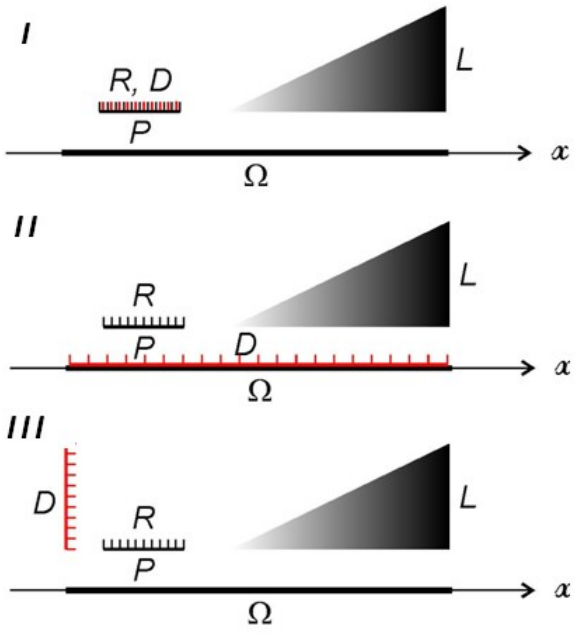
Model Assumptions

We modeled a chemotactic movement of a single cell of a length *P* in a one-dimensional domain Ω. The chemoattracting ligand *L* is delivered at the right boundary of a domain. Functional receptor for this ligand, R, is expressed on the cell. We assumed that binding of L to R induces cell migration, but the direction and velocity of cell movement is regulated by the spatial inequality in the ligand-bound receptor complexes over the cell body. We assumed that decoy receptor *D* binds ligand L but does not induce signals in the cell. D can be localized on the surface of the cell, on bystander cells (assumed to be present along the length of the domain), or at the origin of moving cell (assumed to be opposite to the origin of ligand gradient) (Fig. 1). Decoy receptor *D* can be present in a membrane bound or soluble form.

Figure 1: Schematic representation of three cases



Model development

The first model is constructed assuming that signaling and decoy receptors are present on the moving cell in a membrane bound form at the levels R_T and D_T respectively, and that they bind ligand through similar mechanisms. Ligand binds to normal receptors with association rate k_{1r} creating a signaling complex R_b. This complex dissociates back to ligand and normal receptor with dissociation rate k_{2r} or is degraded with a degradation rate k_{3r}. Similar processes occuring between ligand and decoy receptor are described by parameters k_{1d} , k_{2d} and k_{3d}. In addition, both

receptors are transported as the cell moves along the ligand gradient. The resulting equiations are:

$$\frac{\partial R_b}{\partial t} = k_{1r}(R_T - R_b)\cdot L - (k_{2r}+k_{3r})R_b + V\frac{\partial R_b}{\partial x}$$

$$\frac{\partial D_b}{\partial t} = k_{1d}(D_T - D_b)\cdot L - (k_{2d}+k_{3d})D_b + V\frac{\partial D_b}{\partial x}$$

where, R_T (D_T) is the dencity of all signaling (decoy) receptors on the cell; R_b (D_b) is the dencity of ligand-bound signaling (decoy) receptor equals; L is the concentration of ligand; *V* is the velocity of cell movement.

Since degradation of receptor-ligand complex removes the receptors from the total receptor pool, we also described the change in the density of all receptors R_T and D_T , assuming that the process of replenishing of these receptors on the cell surface occurs with the rate k_{4i} and aimes to maintain the optimal densities of these receptors , R_0 and D_0. The receptors are transported as the cell moves along the ligand gradient:

$$\frac{\partial R_T}{\partial t} = k_{4r}(R_0 - R_T) - k_{3r}R_b + V\frac{\partial R_T}{\partial x}$$

$$\frac{\partial D_T}{\partial t} = k_{4d}(D_0 - D_T) - k_{3r}D_b + V\frac{\partial D_T}{\partial x}$$

We assumed that ligand L is produced at the rate S(x,t) by the sourse positioned on the far right of the domain, and is diffuses through the domain with the diffusion coeffiecient of γ. The ligand is removed when it binds to the signaling and decoy receptor with rate constrant k_1, it is returned to the environment when the receptor-ligand complex dissociates with the rate constant k_2, and is degraded together with the receptors at the degradation rate k_3.

