S1 Supplementary model information

S1.1 Model equations

Equations for tissue growth and reaction-diffusion of the chemoattractant were used as previously described in McLennan *et al.* (2012) (Supplementary Material), with a minor correction in the scaling of chemoattractant internalisation with domain length (See Eq. (2), where the factor of L^2 in the exponential function was missing in McLennan *et al.* (2012)).

S1.1.1 Domain growth

The length of the migratory domain at any time between $t = 0$ and $t = 24h$ is given by the logistic equation

$$L_x(t) = L_0 \left(\frac{L_\infty e^{a(t-t_s)L_\infty}}{L_\infty - 1 + e^{a(t-t_s)L_\infty}} + 1 - \frac{L_\infty e^{a(-t_s)L_\infty}}{L_\infty - 1 + e^{a(-t_s)L_\infty}} \right), \tag{1}$$

with $L_0 = 300\mu\text{m}, a = 0.08h^{-1}\mu\text{m}^{-1}, t_s = -16h, L_\infty = 870\mu\text{m}$, determined by least-squares fitting to experimental domain length measurements (McLennan *et al.* 2012).

S1.1.2 Chemoattractant reaction-diffusion

The change of chemoattractant cocentration at a point (x, y) is given by the reaction-diffusion equation (RDE) (McLennan *et al.* 2012)

$$\frac{\partial c}{\partial t} = D \left(\frac{1}{L^2} \frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2} \right) - c \sum_{i=1}^{N(t)} \frac{\lambda}{2\pi R^2} \exp \left[-\frac{L^2(x - x_i)^2 + (y - y_i)^2}{2R^2} \right] + \chi c(1 - c) - \frac{\dot{L}}{L} c, \tag{2}$$

where the terms on the left hand side describe diffusion, internalisation, production and dilution (by tissue growth, the dot denoting time derivative), respectively. Scaling factors of L are introduced by rescaling to a stationary domain to solve numerically (McLennan *et al.* 2012). Parameter names and values are given in Table 1.

S1.2 Sensing accuracy

Berg & Purcell (1977) derive a fundamental biophysical limit to the accuracy with which a cell can sense a chemical gradient. We briefly outline their derivation here before commenting on parameterisation. For a more detailed derivation, see the original work (Berg & Purcell 1977).

The limit in sensing accuracy is due to fluctuations in the numbers of molecules[1], and is derived for the case of a perfect sensor[2]. Let a perfect sensor be counting N molecules in a volume V with background (or average) concentration $\bar{c}$. The inaccuracy in a single concentration measurement will be

$$\frac{\Delta c}{\bar{c}} \approx \frac{1}{\sqrt{N}} = \frac{1}{\sqrt{V\bar{c}}}, \tag{3}$$

in three dimensions, or $1/\sqrt{A\bar{c}}$ in two dimensions. The count of molecules can be improved by repeated measurements. In a time T our perfect instrument can make $n = TD/V^{2/3}$ independent measurements, based on the timescale of a molecule diffusing through the measurement volume V. This will improve the (root mean square) measurement error by $1/\sqrt{n}$ (Berg & Purcell 1977). Thus, with $V \sim R^3$, the measurement uncertainty reduces to

$$\frac{\Delta c}{\bar{c}} \approx \frac{1}{\sqrt{DT\bar{c}R}}, \tag{4}$$

in three dimensions, or $\Delta c/\bar{c} \approx 1/\sqrt{DT\bar{c}}$ in two dimensions. The exact derivation introduces a numerical factor of order unity, but since we can only parameterise the sensing accuracy to orders of magnitude, we will ignore this.

[1]The fluctuations in particle number N are proportional to $1/\sqrt{N}$. This statement is reasonable despite our continuum treatment of the chemoattractant. If particle numbers (and hence concentrations) are very high, then this will simply drive the sensing accuracy to very small values. If one was to assume a complete lack of fluctuations, cells could sense arbitrarily small concentrations, and gradients, of chemoattractant, which seems unrealistic. Some of the noise in measurement may also come from the intracellular machinery downstream of the receptor.

[2]The sensing accuracy is in fact different for a perfect sensor and a perfect absorber, but only up to a numerical factor of about two (Endres & Wingreen 2008). Endres & Wingreen (2008) show that this factor is larger for gradient sensing by a sensor. We consider cells sensing the concentration at the cell body and the tip of a protrusion. Thus the gradient is determined from two individual concentration measurements, and the concentration, rather than gradient, sensing limit applies.

