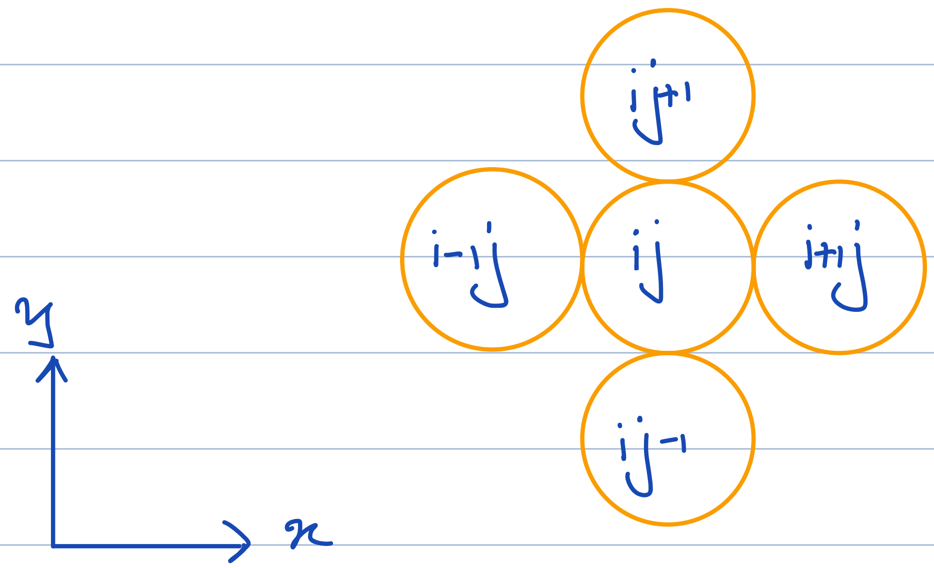
① Stochastic simulations

2D square lattice, $\Delta > 0$

P_m probability attempt to hop Δ during an interval of duration $\tau > 0$.



$(x_i, y_j) = (i\Delta, j\Delta)$

model input Δ, τ, P_m.

Nondimensionalize $\Delta = \tau = 1$.

