1210 lymphoblasts along a lineage ($T_1, T_2, T_3, \ldots$), we found that the effective number of variables is of the order of 3 (Fig. 3c and Extended Data Figs 4 and 5).

This analysis indicated that variability in cell-cycle duration is controlled by a deterministic process with a small number of dynamical factors. Note that in contrast to the typical time series on which the Grassberger–Procaccia analysis has been used, the lineage data provide an independent and more robust indication of deterministic inheritance through the cousin–mother inequality.

In order to illustrate how a deterministic process with a few factors can reproduce the cousin–mother inequality, we searched for a deterministic toy model that fulfils the following requirements, as dictated by our experimental observations: (1) deterministic factors are inherited from mother to daughter; (2) their effect on the cell-cycle duration is non-monotonic, in order to account for the low mother–daughter correlation; and (3) the nonlinear deterministic inheritance does not necessarily reach a fixed point.

A known nonlinear process affecting the cell-cycle duration and fulfilling all of the above requirements is the circadian clock. The coupling between circadian phase and cell cycle has been demonstrated in different organisms, including tissue culture cells, and quantitative characterizations have been carried out in Cyanobacteria. We developed a discrete model of cell-cycle duration inheritance, the ‘kicked cell cycle’ model, the main feature of which is the deterministic influence of the circadian phase at birth on the cell-cycle duration. The kicked cell cycle model predicts that correlations in cell-cycle duration between sisters ($\rho_{s-s}$) should be high, as the cell cycles of sister cells inherit the same phase of the cellular oscillator (Fig. 3d). In contrast, the correlation of cell-cycle duration between mother and daughter cells, $\rho_{m-d}$, is predicted to vary between positive and negative values, depending on the mean cell-cycle duration (Extended Data Fig. 6a). Finally, the model predicts that the cousin–mother inequality holds. Indeed, analysing the Cyanobacteria data confirmed all these predictions (Extended Data Fig. 7).

Next we applied the kicked cell cycle model to mammalian cells using a different set of parameters (Extended Data Table 1 and Fig. 4a–c), reproducing our main results. The model resolves the seemingly paradoxical cousin–mother inequality by showing that deterministic inheritance of cell-cycle duration can result in an apparent absence of correlation between mother and daughter cells (Extended Data Figs 6a and 8). Similar conclusions have been proposed in refs 6 and 25.

In agreement with the model’s predictions, our measurements validate that $\rho_{c-c} > |\rho_{m-d}|$ (Fig. 4c, d). Specifically, for our data as well as for compiled correlations in cell-cycle duration reported for various mammalian cells (Extended Data Table 2), mother–daughter correlations vary between positive and slightly negative values (Fig. 4d), whereas intrageneration correlations in cell-cycle duration are positive and significant. In particular, we were able to run our analysis using cell-cycle duration measurements from a detailed study of EMT6 cells and found that it fits our model’s predictions (magenta dot in Fig. 4d).

The empirical data and modelling presented here reveal that deterministic factors control an important part of cell-cycle variability in mammalian cells. Our analysis shows that the oscillating term of this model results in the high correlation between cousins observed in Cyanobacteria.

Figure 1 | Schematic illustration of stochastic versus deterministic variability. a, A small object’s movement in an empty box. Prediction of its future location requires the knowledge of only its current location and velocity, thus the object’s movement is deterministic, in contrast to the stochastic motion observed in e when the box is filled with a large number of colliding molecules. b, The logistic map (equation 1, see Supplementary Information) as an illustration of a low-dimensional deterministic process resulting in seemingly stochastic output with $a \approx 3.99$. c, Same data as in b plotted in embedding dimension $D_{\text{emb}} = 2$, namely each point is associated with the coordinates $(x_n, x_{n+1})$, revealing its low dimensionality. d, Same data as in b plotted in embedding dimension $D_{\text{emb}} = 3$, namely each point is associated with the coordinates $(x_n, x_{n+1}, x_{n+2})$. These points do not fill the 3D space but rather lie on a one-dimensional trajectory. This dimension is computed by evaluating the typical number of pairs of points inside a sphere whose radius $r$ shrinks to zero. The number of points decreases as $r^{D_{\text{corr}}}$, where $D_{\text{corr}}$ is the correlation dimension. e, Same small object as in a but the box is filled with a very large number of colliding molecules. Now the motion is governed by a very large number of variables thus, the object’s movement is considered stochastic. f, Uncorrelated random numbers time series, $R_n$. g, h, Embedding of the random numbers time series in a higher-dimensional space. In contrast to the logistic map, here the points occupy the same dimension as the space in which they are embedded. Note that this simplified white noise example is given for illustrative purposes only and the more realistic case of coloured noise is discussed in the Supplementary Information.