Kaizu *et al.* (2014) revisit the Berg-Purcell limit and derive corrections to the sensing limit by considering diffusive ligand transport as well as receptor binding kinetics. Since we assume our reactions to be diffusion limited, these corrections do not apply. Similarly, one can correct for movement of the cell relative to the medium to derive the apparent gradient seen by the cell and its detection limit, but we assume this to be neglible.

S1.2.1 Parameterisation of the sensing accuracy for neural crest cells

Most of the variables upon which the sensing accuracy depends are underdetermined in the case of chick cranial neural crest migration, such as VEGF diffusivity, D, VEGF background concentration, $\bar{c}$ and the sensing time, T. Nevertheless, we can proceed to make order of magnitude estimates, which can serve as bounds for our model simulations.

The concentration of VEGF used in *in vitro* experiments is 1μg/ml, which, at a molecular weight of 19.2kDa $\approx$ 20kg/mol, leads us to estimate $\bar{c} \approx 3 \cdot 10^7/\mu\text{m}^3$ (50mM).

The timestep of our simulations is $\Delta t = 1$min, and we assume that a cell takes up only a fraction of this time with sensing, and most of it with movement. We could therefor estimate $T \leq 0.1 \cdot \Delta t = 0.1$min. If we relax our assumptions this estimate might change by an order of magnitude, which would only change the sensing accuracy by a factor of roughly 1/3, which will give qualitatively similar results in typical model simulations.

For the measurement of a gradient, i.e., the difference between two concentration measurements, the Berg-Purcell limit (4) will increase by a factor of $\sqrt{2}$ (Goodhill & Urbach 1999). With the estimates for $\bar{c}$ and T as above, and the parameter values $D = 0.1\mu\text{m}^2/\text{h}$ and $R = 7.5\mu$m (Table 1), we get an estimate of the sensing accuracy (4) of $\Delta c/c \approx 0.002$ in three dimensions, or $\Delta c/c \approx 0.01$ in two dimensions. These can be taken as a lower bound for the (order of magnitude of) sensing accuracy of neural crest cells in our model. Note that the sensing accuracy rescales with changing background concentration, which has to be taken care of in the implementation (see Section S1.3).

S1.3 Pseudocode

initialise model parameters and first cells ▷ see Table 1
for $t = 6$ to 24 **do**
  if t = insertion time **then**
    insert a new cell at start of domain
  end if
  solve chemoattractant profile ▷ see Eq. (2)
  grow domain, update cell positions ▷ see Eq. (1)
  move cells
end for

move cells

for $i = 1$ to number of cells **do**
  pick a cell at random without replacement
  pick n_{filo} random directions
  if cell is a leader **then**
    measure chemoattractant concentration at cell positon, $c_{\text{old}} = \int c(x,y) \exp\left[-\frac{x^2+y^2}{2R^2}\right] \text{d}x\text{d}y$
    measure chemoattractant concentration in random direction(s) at distance l_{filo} away (pick highest), c_{new}
    if $\frac{c_{\text{new}} - c_{\text{old}}}{\sqrt{c_{\text{old}}}} \geq$ sensing accuracy **then**
      move in chosen direction
    else ▷ cell has not found a favourable chemoattractant gradient
      move in random direction
    end if
  else if the cell is attached **then** ▷ cell is a follower in contact with another cell
    if other cell is within l_{filo} **then**
      move in same direction as other cell
    else ▷ other cell is out of reach
      dettach cell
    end if
  else ▷ the cell is a dettached follower
    check if there is another cell in random direction(s) at distance l_{filo} (pick closest)

20: **if** a cell was found and is a leader (or part of a chain in contact with a leader) **then**
21: move in same direction as other cell
22: **else**
23: move in a random direction
24: **end if**
25: **end if**
26: **end for**

Note: Any attempted movement is aborted if it would lead to overlap with another cell or the domain boundary.

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Table 1: **Model parameters**

Parameter values listed were used as a default, unless otherwise stated. Where a range is given, the model gives qualitatively similar results within that range, and the italicised value is the one used for the figures in this paper.

