Supplementary Material for "Identifying density-dependent interactions in collective cell behaviour"

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1 ABC algorithms

Here, we present the ABC rejection algorithm (algorithm 1) and ABC SMC algorithm (algorithm 2).

1.1 ABC rejection algorithm

Algorithm 1 ABC rejection sampling algorithm.

1: Draw parameter samples from the joint prior $\boldsymbol{\theta}_j \sim \pi(\boldsymbol{\theta})$.
2: Set discrepancy of jth sample $\kappa_j = 0$, experiment index $i = 1$.
   2.1: Set agent locations, $\{\mathbf{x}_n\}_{n=1}^{N(0)}$, to match experimental data $\mathbf{X}_{\text{obs}}^{(i)}$ at $t = 0$.
   2.2: Simulate model with parameters $\boldsymbol{\theta}_j$ for $t \leq 36$, storing the agent locations at $t = 18$ h and $t = 36$ h, denoted $\mathbf{X}_{\text{sim}}^{(i)}$.
   2.3: Update the discrepancy $\kappa_j \leftarrow \kappa_j + d(\mathbf{X}_{\text{obs}}^{(i)}, \mathbf{X}_{\text{sim}}^{(i)})$, where $d(\cdot, \cdot)$ is the discrepancy function.
   2.4: Move to the next replicate by setting $i = i + 1$ and repeat steps 2.1–2.4 until $i = 9$.
3: Repeat steps 1–2 until 10^5 samples $\{\boldsymbol{\theta}_j, \varepsilon_j\}_{j=1}^{10^5}$ are simulated.
4: Order $\{\boldsymbol{\theta}_j, \kappa_j\}_{j=1}^{10^5}$ by κ_j such that $\kappa_j < \kappa_{j+1}$.
5: Retain the first 1% ($\alpha = 0.01$) of prior samples $\boldsymbol{\theta}_j$, as posterior samples, $\{\boldsymbol{\theta}_j\}_{j=1}^{10^5\alpha}$.

1.2 SMC algorithm

We apply the SMC model selection algorithm of Toni *et al.* [1], given in algorithm 2. We choose the perturbation kernel to be a multivariate Gaussian with independent components and variances approximately equal to the ABC rejection posterior variances [2].

Algorithm 2 ABC SMC sampling algorithm for model selection with uniform priors [1].

1: Choose $\varepsilon_1, ..., \varepsilon_T$ such that $\varepsilon_k > \varepsilon_{k+1}$ and the desired total number of particles, N_{samples}. Set the population indicator $k = 1$.
2: Set the particle indicator $j = 1$.
  2.1: Sample model indicator, $M_a^* \sim \pi(M_a)$.
  2.2: If $k = 1$, sample proposal $\boldsymbol{\theta}^{**} \sim \pi_a(\boldsymbol{\theta})$ where $\pi_a(\boldsymbol{\theta})$ is the prior given model M_a^*. Go to step 2.4.
  2.3: If $k > 1$, sample $\boldsymbol{\theta}^*$ from the subset of the previous population of particles for M_a, $\boldsymbol{\Theta}^{(a)}(k-1)$. If population is empty, return to 2.1. Perturb $\boldsymbol{\theta}^{**} \sim K(\boldsymbol{\theta}|\boldsymbol{\theta}^*)$, where $K(\cdot,\cdot)$ is a symmetric perturbation kernel. If $\pi_a(\boldsymbol{\theta}^{**}) = 0$, return to step 2.1.
  2.4: Set discrepancy $\kappa = 0$, experiment index $i = 1$.
    2.4.1: Set agent locations, $\{\mathbf{x}_n\}_{n=1}^{N(0)}$, to match experimental data $\mathbf{X}_{\text{obs}}^{(i)}$ at $t = 0$.
    2.4.2: Simulate model M_a with parameters $\boldsymbol{\theta}^{**}$ for $t \leq 36$, storing the agent locations at $t = 18$ h and $t = 36$ h, denoted $\mathcal{X}_{\text{sim}}^{(i)}$.
    2.4.3: Update the discrepancy $\kappa = \kappa + d(\mathbf{X}_{\text{obs}}^{(i)}, \mathbf{X}_{\text{sim}}^{(i)})$, where $d(\cdot,\cdot)$ is the discrepancy function.
    2.4.4: If $\kappa > \varepsilon_k$, reject particle and go back to 2.1. Else, move to next replicate by setting $i = i + 1$ and repeat steps 2.4.1–2.4.4 until $i = 9$.
  2.5: Add $\boldsymbol{\theta}^{**}$ to the population of particles $\boldsymbol{\Theta}^{(a)}(k) = \{\boldsymbol{\theta}_j(k)\}_{j=1}^{N_{\text{samples}}^{(a)}}$, and calculate its weight as

$$w_j^{(a)}(k) = \begin{cases} 1, & k = 1, \\ \left(\sum_{j=1}^{N_{\text{samples}}^{(a)}} w_j^{(a)}(k-1) K(\boldsymbol{\theta}^{**}|\boldsymbol{\theta}_j(k-1)) \right)^{-1}, & k > 1. \end{cases}$$

  2.6: Set $j = j + 1$ and repeat steps 2.1–2.6 until $j = N_{\text{samples}}$.
3. Set $k = k + 1$ and normalise the weights within each model. Repeat step 2 until $k = T$.

2 Pilot ABC results

2.1 Pilot ABC to determine σ

In order to reduce the number of unknown parameters, we estimate and fix the kernel width parameter, σ. To do this, we perform a pilot ABC run where $\pi(\sigma) = U(2, 30)$ using algorithm 1, the results of which are shown in figure S1. These results show a posterior mode of approximately $\sigma \approx 12\,\mu\text{m}$, and we fix this for the rest of the study. In this supporting material document, we reproduce some results in the case that $\sigma = 24\,\mu\text{m}$.