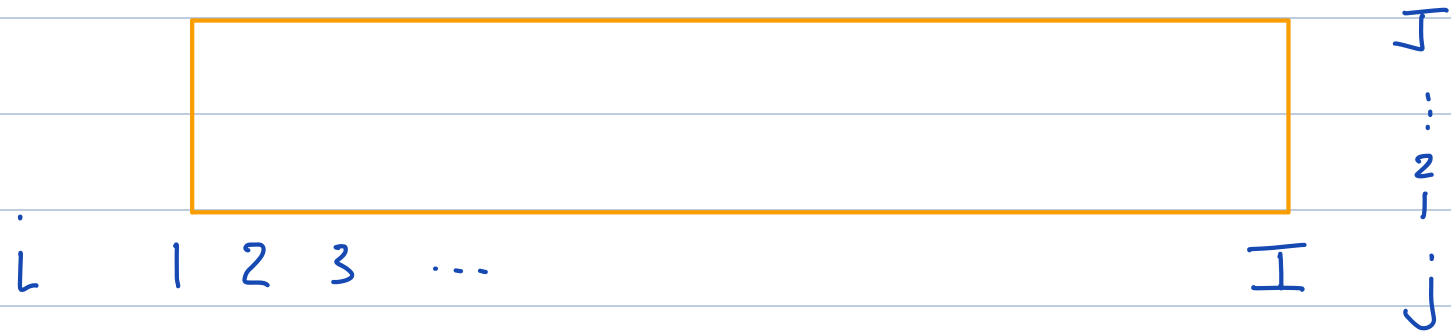
Key question : Given $N(x_i, y_j, t)$,

determine $N(x_i, y_j, t+\tau)$

① stochastic simulation

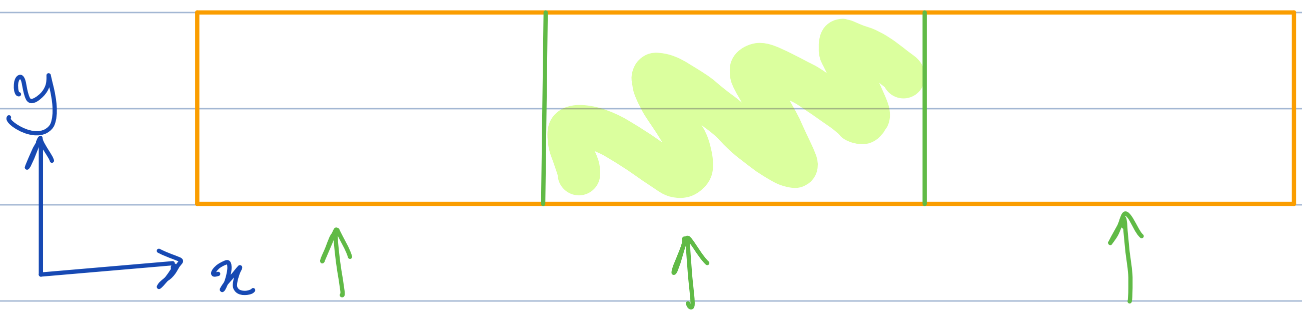
② mean-field, continuum limit.

Stochastic simulations



No flux boundary conditions $i = 1$, $i = I$
and $j = 1$, $j = J$

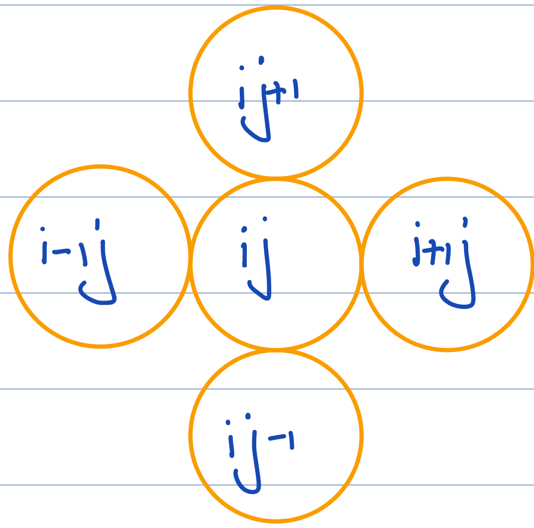
2D simulations produce 1D data like experiments



agent free | uniform density | agent free

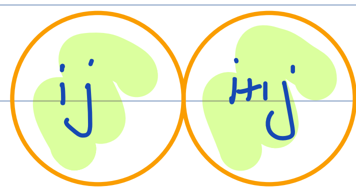
or uniform density | agent free | uniform density

Simulation algorithm



$\mathbb{P}(i{+}1j \mid ij) = P_m/4 \qquad \mathbb{P}(i{-}1j \mid ij) = P_m/4$

$\mathbb{P}(ij{+}1 \mid ij) = P_m/4 \qquad \mathbb{P}(ij{-}1 \mid ij) = P_m/4$



$\mathbb{P}(\text{attempt } i{+}1j \mid ij) = P_m/4$

$\mathbb{P}(\text{sucess move } i{+}1j \mid ij) = 0$

$\mathbb{P}(\text{attempt } ij \mid i{+}1j) = P_m/4$

$\mathbb{P}(\text{sucess move } ij \mid i{+}1j) = 0$

Assess potential moves
① does the agent attempt to move?
② which direction?
③ is the target site vacant?

Interactions mean the order in which we ask these questions matters!

Random Sequential Update
① $t = t'$, Q = total number of agents

② Randomly select Q agents, with replacement, give each agent an opportunity to move.

③ $t = t + \tau$, repeat

Consequences
① In any time step a particular agent may not be chosen
② In any time step a particular agent may be chosen more than once
③ On average, each agent will be chosen once

per time step.

