

Eden model with nonlocal growth rules and kinetic roughening in biological systems

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We investigate an off-lattice Eden model where the growth of new cells is performed with a probability dependent on the availability of resources coming externally towards the growing aggregate. The concentration of nutrients necessary for replication is assumed to be proportional to the voids connecting the replicating cells to the outer region, introducing therefore a nonlocal dependence on the replication rule. Our simulations point out that the Kardar–Parisi–Zhang (KPZ) universality class is a transient that can last for long periods in plentiful environments. For conditions of nutrient scarcity, we observe a crossover from regular KPZ to unstable growth, passing by a transient consistent with the quenched KPZ class at the pinning transition. Our analysis sheds light on results reporting on the universality class of kinetic roughening in akin experiments of biological growth.

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I. INTRODUCTION

Pattern formation in biological growth is a nonequilibrium process that has attracted a lot of attention [1–3]. Particular interest is given to the rough interfaces of compact and spherical patterns observed in bacterial colonies [4–8] and clusters of normal [9–11] and tumor [12,13] cells grown on culture under controlled experimental conditions.

The Eden model [14] is a benchmark of stochastic processes, in the important class of growth models on expanding substrates [15–21], which forms radial clusters with irregular (fractal) borders. In this model, new cells are irreversibly added at random positions of the neighborhood of previously existent cells. Off-lattice simulations of the radial growth of the Eden model [22–26] show that it belongs to the Kardar–Parisi–Zhang (KPZ) [27] universality class introduced with the equation

$$\frac{\partial h}{\partial t} = F + v\nabla^2 h + \frac{\lambda}{2} |\nabla h|^2 + \eta(\mathbf{x}, t) \quad (1)$$

in studies of nonequilibrium kinetic roughening. In Eq. (1), h is the distance to the initial d -dimensional flat substrate, η is an uncorrelated Gaussian noise given by $\langle \eta(\mathbf{x}, t)\eta(\mathbf{x}', t') \rangle = 2D\delta^d(\mathbf{x} - \mathbf{x}')\delta(t - t')$, and F is a constant flux driven the surface front. The Laplacian accounts for surface tension while the quadratic term produces an excess velocity and represents lateral growth along the normal direction in the substrate, a hallmark of the KPZ universality class. For radial growth the height is replaced by the distance r to the origin, is where the process usually starts. The Eden model is a Markovian, local growth process just as the KPZ equation. If the white noise of Eq. (1) is replaced by a position-dependent noise $\eta_q(\mathbf{x}, h)$ we obtain the quenched KPZ (qKPZ) equation [28,29]

$$\frac{\partial h}{\partial t} = F + v\nabla^2 h + \frac{\lambda}{2} |\nabla h|^2 + \eta_q(\mathbf{x}, h). \quad (2)$$

In the qKPZ equation, the surface can be pinned if the driving force is below a threshold F_c [29].

The basic characterization of self-affine kinetic roughening can be done by means of the growth, roughness, and dynamical exponents β , α , and z , respectively. The first one is related to the evolution of the variance of the surface radii (or heights in a flat initial condition) given by

$$W^2 = \langle r^2 \rangle_c = \langle r^2 \rangle - \langle r \rangle^2 \sim t^{2\beta}, \quad (3)$$

where the notation $\langle r^n \rangle_c$ represents the n th cumulant of r averaged over both the whole surface and independent samples. In the absence of anomalous scaling [30], the second exponent gives the point-to-point fluctuations along the surface and can be calculated from the local interface width within sectors¹ of length l as $w_{\text{loc}}^2 \sim l^{2\alpha}$ [29]. Finally, the third exponent gives the spreading of the characteristic surface correlation length as $\xi \sim t^{1/z}$. In case of self-affine growth the exponents obey the scaling relation $\alpha = \beta z$ [29]. The KPZ equation has exponents $\beta = 1/3$, $\alpha = 1/2$, and $z = 3/2$ in $d = 1$ [27], which are observed in numerical simulations of several models [2,29]. These exponents also hold for qKPZ equation above the critical driving force, $F > F_c$. Exactly at the pinning transition, the exponents are given by $\alpha \approx \beta \approx 0.633$ [29,31] which are related to the directed percolation universality class [32].