‘correlation dimension’ which the Grassberger–Procaccia algorithm extracts from the data. Whereas the effective number of variables for simulated normally distributed random data is above 10 (the limit of the analysis) (Fig. 3c), it is found to be 1 for the logistic map series (Eq. 1.
Whether the circadian clock is a key parameter underlying cell-cycle variability in mammalian cells, via the kicked cell cycle model, or other proposed models, such as size control or ageing, remains to be determined in future studies.

We extended our approach to ask if stochasticity dominates in either G1 or S/G2/M phases. We found that both $T_{G1}$ and $T_{G2}$ correlations follow the same pattern as $T_{tot}$, namely that the cousin–mother inequality is satisfied (Fig. 2g), suggesting that deterministic variability is present in both G1 and S/G2/M phases (Extended Data Fig. 8a). Furthermore, the model reproduces the surprising absence of correlation between G1 and G2 (Extended Data Fig. 8b).

The analysis of the lineage correlations, together with the ability to measure the correlation dimension in cell-cycle inheritance, as demonstrated in the present study, should enable discrimination between...
The novelty of the present study, when compared to searches for deterministic chaos in a biological system, is the combination of correlation analysis with intra- and inter-generation correlations providing two independent indicators of deterministic inheritance. When the data are shuffled, both indicators vanish. More generally, the approach taken in this study can be applied to the identification of deterministic components controlling the inheritance along lineages of other phenotypes, such as expression levels, cell size and growth rate. Finally, the realization of the importance of an underlying non-linear process in the determination of cell-cycle duration variability will pave the way for new types of models addressing cell-cycle inheritance.

Online Content Methods, along with any additional Extended Data displays and Source Data, are available in the online version of the paper; references unique to these sections appear only in the online paper.

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Author Contributions O.S. constructed the Fucci cell lines; S.P.M. performed the time-lapse experiments; O.S. and S.P.M. wrote the image analysis codes; N.Q.B., I.S., N.W. and S.P.M. designed the experiments; N.Q.B., I.S., N.W. and S.P.M. wrote the manuscript.

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METHODS

Time-lapse microscopy. A polydimethylsiloxane (PDMS) square mould was filled with medium containing cells (10^4–10^5 cells per ml) and sealed with a coverslip (Supplementary Video 1). Alternatively, cells were introduced in microfluidic devices and placed under a constant flow of pre-conditioned medium. Cells were monitored using our automated microscope system. Fluorescence images were acquired with minimal excitation to minimize bleaching and photodamage. Cells exposed to one-tenth of the integrated illumination did not show measurable growth difference.

Extraction of T^tot, T^G1, T^G2. We used an automatic cell-tracking platform written in MATLAB (MathWorks), which was further developed to allow tracking of L1210 lineages. T^tot was determined from phase-contrast images acquired at ~5 min intervals. Together with the sharp division process of L1210 cells, this resulted in less than 1–2% experimental noise in T^tot. Some of the movies were tracked semi-automatically for supervised analysis using a plugin that we developed for ImageJ (http://rsbweb.nih.gov/ij/). T^G1 was determined from the maximum of the mKO2 signal and T^G2 from the subtraction of T^G1 from T^tot.