Averaging and visualisation

- $N^{(m)}(x_i, y_j, t) = \begin{cases} 0 & \text{vacant} \\ 1 & \text{occupied} \end{cases}$

- each realisation

$$\bar{N}^{(m)}(x_i, t) = \frac{1}{J} \sum_{j=1}^{J} N^{(m)}(x_i, y_j, t)$$

$\bar{N}^{(m)}(x_i, t) \in [0, 1]$

- After M realisations

$$\langle N(x_i, t) \rangle = \frac{1}{M} \sum_{m=1}^{M} \bar{N}^{(m)}(x_i, t)$$

Fluctuations vanish as (MJ) increases.

- Continuum limit

Write $\langle N(x_i, t) \rangle$ as $u(x, t)$

will show $$\frac{\partial u}{\partial t} = D \frac{\partial^2 u}{\partial x^2}$$

$$D = \lim_{\Delta, \tau \to 0} \left[\frac{P_m \Delta^2}{4\tau} \right]$$

exact solution $-\infty < x < \infty$

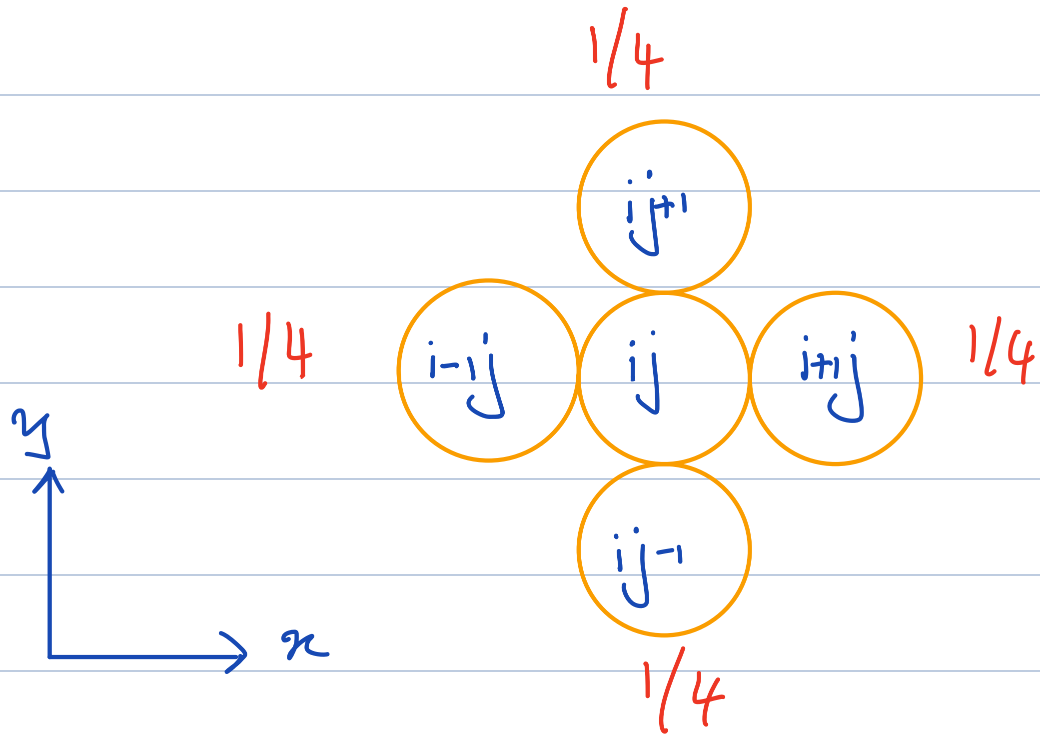
$$u(x,0) = \begin{cases} U_0 & |x| \leq h \\ 0 & |x| > h \end{cases}$$

$$u(x,t) = \frac{U_0}{2} \left[\operatorname{erf}\left(\frac{h-x}{\sqrt{4Dt}} \right) + \operatorname{erf}\left(\frac{h+x}{\sqrt{4Dt}} \right) \right]$$