A breakthrough in the field was surveyed by the exact one-point solutions of the one-dimensional KPZ equation [33–36]. It was shown that a surface point asymptotically evolves as²

$$r \simeq v_\infty t + s_\lambda (\Gamma t)^\beta \chi, \quad (4)$$

¹For a flat substrate of constant size L , the roughness exponent can be defined in terms of the asymptotic value of the interface width that saturates at long times as $W_{\text{sat}}^2 \sim L^{2\alpha}$ [29]. However, in the inflating geometry investigated in the present work, the interface width does not saturate and this definition loses meaning. See also discussions in Refs. [15,21].

²The ansatz of Eq. (4) was first considered in Ref. [37] and obtained later in analytical solutions of the polynuclear growth model [38] and single step model [39]. Chronological events related to the progress of the KPZ universality class can be found elsewhere [40].

where $s_\lambda = \text{sgn}(\lambda)$, v_∞ is the asymptotic average velocity of the surface, Γ is a system-dependent parameter, and χ is a stochastic variable that follows the Tracy–Widom (TW) probability distribution function [41] of the largest eigenvalue of the Gaussian unitary ensemble (GUE) for radial growth (or Gaussian orthogonal ensemble for flat geometries).

Contrasting with the plenty of models reporting great accordance with the KPZ exponents in $d = 1$ [2,29], the experimental counterparts were just a few [42–44]. The situation has changed recently after a thorough statistical analysis of patterns produced between distinct turbulent phases of liquid crystals [45–47] which was followed by other experiments reporting KPZ exponents [9,10,13,48–50]. Regarding biological growth, essentially all experimental essays on compact bacteria colonies [4,5,7,8] or cell aggregates [12,51] ruled out the KPZ universality class until quite recently when *in vitro* experiments with eukaryotic cells; namely, *Vero* [9,10] and cancer HeLa [13] cells, yielded exponents in pretty good agreement with the KPZ class. The necessary conditions to observe the KPZ exponents are high renewal rate of the culture medium granting sufficient nutrients for cells and removing the waste products produced by the cellular processes and soft medium permitting cell motility. When the same cell colonies are grown on highly viscous gelled media, the exponents change to $\beta \approx 0.75$ and $\alpha \approx 0.63$, which were associated with the qKPZ class at the pinning transition [11].

A fundamental difference between the Eden model and biological growth is the locality inherent to the former, which is generally absent in the latter. The cell replication and motility depend on several factors, including nutrient resources and intercellular signaling mediated by proteins [52]. The chemicals diffuse and react (are absorbed or released by cells) in a culture medium such that cellular responses are diffusion limited and, in principle, nonlocal processes. So, the experimental evidence for KPZ presented by Huergo *et al.* [9,10,13] is, in principle, surprising and one would wonder how sensitive to the experimental conditions is this kind of experiments.

In this paper, we tackle this problem investigating an off-lattice Eden model with a nonlocal growth rule, in which the replication of a cell depends on the empty space bridging its position at the colony and the outer medium of the culture. This simple shadowing model mimics inward nutrient diffusion and was introduced in Ref. [8] for the modeling of bacteria colonies. We observe that the KPZ regime can be seen for long times if the shadowing effects are weak. Under resource scarcity a crossover from regular KPZ to unstable growth passing by a transient consistent with the qKPZ class at the pinning transition can be observed. Therefore our results help to understand the recent observations of KPZ class on biological growth [9–11,13].

The sequence of the paper is organized as follows: The model and its computer implementation are presented in Sec. II while the results obtained from numerical simulations are presented in Sec. III. Our conclusions and prospects are drawn in Sec. IV.

II. MODEL AND METHODS

We perform simulations in two dimensions of a modification of the off-lattice Eden model introduced in Ref. [24].

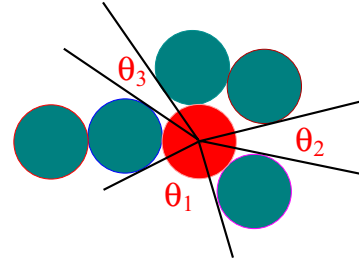


FIG. 1. Determination of the aperture angle Θ_s ruling the replication probability of the model and given by Eq. (5). The red cell is the replicating one. The angle is given by the sum of all available apertures, $\Theta_s = \sum_i \theta_i$.

The cells are represented by discs of diameter $a = 1$. The simulation starts with a single cell at the origin. New cells are added one at a time according to the following rules: A cell of the aggregate is chosen at random with equal chance and accepted with probability P (originally we have $P = 1$ [24,26]). A randomly selected position, tangent to the parent cell, is chosen and a daughter cell is added at this position if this attempt does not produce an overlap with any other cell. The time is incremented by $\Delta t = 1/N_{\text{cell}}$, where N_{cell} is the number of cells in the aggregate, independently of whether a new cell was added.