$$\frac{\partial L}{\partial t} = S(x,t) + \gamma\frac{\partial^2 L}{\partial^2 x} - k_{1r}(R_0 - R_b)L + k_{2r}R_b - k_{3r}R_b - k_{1d}(D_0 - D_b)L + k_{2d}D_b - k_{3d}D_b$$

The velocity of the chemotactic cell movement was assumed to be proportional to the difference between the number of ligand-bound signaling receptors on the front and rear halves of the cell.

$$V = c\left(\int_{\frac{P}{2}}^{b} R_b dx - \int_{a}^{\frac{P}{2}} R_b dx\right)$$

Taken together, the following model describes ligand-receptor interactions and cell movement

$$
\begin{cases}
\dfrac{\partial R_b}{\partial t} = k_{1r}(R_T - R_b)\cdot L - (k_{2r}+k_{3r})R_b + V\dfrac{\partial R_b}{\partial x} \\
\dfrac{\partial R_T}{\partial t} = k_{4r}(R_0 - R_T) - k_{3r}R_b + V\dfrac{\partial R_b}{\partial x} \\
\dfrac{\partial D_b}{\partial t} = k_{1d}(D_T - D_b)\cdot L - (k_{2d}+k_{3d})D_b + V\dfrac{\partial D_b}{\partial x} \\
\dfrac{\partial D_T}{\partial t} = k_{4d}(D_0 - D_T) - k_{3r}D_b + V\dfrac{\partial D_b}{\partial x} \\
\dfrac{\partial L}{\partial t} = S(x,t) + \gamma\dfrac{\partial^2 L}{\partial^2 x} - k_{1r}(R_T - R_b)L + k_{2r}R_b - k_{3r}R_b - k_{1d}(D_T - D_b)L + k_{2d}D_b - k_{3d}D_b \\
V = c\left(\int_{\frac{P}{2}}^{b} R_b\,dx - \int_{a}^{\frac{P}{2}} R_b\,dx\right)
\end{cases}
$$

Estimation of characteristic values of the variables and parameters

1) Table of variables and parameters used in the model:

R_b (D_b)	dencity of lignd-bound signaling (decoy) receptors at a given cell location
R_T (D_T)	dencity of all signaling (decoy) receptors at a given cell location
R_0 (D_0)	optimal dencity of all signaling (decoy) receptors at a given cell location
k_{1r}: k_{1d}:	receptor-ligand association rate for signaling (decoy) receptors
k_{2r}: k_{2d}:	receptor-ligand dissociation rate for signaling (decoy) receptors
k_{3r}: k_{3d}	rate of degradation of receptor-ligand complex for signaling (decoy) receptors
k_{4r}: k_{4d}	rate of signaling receptor production (recycling) back to the mambrane
L	Ligand concentration
S	rate of the ligand production at the source
γ	diffusion coefficient for ligand
V	velocity of cell movement
c	velocity coefficient

Estimating receptor densities: The size of an individual receptor as on the order of 5 nm, different chemokine receptors were measured to be expressed at $2x10^3$ – $8x10^4$ molecules/cell [Kelsen, 2004; Soriano-Sarabia, 2007], which we approximated as 10^3 – 10^5 molecules/cell. Assuming the cell as a sphere with a diameter of ~10-100 μm, surface are can be calculated as

~300-30000 μm^2, resulting in the surface density of the receptors between $3x10^{-2}$ and $3x10^2$ molecules/μm^2, which corresponds to $4x10^{-4}$ and 40 molecules/μm residing on the cell diameter. A different approach is to assume that we take into account all the action of receptors present on the cells but account for their contribution along the principle axis only, then all the receptors are virtually transposed on the line representing the cell, resulting in a linear densities between 10 and 10^4 molecules/μm. We assumed that initially the total number of receptors is at the optimal level: $R_T(0)=R_0$, $D_T(0) = D_0$, and that R_b is always less than R_T.