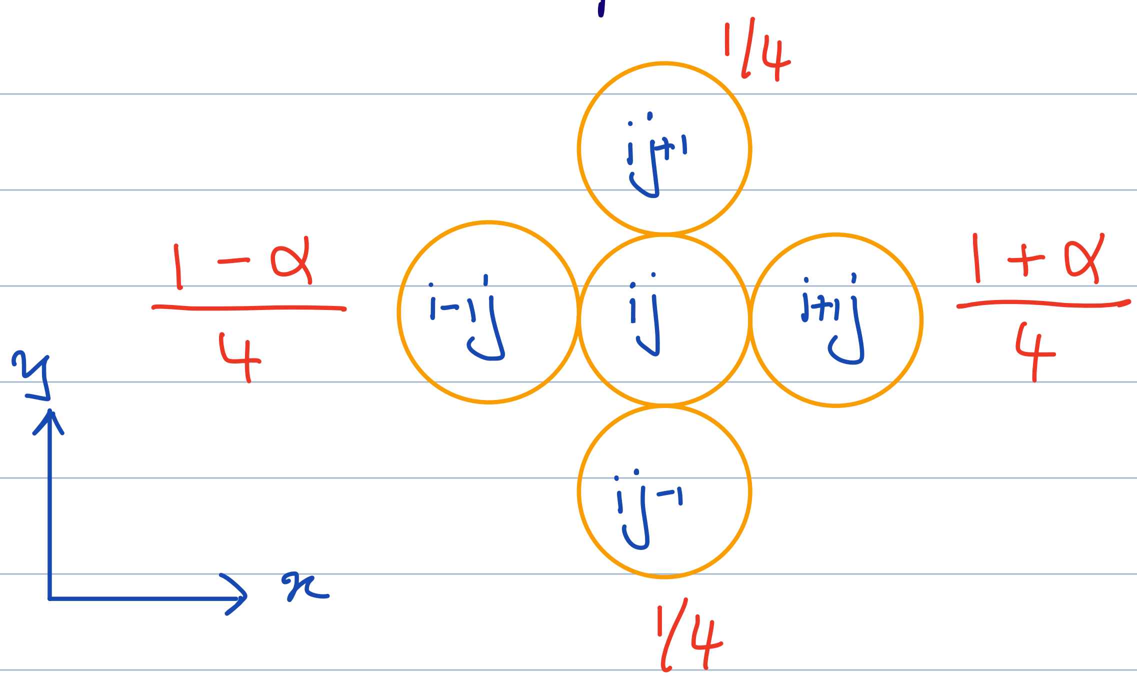
$$\operatorname{erf}(z) = \frac{2}{\sqrt{\pi}} \int_0^z e^{-s^2} \, ds.$$

explore in Julia

Biased motion



introduce bias parameter $|\alpha| \leq 1$



same discrete algorithm as before

inputs $\Delta, \tau, P_m, \alpha$

Unbiased motion and proliferation

Same motion as before (i.e. as above, $\alpha = 0$)

Proliferation, P_p probability that an agent attempts to divide into two agents. If so, the mother agent remains at the same site, and the daughter agent is placed on a nearest neighbour site, provided that the target site is vacant.

Random sequential update

$t = t \qquad Q = Q(t)$

① select $Q(t)$ agents, with replacement and give them the opportunity to move with probability P_m