	Description	Value	Reference
t_{LF}	time after which newly inserted cells are followers	variable	see results section
n_{filo}	directions sampled per timestep	2	n/a, see notes
Δt	simulation time step	1 min	n/a
R	cell radius (nuclear)	7.5μm	McLennan & Kulesa (2010)
v_{lead}	cell speed (leader cells)	41.6μm/h	Kulesa *et al.* (2008)
v_{follow}	cell speed (follower cells)	49.9μm/h	Kulesa *et al.* (2008)
L_y	height of migratory domain	120μm	McLennan *et al.* (2012)
L_x	length of migratory domain (grows logistically, Eq. (1))	300μm to 1100μm	McLennan *et al.* (2012)
l_{filo}	sensing radius	27.5μm	see notes
$l_{\mathrm{filo}}^{\mathrm{max}}$	maximum cell separation before contact is lost	45μm	see notes
$\Delta c/c$	sensing accuracy	0.001 to *0.1*	Section S1.2
D	diffusion coefficient of chemoattractant (effective)	*0.1* to $10^5\mu\mathrm{m}^2$/h	see notes
χ	production rate of chemoattractant	*0.0001* to 1/h	see notes
λ	chemoattractant internalisation rate	100 to *1000*/h	see notes
k_{in}	rate at which cells enter the domain	10/h	see notes

Notes

Experimental time: Cell migration starts approximately six hours after electroporation ($t = 0$).

Directions sampled per timestep, n_{filo}: This cannot be directly related to the number of filopodia, which are greater in number, but sample at a lower speed (McLennan *et al.* 2012).

Diffusion coefficient of chemoattractant, D: The primary identified chemoattractant in chick cranial neural crest migration is VEGF^{165} (McLennan *et al.* 2010). Its related isoform VEGF^{164} is known to bind to extracellular matrix (ECM), and studies in angiogenesis estimate as little as 1% may be freely diffusing, the rest bound to ECM and cellular receptors (Mac Gabhann *et al.* 2006). Hence, we choose a low effective diffusivity.

Production rate of chemottractant, χ: In other tissues, VEGF production, or estimates thereof, range from 0.01-0.20 molecules/cell/s (Yen *et al.* 2011), 4.39-5.27$\cdot 10^{-5}$molecules/μm$^-2$/s (Vempati *et al.* 2011) to $0.25 \cdot 10^{-17}$pmol/μm^2/s(Mac Gabhann *et al.* 2006). In our system, the rate of VEGF production is unknown and difficult to measure. Howeever, it is outweighed by internalisation through migrating neural crest cells, as VEGF is not seen to be replenished in trailing portions of the stream (McLennan *et al.* 2010). Thus, we assume χ to be low.

Chemoattractant internalisation rate, λ: To our knowledge, no estimates or measurements of VEGF internalisation rate of chick cranial neural crest exists. Angiogenesis studies have used values of $k_{\mathrm{VEGFR2}} = O(10^{-4})$/s (Mac Gabhann & Popel 2005, Yen *et al.* 2011). Berg & Purcell (1977) estimate the number of receptors needed for a near-optimal sensing accuracy as $N_R = R/s$, where R is the cell radius and s the receptor size. With $s = O(\mathrm{nm})$, we can estimate the number of receptors to be $N_R \geq 10^4$. If receptor internalisation rates are comparable to other tissues, a lower bound on λ would be given by $k_{\mathrm{VEGFR2}} N_R > 1$. However, the concentration of VEGF in our system is unknown, and hence the units of c, and therefore λ, in our model are arbitrary. We assume a high λ to ensure quick consumption of chemoattractant by cells.

Rate at which cells enter the domain, k_{in}: This is the rate of attempted cell insertions, in a typical simulation on the order of 10% of insertions are unsuccessful. It should be noted here again that our simulations are a two-dimensional abstraction of the three-dimensional migratory stream, which may contain 4-5 times as many cells *in vivo* in the transverse (z) direction.

Sensing radius, l_{filo}: This was calculated as the sum of the cell radius (7.5μm) and the mean filopodial length (which was directly measured from the cell body (Fig. S4B) to be 9μm and estimated from total cell size (Fig. S4A) to be circa 20μm). Since we have only implemented contact between filopodium and cell body, but not between two filopodia, which does occur *in vivo* (Teddy & Kulesa 2004), we allow for a greater effective length.

Maximum cell separation before contact is lost, $l_{\mathrm{filo}}^{\mathrm{max}}$: The maximum cell size including filopodia was measured to be 86.3μm (Fig. S4A), half of which gives an estimate of maximum cell separation of 43.15μm. Independent measurements of filopodial lengths gave a maximum of 30.4μm (from the cell body, Fig. S4B), which, together with the cell radius $R = 7.5\mu$m and the average filopodial length (allowing for interfilopodial contact) of 9μm gives an estimate of 46.5μm.