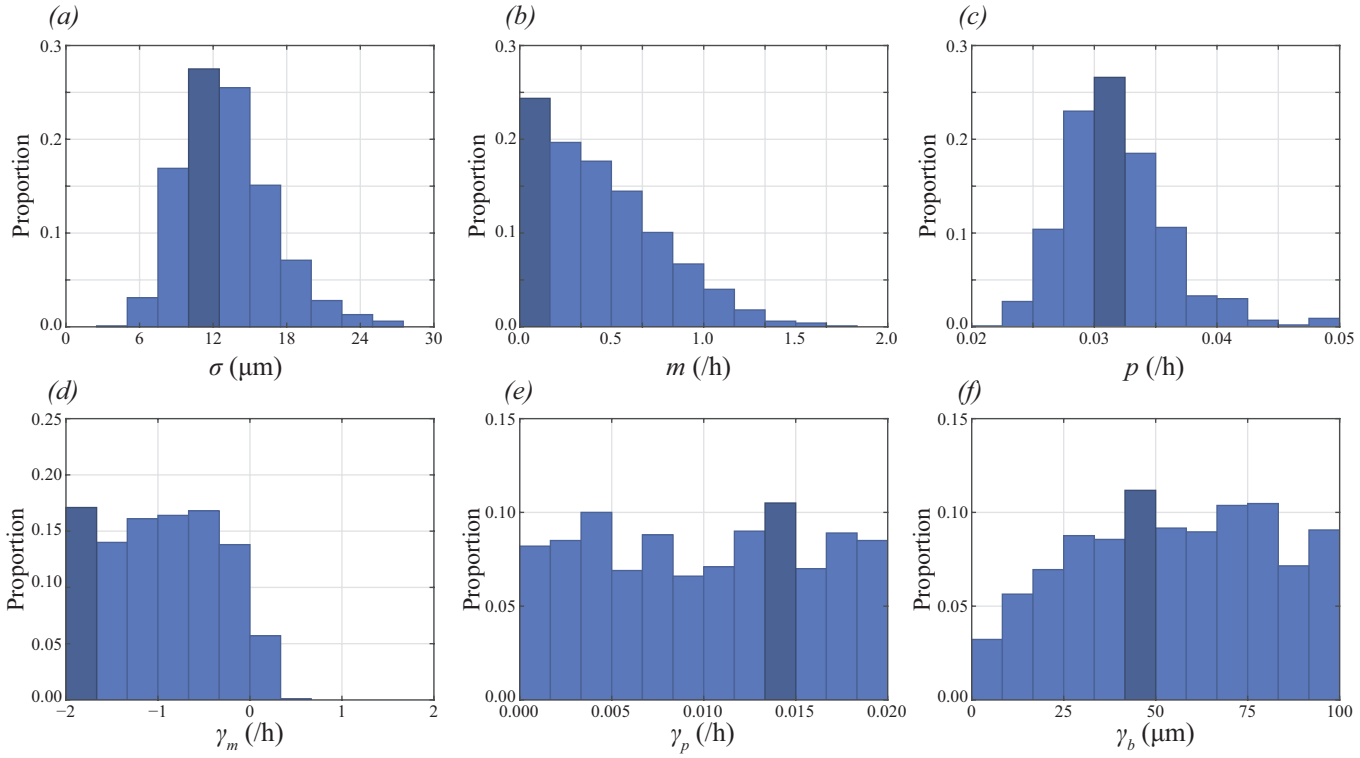

Figure S1: ABC rejection with σ as an unknown with $\pi(\sigma) = U(2, 30)$.

2.2 Wider priors

We notice in figure S1*e,f* that the posterior support appears to cover the prior support. To investigate this, we widen the corresponding priors for γ_p and γ_b by a factor of two and perform ABC rejection. The results are shown in figure S2. These results suggest that γ_p and γ_b are non-identifiable.