② randomly select $Q(t)$ agents, with replacement and give them the opportunity to proliferate with probability P_p

$$t = t + \tau$$

$Q(t+\tau) = Q(t)$ + number of sucessful proliferation events

Remember ① cells move constantly $t^* \sim 5$ minute

② cells proliferate slowly $t^* \sim 1$ day

$$\frac{P_p}{P_m} \ll 1 \qquad \sim \frac{5\ min}{1 \times 24 \times 60\ min} \sim \frac{1}{288}$$

we can simulate by setting

$P_m = 1$ $\qquad P_p = 10^{-3}$ to 10^{-2}

Mean-field 2D unbiased migration

$\langle N(x_i, y_j, t)\rangle$ denote as $N_{ij} \in [0,1]$

$$\delta N_{ij} = \frac{P_m}{4} N_{i-1j}(1-N_{ij}) + \frac{P_m}{4} N_{i+1}(1-N_{ij})$$

$$+ \frac{P_m}{4} N_{ij-1}(1-N_{ij}) + \frac{P_m}{4} N_{ij+1}(1-N_{ij})$$

$$- \frac{P_m}{4} N_{ij}(1-N_{i-1j}) - \frac{P_m}{4} N_{ij}(1-N_{i+1j})$$

$$- \frac{P_m}{4} N_{ij}(1-N_{ij-1}) - \frac{P_m}{4} N_{ij}(1-N_{ij+1})$$

$$\delta N_{ij} = \frac{P_m}{4}(1-N_{ij})(N_{i-1j} + N_{i+1j} + N_{ij-1} + N_{ij+1})$$

$$- \frac{P_m}{4} N_{ij}(4 - N_{i-1j} - N_{i+1j} - N_{ij-1} - N_{ij+1})$$

$$= \frac{P_m}{4}(N_{i-1j} + N_{i+1j} + N_{ij-1} + N_{ij+1} - 4N_{ij})$$

associate $N(x_i\ y_j\ t)$ with smooth function $u(x, y, t)$

$$u(x \pm \Delta, y, t) = u(x, y, t) \pm \Delta \frac{\partial u}{\partial x}(x, y, t) + \frac{\Delta^2}{2} \frac{\partial^2 u}{\partial x^2}(x, y, t) + O(\Delta^3)$$

$$u(x, y \pm \Delta, t) = u \pm \Delta \frac{\partial u}{\partial y} + \frac{\Delta^2}{2} \frac{\partial^2 u}{\partial y^2} + O(\Delta^3)$$

$$\delta u = \frac{P_m \Delta^2}{4} \left[\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} \right]$$

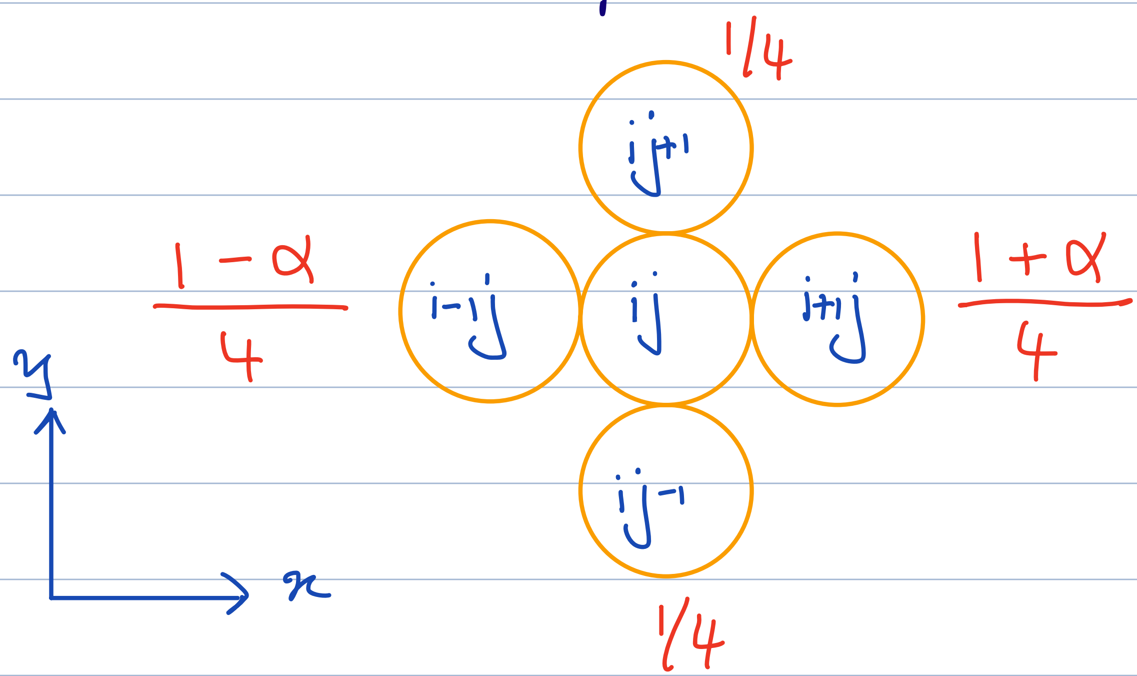
$$\frac{\delta u}{\tau} = \frac{P_m \Delta^2}{4\tau} \left[\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} \right]$$