The nonlocal effects are included with the probability

$$P = 1 - \exp\left(-A_s \frac{\Theta_s}{2\pi}\right), \quad (5)$$

where Θ_s is the total local aperture angle defined as the fraction of rays emanating from the center of the progenitor cell that do not intersect the aggregate, as illustrated in Fig. 1. The parameter A_s controls the shadowing-effect strength. This probability simulates in a simple fashion the dependence on the nutrients that are scarcer at the innermost regions of the aggregate. The higher the value of A_s , the higher the density of nutrients, implying that a small value of A_s would require a large free region to permit replication.

We consider two types of simulations. In the first one, we run 2000 samples and clusters with diameter $10^3 a$. In the second one, 200 samples and a diameter of $5 \times 10^3 a$ are used. Simulations in the second group were optimized by removing from the list of cells elective for replication those that did not replicate after $M = 40$ attempts. We varied this number of attempts and observed that simulations become independent of this parameter for $M \geq 40$. In both cases, the outer borders are converted into single-valued profiles with respect to the angle, permitting the analysis of self-affine surfaces.

Figure 2 shows three aggregates for different values of A_s . Spherical aggregates with rough borders, resembling those of the original Eden model, are obtained for large values of A_s or, equivalently, a weak shadowing effect. For small A_s , where shadowing is strong, the surface presents more overhangs forming protrusions that resemble unstable growth of reaction-diffusion models with explicit modeling of nutrient concentration fields by means of continuous diffusion equations [53–56].

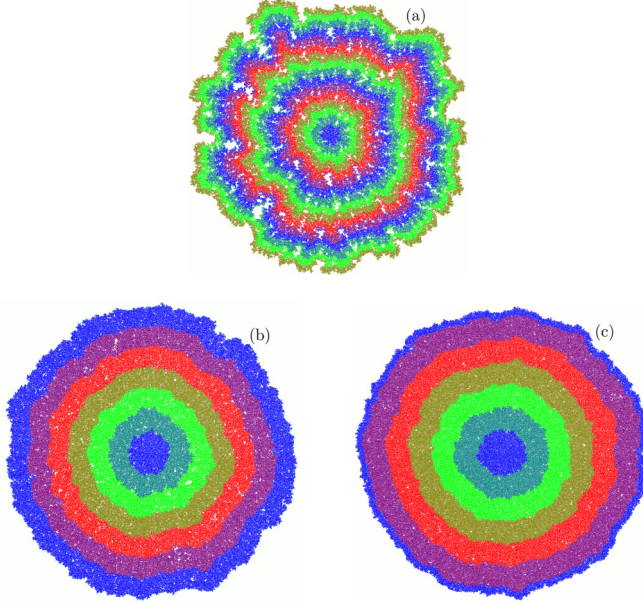


FIG. 2. Aggregates for different levels of shadowing: (a) $A_s = 1$ (strong), (b) $A_s = 5$ (intermediary), and (c) $A_s = 9$ (weak). Colors change every 150 time units. Square regions correspond to a length $1000a$. Optimizations were not used in these simulations.

III. RESULTS

The interface velocity in the KPZ regime given by Eq. (1) reads

$$v = \frac{d\langle r \rangle}{dt} = v_\infty + \beta \Gamma^\beta t^{-1+\beta}, \quad (6)$$

so that velocity plotted against $t^{-1+\beta}$ should be a linear curve. These plots are shown in Fig. 3 using $\beta = \beta_{\text{KPZ}} = 1/3$ for all investigated parameters. We can see the linear behavior expected in the KPZ regime for weak shadowing (large A_s) which means a correction $t^{-2/3}$ in the velocity. For strong shadowing, corrections in the asymptotic velocity are negligible, being apparently null and corresponding to a non-KPZ regime. For the investigated range of the parameter A_s , the asymptotic velocity depends on this parameter as

$$v_\infty \simeq v_\infty^{(\text{Eden})} - 0.525 \exp(-0.458A_s), \quad (7)$$

where $v_\infty^{(\text{Eden})} = 0.51371$ is the asymptotic velocity of the pure Eden model [26]. This exponential dependence of the asymptotic velocity with the shadowing parameter A_s can be seen in Fig. 3(b).