Computation of correlation coefficients. Spearman correlation coefficients were computed on the experimental data. To avoid spurious dependencies, we were careful to include only one pair of cells chosen at random from each lineage. Reported values are the mean and s.d. of 100 different samples. In addition, as pointed out in ref. 18, we avoided the bias towards shorter generation times due to artificial ending of the observation time by limiting the analysis to generations for which lineages were completed. Effects of microenvironment were ruled out (Fig. 3a, b). Alternatively, cells were introduced in microfluidic devices, such as previously described31 resulting in a pattern of micro-wells (100 µm depth and 450 µm diameter). The cured PDMS layer was separated from the wafer and exposed for 20 s to air plasma (Harrick plasma oven).

A PET transparent membrane (6-well millicell 1 µm PET. Millipore no. PIR30R48) was separated from the plastic hang and cut to the device dimensions. Flow channel: a thick PDMS layer was patterned with a single ‘snake-like’ channel pattern (100 µm depth, 400 µm width).

Both patterns were created using a mould made of SU-8 photoresist (MicroChem Corp.) on silicon wafers. Photomasks were designed in Gimp and printed on transparency at 5080 dpi (Pageworks). The patterned wafers were treated with HMDS. The PDMS (Sylgard 184, Dow Corning) was mixed according to the manufacturer’s instructions. The mixture was poured onto the wafer and cured overnight at 80 °C.

The cells to be observed were trapped in the microwells of the lower patterned PDMS layer. The supernatant of exponentially growing cells, supplemented with 10% fetal calf serum, was constantly flowed in the single channel of the upper PDMS layer, such that nutrients can diffuse through the membrane to the trapped cells, without disturbing their position. This device was placed under the microscope, and single cells were tracked while being constantly exposed to the flowing medium.

Statistical methods. No statistical methods were used to predetermine sample size.
Extended Data Figure 1 | Mean cell-cycle duration during long-term time-lapse microscopy. Cycle durations were binned into eight bins according to time elapsed from the beginning of the experiment to the midpoint of the cell cycles ($T_{\text{mid}}$). For each bin the mean and s.d. were calculated. Both fluorescence and bright-light exposure were minimized to prevent lengthening of the cell-cycle duration. $n = 526$; error bars represent the s.d.
Extended Data Figure 2 | Lineage correlations in different strains and clones. Bar graphs of the measured correlations coefficients for $T^*$ of pairs of mother–daughter (red), sister (blue) and cousin (purple) cells, in different cell lines: two different clones of L1210 Fucci (n = 423, 432) and a wild-type (WT) L1210 (n = 283). The cousin–mother inequality is observed in all cases. Data are mean and s.d. of 100 independent random samples from the data set, as described in the online methods.
Extended Data Figure 3 | No spatial effect detected on the cell-cycle duration.  

**a**, Lineage correlations in microfluidic devices (clone2) (Methods). Cells are monitored under constant media flow, keeping the sample in constant conditions while washing away potential by-products of the cells’ metabolism. Correlation between cousins remains higher than mother–daughter correlation, ruling out micro-environment bias ($\rho_{m,d} = 0.3 \pm 0.03$; $\rho_{s-s} = 0.64 \pm 0.01$; $\rho_{c-c} = 0.57 \pm 0.05$; $n = 381$; standard deviations represent 100 independent random samples from the data set, as described in the online methods).