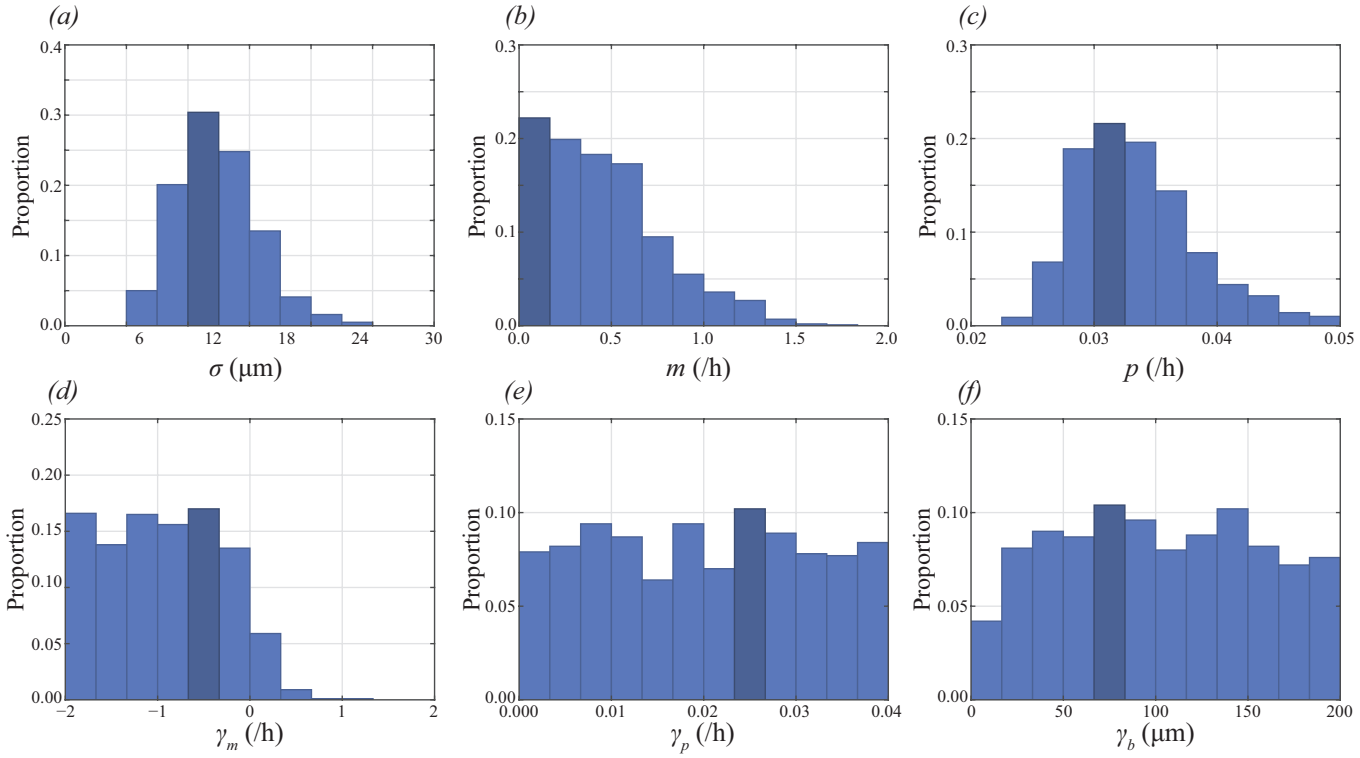

Figure S2: Figure S1 with wider priors for γ_p and γ_b.

2.3 Excluding $\mathcal{P}$ from inference

To investigate the amount of information contained in the pair correlation function, $\mathcal{P}$, we perform ABC rejection in the case $\mathcal{P}$ is removed from the distance metric. The results are shown in figure S3. We see a large reduction in information in the posteriors in figure S3 compared to figure S1. In particularly, the sign of γ_m is less clear in the case the pair correlation is excluded.

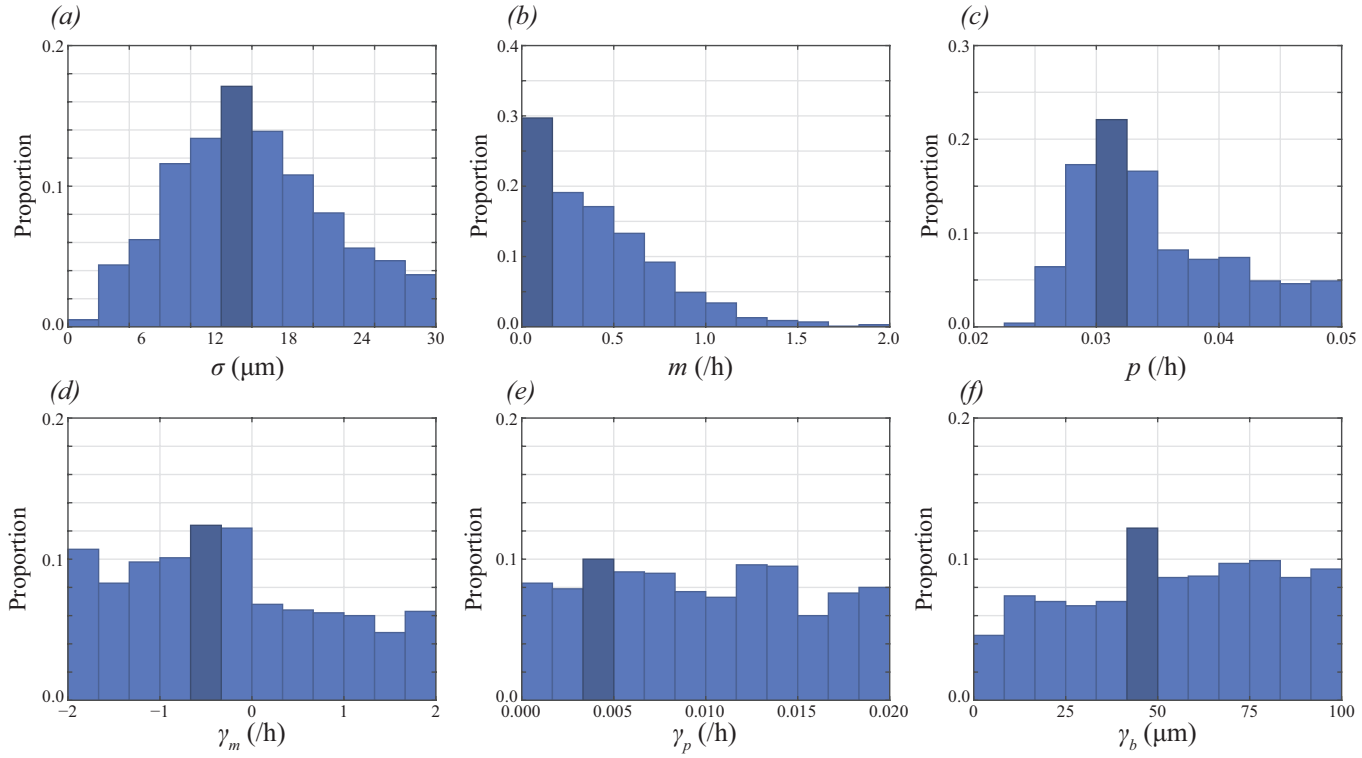

Figure S3: Figure S1 where summary statistics relating the the pair correlation, $\mathcal{P}$ are excluded.