If the KPZ ansatz given by Eq. (4) holds, skewness and kurtosis defined as

$$S = \frac{\langle r^3 \rangle_c}{\langle r^2 \rangle_c^{3/2}} \text{ and } \mathcal{K} = \frac{\langle r^4 \rangle_c}{\langle r^2 \rangle_c^2}, \quad (8)$$

respectively, should asymptotically provide universal cumulant ratios $\mathcal{S}_{\text{GUE}} = 0.2241$ and $\mathcal{K}_{\text{GUE}} = 0.09345$ corresponding to the GUE-TW distribution [38,47]. From Fig. 4, which shows skewness and kurtosis against time for different values of A_s , we observe a convergence to the KPZ cumulants at the longest times we investigated only for the weakest shadowing case. Oppositely, convergence to a constant value was not

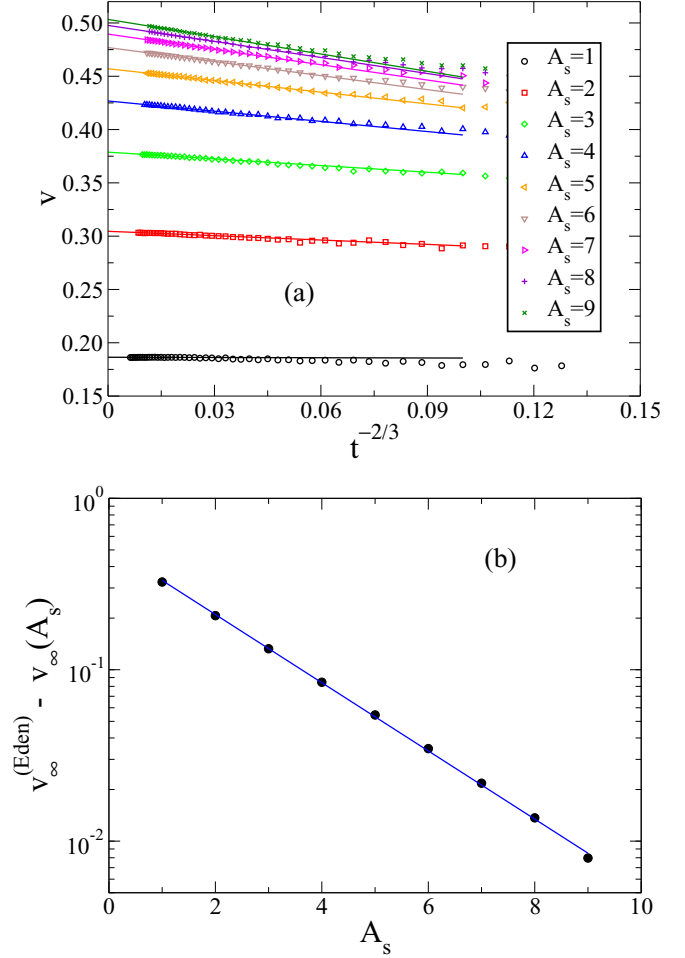


FIG. 3. (a) Surface velocity against $t^{-2/3}$ for different values of the parameter A_s . Lines are linear regressions. (b) Asymptotic interface velocity for the modified Eden model as a function of the shadowing parameter. The line is an exponential regression. Optimizations were not used in these simulations.

observed for strong shadowing effects, here represented by $A_s = 1$. In the moderate shadowing regime $A_s = 3$ to 5 , the skewness exhibits a plateau during some time followed by a deviation at long times, as observed in the strong-shadowing regime. So, our results for intermediate shadowing suggest that the KPZ regime could also be transient for $A_s = 9$ or more generally for any finite A_s . However, this transient would be extremely long and the crossover to an unstable growth regime would not be attainable in doable simulations or experiments, in consonance with the experimental reports of Huerdo *et al.* [9,10,13].

The interface width (3) is expected to scale as $W \sim t^\beta$. Figures 5(a)–5(c) show the evolution of the interface width for distinct shadowing strengths. A local slope analysis provides an effective growth exponent, defined as $\beta_{\text{eff}} = d \ln W / d \ln t$ [26], shown in Fig. 5(d). For weak shadowing, represented by $A_s = 9$ in Fig. 5(c), we obtain $\beta = 0.34(1)$ at the late time plateau of the effective exponent, which is in agreement with the KPZ value $1/3$. For high shadowing, represented in Fig. 5(a), we see a initial regime consistent with Poissonian random growth represented by the exponent $\beta = 1/2$ [29]. For

