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Commentary: The Dynamics of Aerotaxis in a Simple Eukaryotic Model

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A Commentary on

The Dynamics of Aerotaxis in a Simple Eukaryotic Model

by Biondo, M., Panuzzo, C., Ali, S. M., Bozzaro, S., Osella, M., Bracco, E., and Pergolizzi, B. (2021). *Front. Cell Dev. Biol.* 9:720623. doi: 10.3389/fcell.2021.720623

We read with interest the article by Biondo et al. (2021) in *Frontiers in Cell and Developmental Biology*, “*The Dynamics of Aerotaxis in a Simple Eukaryotic Model*.” Reproducing the confinement assay we published in eLife earlier this year (Cochet-Escartin et al., 2021) with the same cell line, they found the same emergent behavior, i.e., the propagation of a ring of cells, which they named corona, from a dense, confined colony through the self-generation of oxygen gradients by cell consumption. The authors claimed that cell division plays no role in the phenomenon, whereas in our study, we insisted on its important role.

This message is wrong. In this commentary, we first clarify that ring formation is independent on cell division but that ring propagation over long times depends on it. Second, we discuss the possible experimental biases that may have led the authors to this conclusion.

Cell division is not necessary for ring formation but is necessary for its sustained propagation.

Biondo et al. observed exactly the same collective phenotype as us for the confined colony in a starving buffer that prevents cell division. A ring forms internally, but as soon as it reaches the colony edge (at ~6 h), it stops and cells aggregate (compare Movie 3 of Biondo et al. with our movie M6 and Figure 5; Supplementary Figure 2, Cochet-Escartin et al.). In contrast, in a nutrient medium, the ring propagates far away from the initial colony for days (see **Figure 1A** below). Biondo et al. neither commented on this fundamental difference between the two conditions nor on our model that demonstrates that cell division is necessary to maintain ring propagation even if it contributes little to the expansion speed (Figures 5A,B and Eq. 6, Cochet-Escartin et al.). Independently of any model, a simple mass balance equation for the total cell number N with N_B cells in the bulk region (core) and N_R cells in the ring region invalidates Biondo’s assertion that division plays no role:

$$N(t) = N_B(t) + N_R(t) = \rho_B \pi (R(t) - L)^2 + \rho_R 2\pi R(t)L \quad (1)$$

Using the experimental observations (Figures 1D,E, Supplementary Figure S3B in Cochet-Escartin et al., **Figures 1B–D** below) that the ring width L and density ρ_R and bulk density ρ_B are constant, and that the ring radius R is expanding at constant speed $R(t) = R_0 + \sigma t$, we predict that $N_B(t)$ increases faster with time (i.e., as $R^2 \sim t^2$) than $N_R(t)$ (i.e., as $LR \sim t$). Experimentally, up to 30 h, $N_B(t)$ increases faster than linearly with time while N_R increases linearly (**Figure 1C**). Initially $N_B/N_R = 1$, but after 24 h, $N_B/N_R = 1.8$, and after 47 h, $N_B/N_R = 2.8$ (**Figure 1C**). Hence, N_B largely contributes to the overall cell number increase $N(t)$. By comparison, Biondo et al. assume a constant $N_R(t)$, and they do not consider bulk cells at all.