3 Quantile plots

To determine the appropriate ABC SMC sequence of thresholds, we produce a quantile plot of the distance metric obtained from 100,000 prior samples where $\sigma = 12\,\mu\text{m}$ (figure S4*a*) and $\sigma = 24\,\mu\text{m}$ (figure S4*b*). In each case, we choose the final discrepancy, ε_U, to correspond to an ABC rejection rate of approximately 1%. We choose the sequence base upon acceptance probabilities of approximately 50%, 25%, 12.5%, 6.25%, 3.125%, 1.5625% and 1% [2]. The sequence of thresholds for results in the main document where $\sigma = 12\,\mu\text{m}$ is $\{9.6, 7.3, 6.3, 5.5, 4.9, 4.6, 4.4\}$; and the sequence of thresholds for results in this supporting material document where $\sigma = 24\,\mu\text{m}$ is $\{11.8, 9.7, 8.4, 7.5, 6.8, 6.3, 6.0\}$.

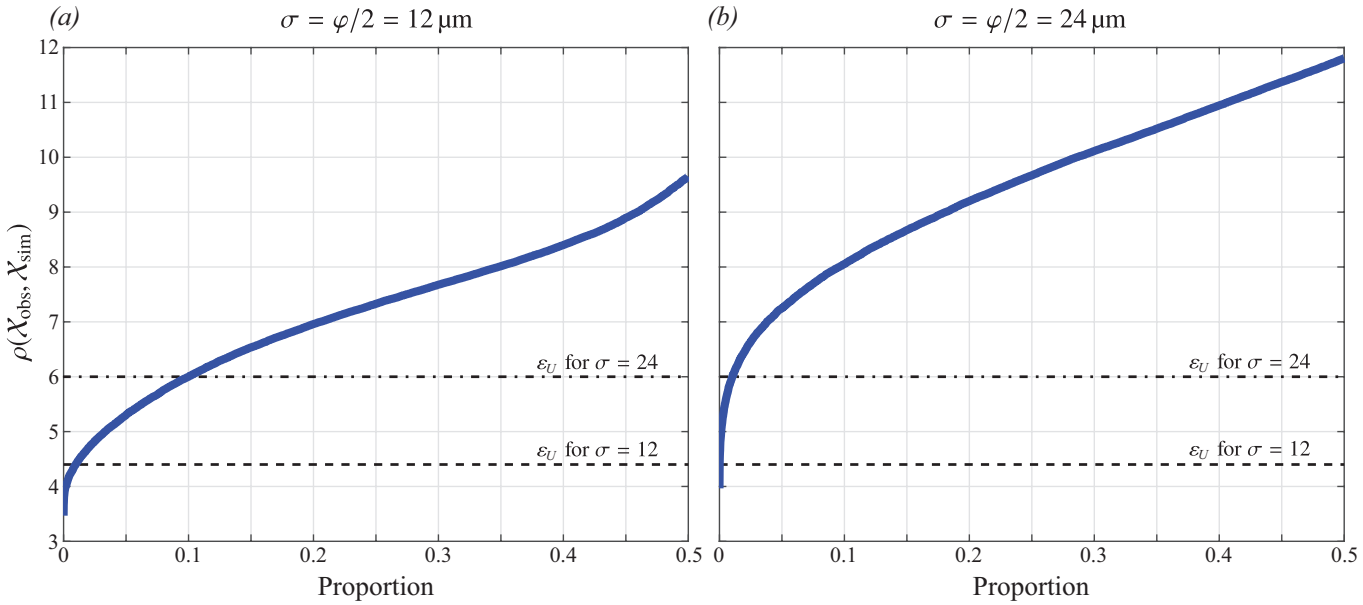

Figure S4: Quantile plot of the distance metric from 100,000 prior samples with (a) $\sigma = 12\,\mu\text{m}$; and, (b) $\sigma = 12\,\mu\text{m}$. The final discrepancy, ε_U, is indicated by a horizontal line in each case.

4 Considering $\gamma_p = 0$

	$\boldsymbol{\theta}_k$	Density Dependence
Model 1	$(m, p, \gamma_m, \gamma_p, \gamma_b)$	Proliferation, Motility and Direction
Model 2	$(m, p, \gamma_p, \gamma_b)$	Proliferation and Direction
Model 3	$(m, p, \gamma_m, \gamma_p)$	Proliferation and Motility
Model 4	(m, p, γ_p)	Proliferation only (Fisher-Kolmogorov)
Model 5	(m, p)	None (Skellam's model [3])
Model 6	$(m, p, \gamma_m, \gamma_b)$	Motility and Direction
Model 7	(m, p, γ_b)	Direction only
Model 8	(m, p, γ_m)	Motility only

Table 1: In the supporting material, we consider three additional models: Models 6, 7 and 8 correspond to Models 1, 2 and 3, where $\gamma_p = 0$.

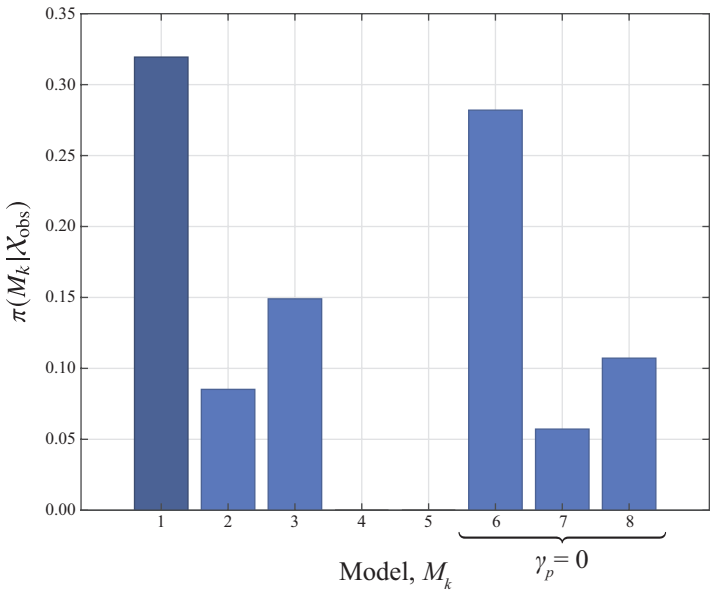

Figure S5: Figure 4 of the main document where we consider three additional models: Models 6, 7 and 8 correspond to Models 1, 2 and 3 where we set $\gamma_p = 0$ to remove the proliferation interaction from the model.