$$\underbrace{\frac{\partial u}{\partial t} = D \nabla^2 u}, \qquad D = \lim_{\Delta, \tau \to 0} \left(\frac{P_m \Delta^2}{4\tau} \right)$$

can solve analytically or numerically (later)

2D biased migration

introduce bias parameter $|\alpha| \leq 1$



$$\delta N_{ij} = \frac{P_m(1+\alpha)}{4} N_{i-1j}(1-N_{ij}) + \frac{P_m(1-\alpha)}{4} N_{i+1j}(1-N_{ij})$$

$$+ \frac{P_m}{4}(N_{ij-1} + N_{ij+1})(1-N_{ij})$$

$$- \frac{P_m(1+\alpha)}{4} N_{ij}(1-N_{i+1j}) - \frac{P_m(1-\alpha)}{4} N_{ij}(1-N_{i-1j})$$

$$- \frac{P_m}{4} N_{ij}(2 - N_{ij-1} - N_{ij+1}).$$

$$\delta N_{ij} = \frac{P_m}{4}\left[N_{i-1j} + N_{i+1j} + N_{ij-1} + N_{ij+1} - 4N_{ij}\right]$$

$$+ \frac{\alpha P_m}{4}\left[(N_{i-1j} - N_{i+1j})(1 - 2N_{ij})\right]$$

Work with $u(x,y,t)$

$$\delta u = \frac{P_m \Delta^2}{4}\left[\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2}\right] + \frac{\alpha P_m}{4}\left[-2\Delta \frac{\partial u}{\partial x}(1-2u)\right]$$

$$\frac{\delta u}{\tau} = \left(\frac{P_m \Delta^2}{4\tau}\right)\nabla^2 u - \left(\frac{\alpha P_m \Delta}{2\tau}\right)(1-2u)\frac{\partial u}{\partial x}$$

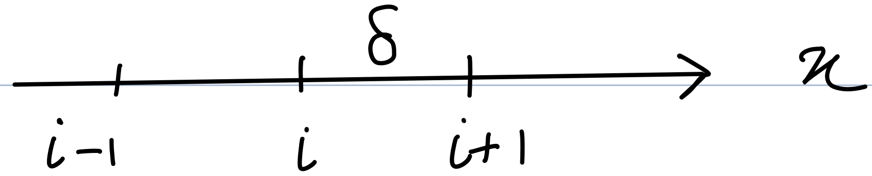
$$\frac{\partial u}{\partial t} = D\nabla^2 u - V\frac{\partial}{\partial x}\left[u(1-u)\right]$$

$$D = \lim_{\Delta,\tau\to 0}\left(\frac{P_m \Delta^2}{4\tau}\right), \quad V = \lim_{\Delta,\tau\to 0}\left(\frac{P_m \alpha \Delta}{2\tau}\right)$$