Estimating the rate constants for receptor-ligand association, dissociation, degradation and restoration. The dissociation constants Kd for different chemokines and their receptors have been measured in the range between 100 pM and 100 nM [Alexander, 2013 (guide to pharmacology)]. Using radiolabeling, the rates of receptor-complex association and dissociation has been measured for some chemokine receptors and their physiological or pharmacological ligands [Swinney, 2014; Arnold, 2006; Scholten, 2015]. The rates of dissociation for the receptor-ligand complexes were reported to be in the similar range, between 0.01 and 0.05 min^{-1}, while the rate of association for each receptor-ligand was between $5x10^6$ and $7x10^9$ M^{-1} min^{-1}. Therefore, we assumed that k_{1r} and k_{1d} can vary between 10^6 and 10^{10} M^{-1} min^{-1} independently for signaling and decoy receptor, while k_{2r} and k_{2d} and similar and of the order 10^{-2} min^{-1}. The characteristic times for chemokine receptor internalization were reported in the range between 5 and 120 min [Escala, 2010; Vila-Goro, 1999; Arai, 1997; Prado, 2007], based on which we assumed k_{3r} and k_{3d} to vary between 0.001 and 0.1 min^{-1}. The recovery of the receptors membrane levels depends on the particular chemokine/chemokine receptor pair and was shown to vary between very slow recovery rate of $7x10^{-5}$ to $5x10^{-4}$ min^{-1} for CCR5-RANTES [Sabbe, 2001] to very rapid recovery rate of $3x10^{-2}$ min^{-1} for CCR7-CCL21 on cancer cells [Patrussi, 2015], but mostly in the range of 0.001-0.01 min^{-1} [Mueller, 2004; Mueller, 2015; Neel, 2007], which we assumed as an estimate for k_{4r} and k_{4d}. For k_{1r} and k_{1d}, we transformed the molar concentration (mol/L) into the number of molecules per μm^3, resulting in an estimate of 10^{-2} - 10^2 $(molecules/\mu m^3)^{-1}$ min^{-1}.

L	Ligand	
V	Velocity of a moving cell	0.015 μm/s (macrophages) [Uchida, 203]

		0.25 μm/s (neutrophils) [Yamauchi, 2014]
P	Length of a single cell	10-100 μm

Table 2: Parameter values in the model, experimental values and units

Parameter	Value in model	Units in the model	Experimental value & units	reference
R_0				
D_0				
k_1				
Kd (k_2/k_1)				
κ				
P				
c				
λ				
Time				
Distance				
Velocity				

3.2.5 Initial and boundary conditions

For mathematical completeness of this model, we need to set the initial conditions for the model. For all three types, the initial ligand-bound normal receptor density was set as zero at all positions on the cell. We set **Q** as the length of the domain **Ω.** Moreover, we set the highest ligand concentration at the right side of the gradient as L_0, and then the initial ligand concentration was described as a linear function of position **A** with L = 0 on the left side of the domain (A = 0) and L = L_0 at the right side of the domain (A = Q). The initial position A_0 of the cell is at position 0.1 on the domain **Ω**. The initial ligand-

bound decoy receptor concentration was set as 0 at all positions. However, the position variable **B** for D_b which represents the position of a certain decoy receptor is different in three types; for type 1 model, it ranges from 0 to the length of the cell **P**; for type 2 model, it belongs to the gradient domain and the range of **B** for D_b will be from 0 to **Q**; for type 3 model, the decoy receptor is limited to the left side of the domain.

Equation 2: Initial conditions of the model

$$\begin{cases} R_b(x, t_o) = 0 \\ D_b(B, t_0) = 0 \\ L(A, t_0) = \dfrac{L_0}{Q}x \\ A(t_0) = 0.1 \end{cases}$$

Additionally, we chose homogeneous von Neumann boundary conditions as the boundary for the ligand field (Equation 3): in other words, the ligand cannot leave the domain.

Equation 3: Boundary conditions for L

$$\begin{cases} \dfrac{\partial L}{\partial A}(0, t) = 0 \\ \dfrac{\partial L}{\partial A}(Q, t) = 0 \end{cases}$$

3.2.6 Numerical algorithm

The numerical simulation of this model was performed by MATLAB. We set the domain length as 30; the cell was initially placed at position 0.1 and started moving from time 0.

For type 1 and type 3 model, we implemented the embedded MATLAB ode solver ode45 to solve the system, which is based on an explicit Runge-Kutta (4, 5) formula, the Dormand Prince pair [128]. For type 2 model, due to the characteristics of stiffness of this system, we implemented the MATLAB ode solver ode23s, which utilizes a modified Rosenbrock formula of order 2 and it is efficient on solving stiff problems [129]. The spatial discretization for the ligand field was performed by means of a second order finite difference scheme.