	$\pi_{\varepsilon_T}(M_k|\mathcal{X}_{\text{obs}})$	$\mathcal{B}_{k1}$
Model 1	**0.3194**	**1.000**
Model 2	0.0852	0.2668
Model 3	0.1490	0.4665
Model 4	0.000	0.000
Model 5	0.000	0.000
Model 6	0.2820	0.8829
Model 7	0.0572	0.1791
Model 8	0.1072	0.3356

Table 2: In the supporting material, we consider three additional models: Models 6, 7 and 8 correspond to Models 1, 2 and 3, where $\gamma_p = 0$. The two other variables, m and p, are always unknown.

5 Model selection for $\sigma = 24\,\mu\text{m}$

Here, we reproduce results from figure 5 of the main document, in the case we fix $\sigma = 24\,\mu\text{m}$.

Results in figure S6*a* differ from those in the main document, in that Model 2 now has the highest posterior density. As such, we show the marginal distributions for each parameter in Model 2 in figure S6*b–f*. These results are consistent with the main document in showing that models without a density dependent motility mechanism (Models 4 and 5) are unable to simultaneously match data from all nine experiments. Examining results in figure S10 shows that $\sigma = 24\,\mu\text{m}$ is not able to match the spatial structure in the experimental data as closely as $\sigma = 24\,\mu\text{m}$, results for which are shown in figure S8.

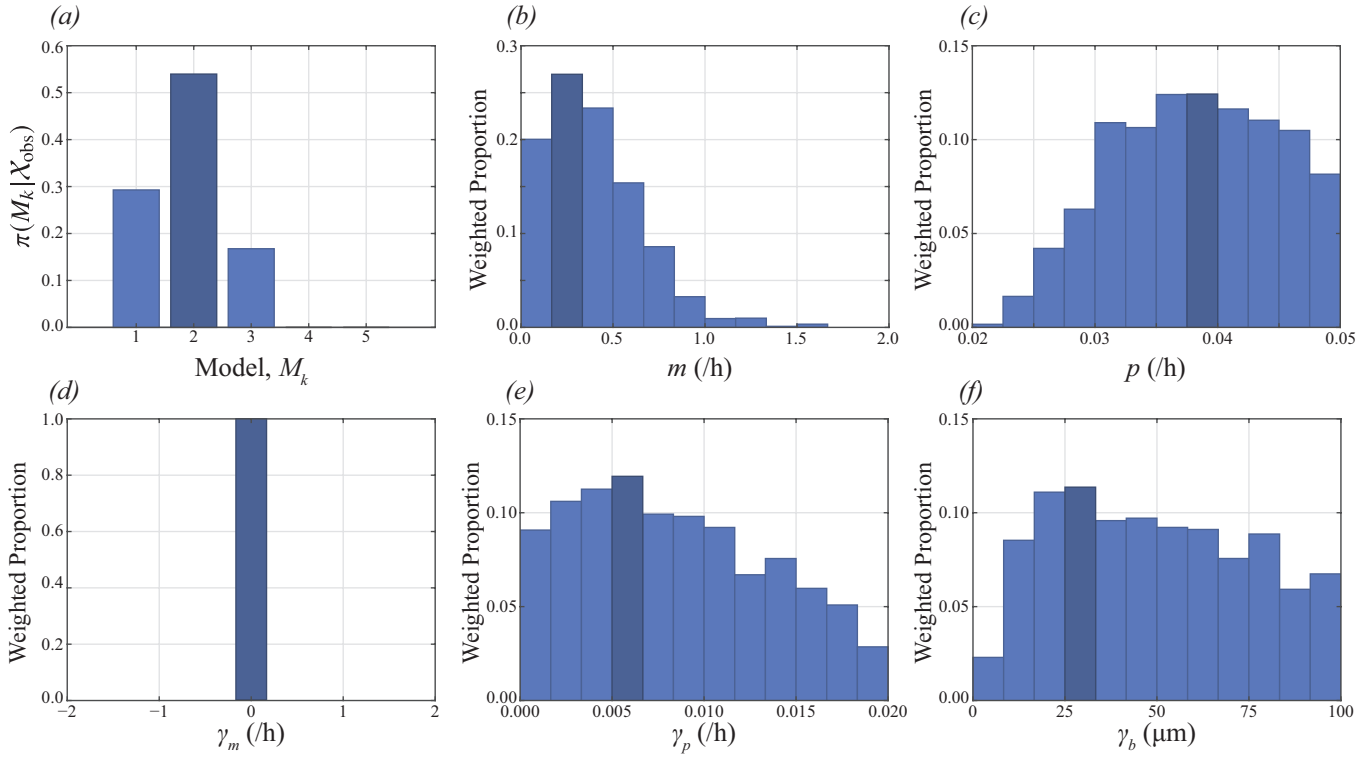

Figure S6: Reproduction of results in figure 6 of the main document, with $\sigma = \varphi = 24\,\mu\text{m}$. (a) Posterior for the model index, $\pi(M_k|\mathcal{X}_{\text{obs}})$, showing that Model 2 (density-independent motility) as the posterior mode. (b)–(f) Marginal posterior distributions for each parameter in Model 2, shown as weighted histograms.