**b**, A schematic representation of a cousin quadruplet. **c**, Cell-cycle duration differences in near and far cousin pairs. No significant difference is found. ($n = 66$; one-tailed Wilcoxon signed rank test, $\alpha = 0.05$, $P > 0.15$).
Extended Data Figure 4 | Correlation dimension. a, Computed dimension versus $D_E$ for a random series (red); L1210 cell-cycle duration data (blue); and the kicked cell cycle model (equations 1–4 (see Supplementary Information); green). b, Correlation dimension for surrogate data obtained from random shuffling of the cell-cycle durations. The mean and s.d. of 59 randomly shuffled data are shown (green), showing that the saturation in the correlation dimension observed for the experimental data (blue) is due to a deterministic process. c, Correlation dimension for random data (red) and data from a simulation of the additive model developed by Cowan and Staudte (green).
Extended Data Figure 5 | Correlation-dimension analysis. The fraction of points closer than a distance $r$, $C(r)$, is plotted versus $r$, on a log–log scale. $C(r)\propto r^{d_{corr}}$ for small values of $r$. Therefore, the correlation dimension $d_{corr}$ is the saturation of the slope of $\log(C(r))$ versus $\log(r)$, with increasing embedding dimension $D_E$. a, Experimental data; b, Simulation data of the kicked cell cycle model. Note the saturation of the slope at $D_E = 3$ and 4. c, Normally distributed random data with same mean and s.d. as experimental data, $n = 236$. 
Extended Data Figure 6 | Inter-generation correlation. **a, b**, Simulation results of the kicked cell cycle model (equations 1–4). **a**, Pearson correlation of mother and daughter cells ($\rho_{m-d}$) is predicted to vary between negative and positive values, depending on $k$ and $T_0$. **b**, Grandmother–granddaughter correlations ($\rho_{gm-gd}$) follow a similar pattern, namely correlations that are close to zero, but can vary between slightly negative and positive values, as observed experimentally. The simulations were run on 300 lineages. **c**, Correlation plot of experimentally observed total cell-cycle duration $T_{tot}$ of grandmother and granddaughter cells (clone2) s.d. of 100 independent random samples from the data set, as described in the online methods is 0.06. Spearman; $\rho_{gm-gd} = 0.22 \pm 0.06$, $n = 380$. 

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Extended Data Figure 7 | Total cell-cycle duration ($T_{\text{tot}}$) measurements and circadian phase at birth in Cyanobacteria. Data of circadian phase and cell cycles of single *Synechococcus elongatus* cells from 29 lineages was obtained from Yang *et al.*\(^a\). a, Mother–daughter correlation ($\rho_{m-d}$); b, Sister–sister correlation ($\rho_{s-s}$); c, Cousin–cousin correlation ($\rho_{c-c}$). Asterisks denote significant ($P < 0.002$) Spearman correlations. d, Cell-cycle duration versus circadian phase. Each dot represents a cell’s circadian phase at birth and its cell-cycle duration. Experimental data (blue) and simulation (red). The black line denotes the expected trend of the model (equation S, see Supplementary Information). Parameters used for the simulation are shown on the right.
Extended Data Figure 8 | Simulation results of the kicked cell cycle model of G1 and G2 durations fit the experimental observations. a–c, Pearson correlations of simulated data of the total ($T_{\text{tot}}$), G1 ($T_{\text{G1}}$) and G2 ($T_{\text{G2}}$) durations between mother-daughter cells (red), sisters (blue) and cousins (purple) (equations 6–8, see Supplementary Information). Parameters as in Extended Data Table 1; $\beta = 0.07$. d, Typical plot of the simulated data for $T_{\text{G1}}$ versus $T_{\text{G2}}$ (in units of $T_{\text{osc}}$). The low correlation ($-0.18; P=0.07$) despite the deterministic inheritance is consistent with the experiments: the correlation coefficients from 4 independent experiments range from $-0.4$ to $0.17$. 

Extended Data Table 1; $\beta = 0.07$. d, Typical plot of the simulated data for $T_{\text{G1}}$ versus $T_{\text{G2}}$ (in units of $T_{\text{osc}}$). The low correlation ($-0.18; P=0.07$) despite the deterministic inheritance is consistent with the experiments: the correlation coefficients from 4 independent experiments range from $-0.4$ to $0.17$. 

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Extended Data Table 1 | Parameters used for the simulations presented in Fig. 3 (equations 1–4)

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$T_0$, the mean cell cycle duration; $\alpha$, the strength of the direct inheritance of the mother's cell cycle duration; $k$, the strength of the coupling to the external oscillator; $T_{osc}$, the period of the cellular oscillator; $\delta$, the strength of the asymmetry between sisters; $\beta$, the relative effect of the asymmetry on cell cycle duration.
Extended Data Table 2 | A literature compilation of correlation coefficients for mother–daughter cells and sister cells

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Note that whereas sister–sister correlations are high and positive, mother–daughter correlations vary between negative and positive values, in accordance with the kicked cell cycle model. It should be noted that the correlation coefficients are calculated in various manners. Also, spurious dependencies were not always avoided. Gen, generation number; NA, data not available.