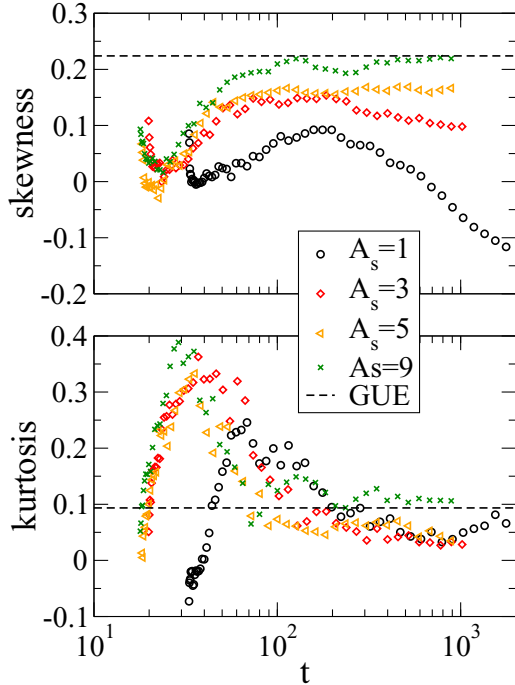


FIG. 4. Evolution of the skewness and kurtosis for different shadowing strengths. Dashed lines are the values of the GUE-TW distribution expected for KPZ on a growing circular geometry [45]. Optimizations were not used in these simulations.

intermediate time a regime consistent with the qKPZ exponent $\beta = 0.633$, manifested as a short plateau or, strictly, an inflection point in the local exponent analysis, is observed. A clear deviation from the scaling regime towards an unstable growth, featured by a large growth exponent, is observed at long times. This transient qKPZ scaling is explained by metastable pinning points which appear in the surface due to the shadowing mechanism; see voids in Fig. 2(a). These pinning points play the role of a quenched disorder for some time. After sufficient

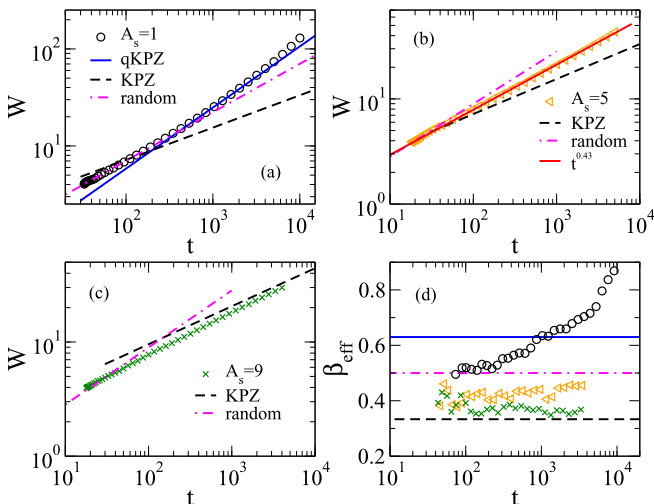


FIG. 5. (a)–(c) Interface width against time for three levels of shadowing and the (d) effective growth exponent $\beta_{\text{eff}} = d \ln W / d \ln t$. Lines represent scaling laws of KPZ ($t^{1/3}$), qKPZ ($t^{0.633}$), and random deposition ($t^{1/2}$) growth regimes. Optimized simulations were used.

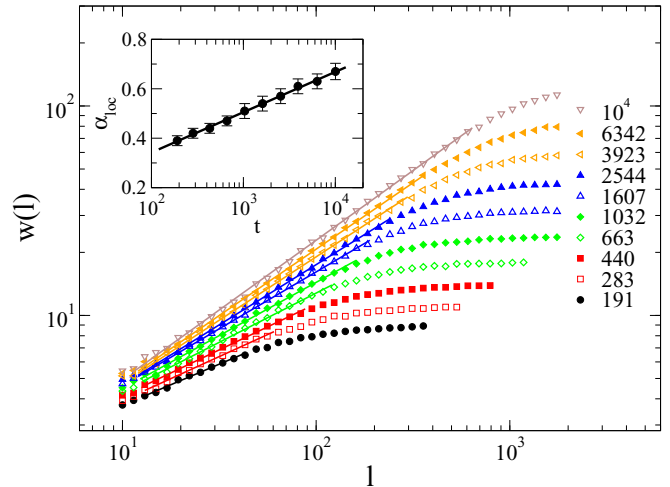


FIG. 6. Local interface width for different times indicated in the legend using a high shadowing parameter $A_s = 1$. Lines are power-law regressions. Inset shows the local roughness (Hurst) exponent and the solid line is a logarithmic regression $\alpha_{\text{loc}} = 0.0158(9) + 0.071(1) \ln t$. Optimized simulations were used.