6 Results for all nine experiments

In the main document, we show results for experimental replicates 1, 3, 6 and 9 at $t = 36\,\text{h}$ in figure 6. Here, we reproduce figure 6 and show results for all nine experimental replicates at both $t = 18\,\text{h}$ and $t = 36\,\text{h}$.

In section 6.1 we show these results for $\sigma = 12\,\mu\text{m}$, the value from the main document. In section 6.2 we show these results for $\sigma = 24\,\mu\text{m}$.

6.1 Full results for $\sigma = 12\,\mu\text{m}$

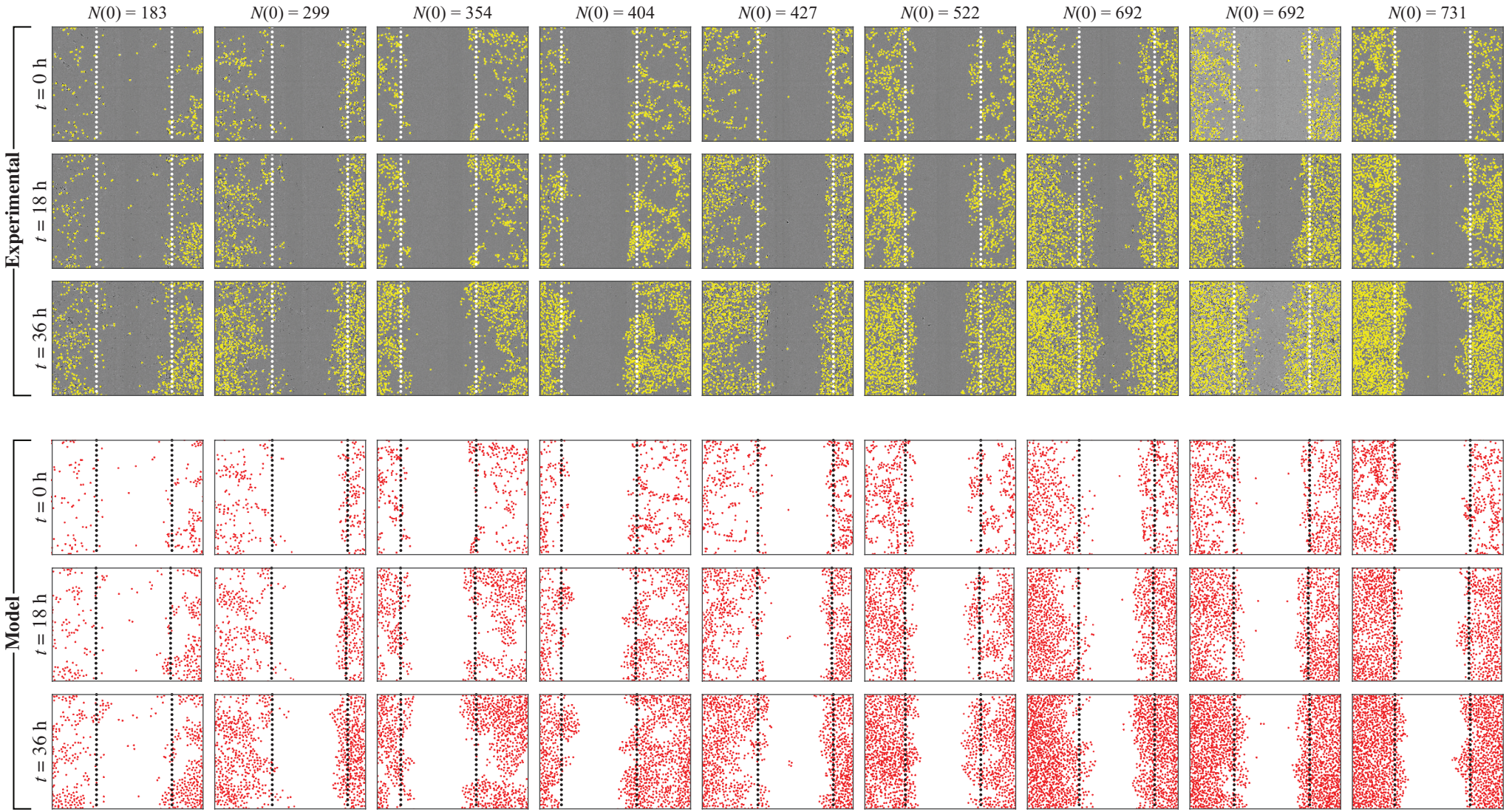

Figure S7: Reproduction of results in figure 6*a*–*l* of the main document, for all replicates, for $\sigma = 12\,\mu\text{m}$.