To obtain a well-defined limit we require $\alpha = O(\Delta)$,

$$\frac{\Delta^2}{\tau} = O(1) \qquad \frac{\alpha\Delta}{\tau} = O(1)$$

Numerical solution



$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} - v\frac{\partial}{\partial x}\left[u(1-u)\right] = -\frac{\partial J}{\partial x}$$

$$J = -D\frac{\partial u}{\partial x} + v\,u(1-u)$$

$i=1$, $J_1=0$, $\frac{du_1}{dt} = \frac{-(J_2-J_1)}{\delta} = \frac{D}{\delta^2}\left[u_2-u_1\right] - v\,u_2(1-u_2)$

$i = 2, 3, \ldots I-2, I-1$

$$\frac{du_i}{dt} = \frac{D}{\delta^2}\left(u_{i+1} - 2u_i + u_{i-1}\right) - \frac{v}{2\delta}\left[u_{i+1}(1-u_{i+1}) - u_{i-1}(1-u_{i-1})\right]$$

$i = I$, $J_I = 0$, $\frac{du_I}{dt} = -\frac{(J_I - J_{I-1})}{\delta}$

$$\frac{du_I}{dt} = \frac{D}{\delta^2}\left[u_{I-1} - u_I\right] - \frac{v}{\delta}u_{I-1}(1-u_{I-1})$$

2D unbiased migration + proliferation

$$\delta N_{ij} = \frac{P_m}{4}\left[N_{ij-1} + N_{ij+1} + N_{i-1j} + N_{i+1j} - 4N_{ij}\right]$$

$$+ \frac{P_p}{4}(1-N_{ij})(N_{ij-1} + N_{ij+1} + N_{i-1j} + N_{i+1j})$$

N_{ij} $\qquad u(x,y,t)$

$$\frac{\delta u}{\tau} = \left(\frac{P_m \Delta^2}{4\tau}\right)\nabla^2 u + \left(\frac{P_p}{4\tau}\right)(1-u)\left[\Delta^2 \nabla^2 u + 4u\right]$$

$$= \left(\frac{P_m \Delta^2}{4\tau}\right)\nabla^2 u + \left(\frac{P_p}{\tau}\right) u(1-u) + \left(\frac{P_p \Delta^2}{4\tau}\right)\nabla^2 u(1-u)$$

let $\Delta \to 0$, $\tau \to 0$ so Δ^2/τ is $O(1)$

$$D = \lim_{\Delta,\tau \to 0}\left(\frac{P_m \Delta^2}{4\tau}\right)$$

two options

① $\left(\frac{P_p \Delta^2}{4\tau}\right)$ is $O(1)$ implying $\frac{P_p}{\tau} \to \infty$

(2) $\left(\frac{P_p}{\tau}\right)$ is $O(1)$ as $\tau \to 0$

which implies $P_p = O(\tau)$ as $\tau \to 0$

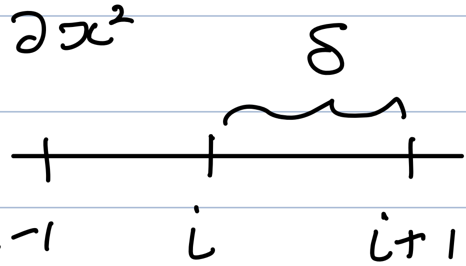
and $\left(\frac{P_p \Delta^2}{4\tau}\right) \to 0$ as $\tau \to 0$

option 2 leads to a partial differential equation that can be written in a standard conservation form

$$\frac{\partial u}{\partial t} = -\frac{\partial J}{\partial x} + S$$

Numerical Solution

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + \lambda u(1-u)$$



$$\frac{du_i}{dt} = \frac{D}{\delta^2}\left(u_{i+1} - 2u_i + u_{i-1}\right) + \lambda u_i(1-u_i)$$