time, tips in the surface start to advance around the pinning points and the dynamics undergoes a crossover to unstable growth. For moderate shadowing, represented by $A_s = 5$ in Fig. 5(b), the growth exponent quickly deviates from the KPZ and settles on a nontrivial exponent $\beta \approx 0.43(2)$ for the whole time interval we investigated. We expect that this would also deviate towards an unstable growth regime with large β if longer times could be attained.

The large growth exponent can also indicate anomalous scaling [30,57–59] associated with a nonlocal unstable growth [60]. For example, the Matthew effect in which tips grow faster than grooves amplifying differences in the interface, a mechanism which is present in our model, can be associated with anomalous scaling and be misleadingly mixed up with qKPZ behavior [61]. To investigate the presence of anomalous scaling, we analyzed the interface width $w(l, t)$ within windows of size l , which is shown in Fig. 6 for the case of high shadowing ($A_s = 1$). For anomalous scaling one expects $w(l, t) \sim l^{\alpha_{\text{loc}}} t^{\kappa}$ where α_{loc} is the Hurst exponent [29] and $\kappa = (\beta z - \alpha_{\text{loc}}) / z$ where $\alpha_{\text{loc}} = \beta z$ restores the normal scaling. For short times (and consequently short interface lengths) we see an apparent anomalous scaling where the curves are shifted upwards as time is increased suggesting $\kappa > 0$. However, the local roughness exponents for different times, shown in the inset of Fig. 6, is increasing logarithmically within the range $0.39(2) < \alpha_{\text{loc}} < 0.67(3)$ for the time interval $191 < t < 10^4$. Notice that, for the largest times we were able to simulate, the exponent is consistent with the qKPZ exponent $\alpha_{\text{qKPZ}} = 0.633$. The Hurst exponent continues increasing for longer times and this system may present a super-roughness regime with $\alpha_{\text{loc}} = 1$ and $\alpha > 1$ in the limit of very large times, as reported for other systems with morphological instabilities [58,61,62].

IV. CONCLUDING REMARKS

Recent experiments involving growth of cell aggregates in dish cultures [9,10,13] have provided the realization of

the exponents associated with the kinetic roughening of the KPZ universality class including the version with quenched noise (qKPZ) at the pinning transition [11]. These findings are not trivial for two reasons: First, because cell growth is usually mediated by chemical signaling and nutrient diffusion being, consequently, a nonlocal process at odds with the KPZ equation and other models belonging to this class. Second, the realization of the qKPZ class without a tuning parameter to drive the systems towards a pinning transition. This motivated us to investigate an off-lattice Eden model with nonlocality introduced by shadowing effects which mimic the competition for nutrients diffusing from the outer region of the cell aggregate.

We observed a growth regime in agreement with the KPZ class, including the exponents, dimensionless cumulant ratios, and corrections in the average interface velocity, for the weak-shadowing effect, which represents an environment with many resources for cell replication. However, an initial random growth that undergoes a crossover to unstable growth at asymptotic long times is observed for the high-shadowing effects (limited resources). Interestingly, a transient regime with exponents consistent with the qKPZ class is observed in limited-resource regimes. Our results indicate that the KPZ regime is transient and an unstable growth, possibly passing by a qKPZ regime, is expected at long times. The qKPZ transient is due to the formation of metastable pinning points caused by the shadowing mechanism introduced with the models. The actual universality class of this nonlocal Eden model needs further theoretical investigations. One natural possibility is to

consider nonlocal KPZ equations [63–65], as recently done in the context of nonuniversal biological growth [8].

Our numerical simulations support the experimental evidence for the KPZ class in cell aggregates grown in culture, in which a constant replacement of the culture medium, providing thus sufficient nutrients and removing cell waste, was necessary. The qKPZ exponents are expected to take place at the pinning-depinning transition [29] but they have been reported in several experiments, in which the pinning could be justified only dynamically [11,48–50]. The fact we observed a transient behavior consistent with qKPZ in our nonlocal growth model without an explicit quenched disorder can be an alternative or complementary explanation for these experiments. Finally, our analysis was inspired in biological growth but not restricted to it. So, we expect that our results can potentially be of interest for other problems involving asymptotic unstable growth.

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