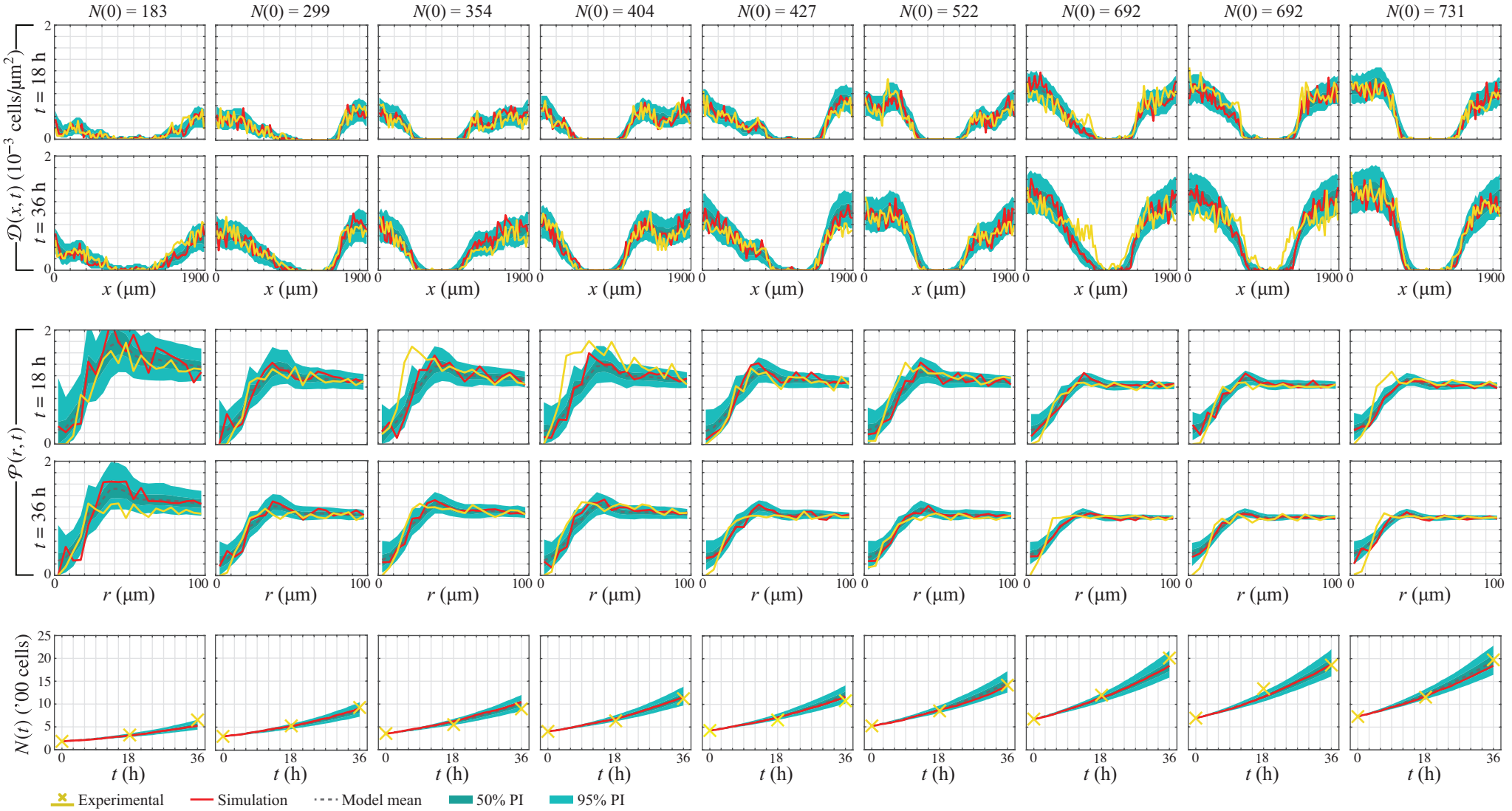

Figure S8: Reproduction of results in figure 6*m*–*x* of the main document, for all replicates, for $\sigma = 12\,\mu\text{m}$.