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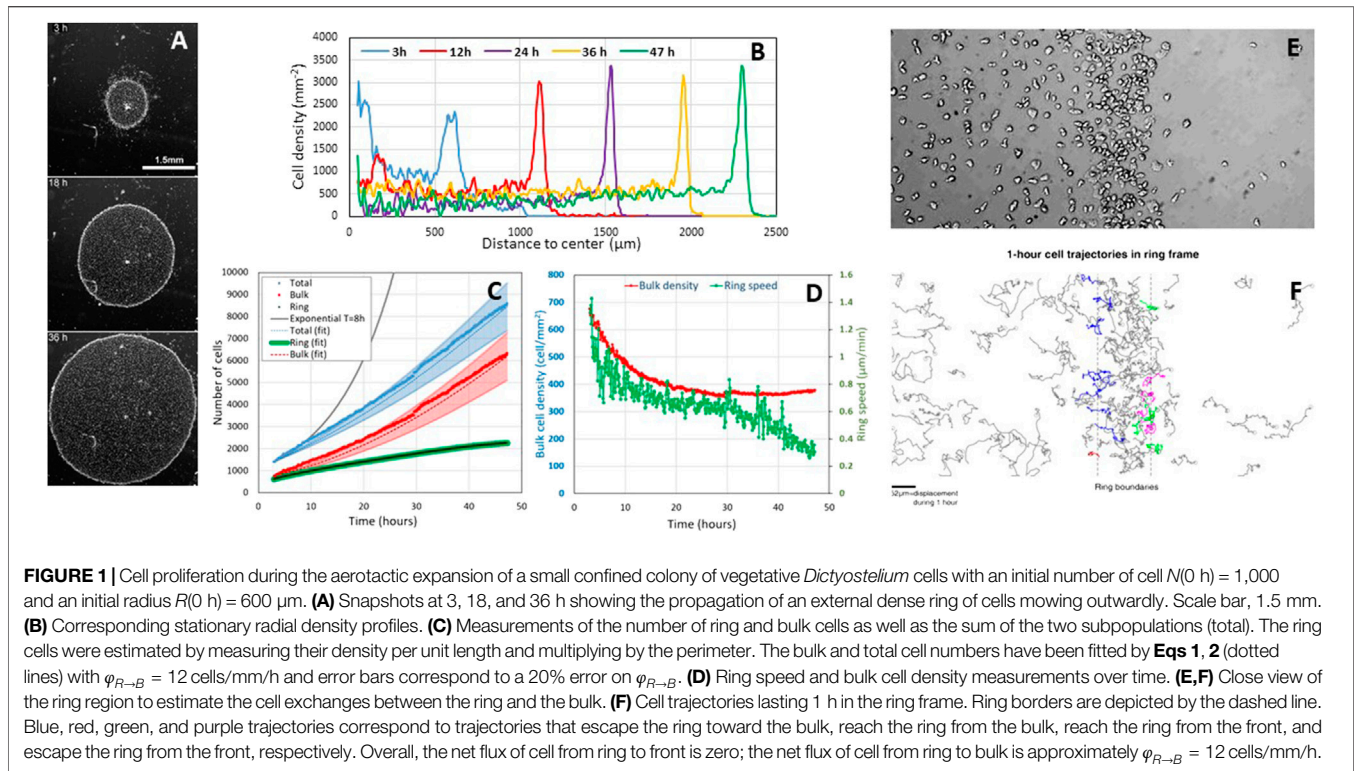
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Cell divisions hold in the ring. Our confined colony grows slower than exponentially (see solid black line with a typical 8 h doubling time (d’Alessandro et al., 2016) in **Figure 1C**), but it grows (i.e., $N(47\text{ h})/N(0\text{ h}) = 8.5$). In Cochet-Escartin et al., we propose a go-or-grow model where aerotaxis holds at low O_2 and cell division at high O_2 . The threshold is around 1% O_2 as estimated by direct aerotaxis investigations using microfluidic devices (Cochet-Escartin et al.) and from literature values for cell division in hypoxic conditions (Schiavo and Bisson, 1989; West et al., 2007). Such value corresponds to the O_2 level measured in the ring (Cochet-Escartin et al.). Hence, divisions occur mostly in the ring, but ring cells are constantly transferred to the bulk to maintain a constant ρ_B while R is increasing. This transfer occurs in our models (see Figure 7 of Cochet-Escartin et al.), but perhaps it was not sufficiently supported by data. In **Figures 1E,F**, we present manually tracked trajectories in the ring frame. A few ones displayed with a green or purple color enter or escape the outward ring position, canceling any ring-to-front flux. Far more trajectories are directed backward (i.e., ring to bulk, in blue). Interestingly, the measured flux of such a cell transfer, $\varphi_{R \rightarrow B} = 12\ \text{cells}/\text{mm}/\text{h}$, explains fairly well the bulk cell number increase using the following equation:

$$dN_B = 2\pi R \varphi_{R \rightarrow B} dt \quad (2)$$

The fit is displayed in **Figure 1C**.

Biondo et al. may have caught a transient regime only. Biondo et al. measured 3% and 5% O_2 in the bulk and ring regions, respectively (Supplementary Figure S1). Above 2% O_2 , aerotaxis should not hold (Cochet-Escartin et al.); the division

rate is fairly the same as in normoxic conditions (Schiavo and Bisson, 1989; West et al., 2007). A possible reason for this discrepancy is that O_2 is overestimated. Their measurements were performed with a commercial sensing film that is not compatible with transmission microscopy, contrary to the technology we developed in Cochet-Escartin et al. They may have a different confinement on plastic (their usual experimental condition) than on the sensing film. A loose (resp. tight) confinement may generate a higher (resp. lower) O_2 value under the colony. They also made colonies with a huge amount of cells (50,000 instead of 1,000 and 2,000 in our case). As the self-generated O_2 field depends on the consumption of every cell, we expect a huge degree of hypoxia. Finally, they never reached a stationary expansion regime due to the large initial excess of inner cells. That excess density slowly decreases with time as visible on their kymograph. We have actually simulated a moderate bulk cell excess in our work (Figure 4 of Cochet-Escartin et al.) which is also transiently visible at 3 h in **Figure 1B**. Such an inner cell mass transfer has to be taken into account to establish a correct mass balance equation, and the only $L(t)R(t)$ quantity tested by Biondo et al. is clearly not sufficient to draw a conclusion on cell divisions.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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