6.2 Full results for $\sigma = 24\,\mu\text{m}$

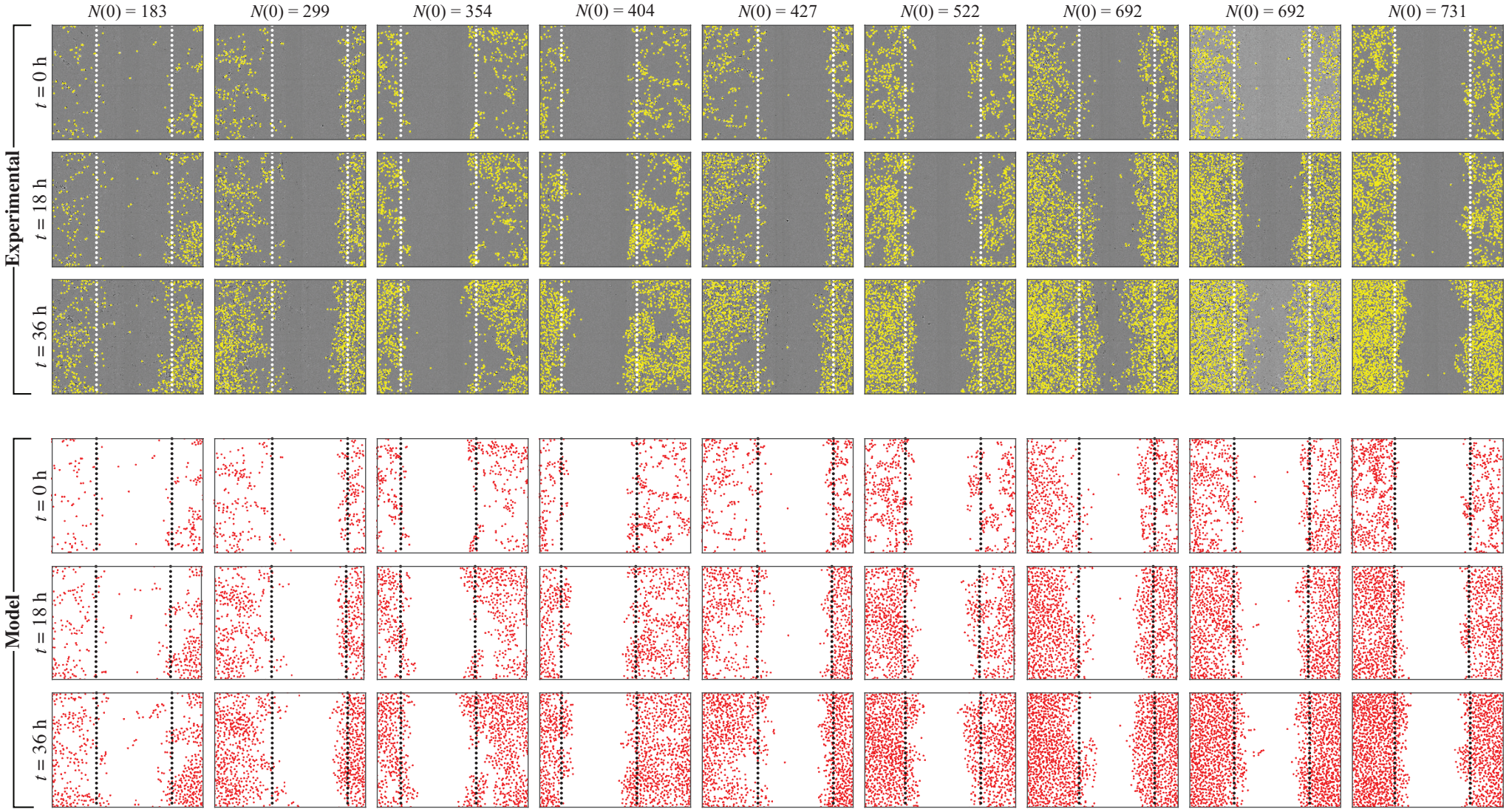

Figure S9: Reproduction of results in figure 6*a*–*l* of the main document, for all replicates, for $\sigma = 24\,\mu\text{m}$.

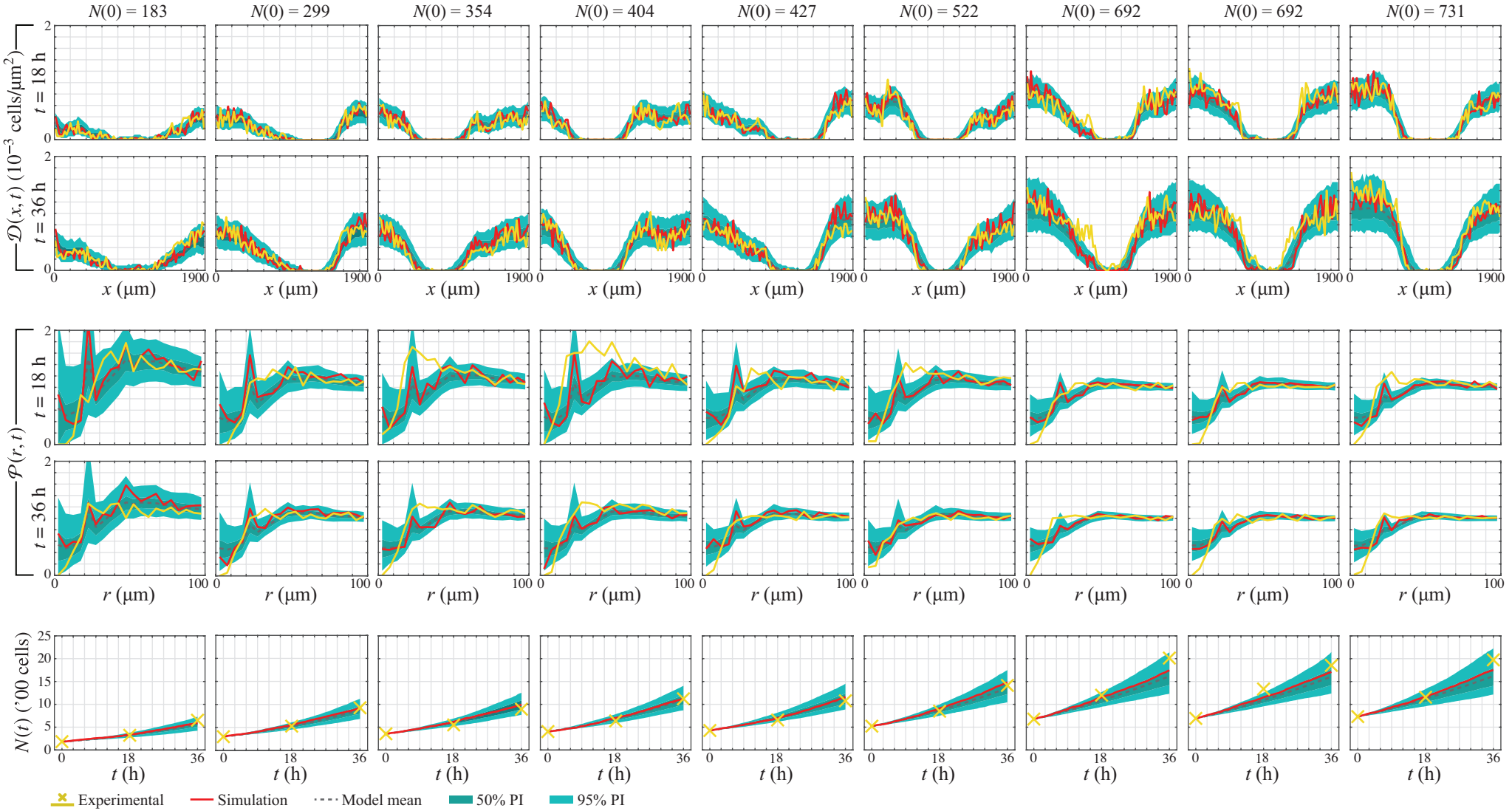

Figure S10: Reproduction of results in figure 6*m*–*x* of the main document, for all replicates, for $\sigma = 24\,\mu\text{m}$.

References

[1] Toni T, Welch D, Strelkowa N, Ipsen A, Stumpf MPH. 2009 Approximate Bayesian computation scheme for parameter inference and model selection in dynamical systems. *J R Soc Interface* **6**, 187–202.

[2] Filippi S, Barnes CP, Cornebise J, Stumpf MPH. 2013 On optimality of kernels for approximate Bayesian computation using sequential Monte Carlo. *Stat Appl Genet Mol Biol* **12**, 87–107.

[3] Skellam JG. 1951 Random dispersal in theoretical populations. *Biometrika* **38**, 196–218.