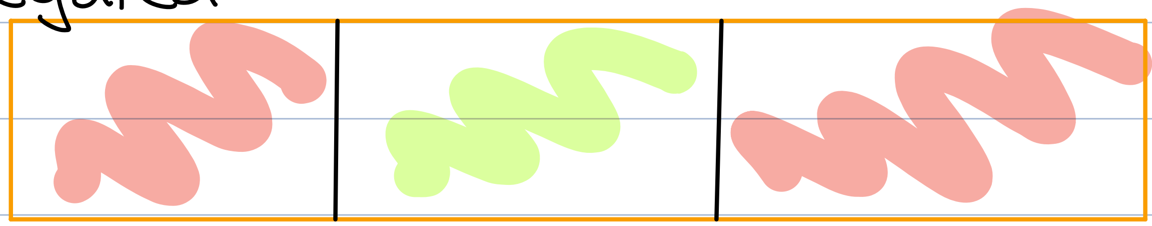
$$i = 2, 3, \dots I-1$$

$$\frac{du_1}{dt} = \frac{D}{\delta^2}\left(u_2 - u_1\right) + \lambda u_1(1-u_1)$$

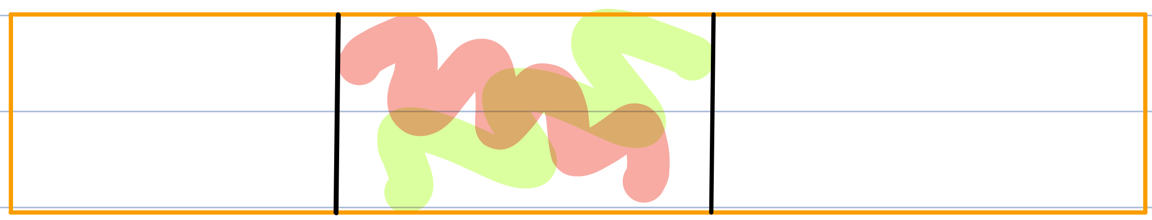
$$\frac{du_I}{dt} = \frac{D}{\delta^2}\left(u_{I-1} - u_I\right) + \lambda u_I(1-u_I).$$

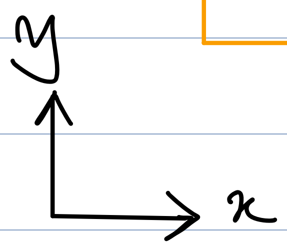
2 populations, migration only

segregated



mixed





simulations – Vacant site 0
– population A 1
– population B 2

input Δ, τ, P_1, P_2

let $A_{ij} \in [0,1]$ average occupancy of subpopulation A at (i,j) time t.

$B_{ij} \in [0,1]$ average occupancy

of subpopulation B at (i,j), time t.

$$S_{ij} = A_{ij} + B_{ij} \in [0,1]$$

$$\delta A_{ij} = \frac{P_1}{4}(1 - S_{ij})(A_{ij-1} + A_{ij+1} + A_{i-1j} + A_{i+1j})$$
$$- \frac{P_1}{4} A_{ij}(4 - S_{ij-1} - S_{ij+1} - S_{i-1j} - S_{i+1j})$$

$$\delta B_{ij} = \frac{P_2}{4}(1 - S_{ij})(B_{ij-1} + B_{ij+1} + B_{i-1j} + B_{i+1j})$$
$$- \frac{P_2}{4} B_{ij}(4 - S_{ij-1} - S_{ij+1} - S_{i-1j} - S_{i+1j})$$

$$A_{ij} \to a(x,y,t)$$

$$B_{ij} \to b(x,y,t)$$

$$S_{ij} \to s(x,y,t)$$

$$\frac{\delta a}{\tau} = \frac{P_1}{4\tau}(1-s)(4a + \Delta^2 \nabla^2 a)$$

$$- \frac{P_1}{4\tau} a (4 - 4s - \Delta^2 \nabla^2 s)$$

$$= \frac{P_1 \Delta^2}{4\tau} \left[(1-s)\nabla^2 a + a \nabla^2 s \right]$$

$\tau \to 0$ $\Delta \to 0$ so that Δ^2/τ $O(1)$

$$\frac{\partial a}{\partial t} = D_1 \left[(1-s)\nabla^2 a + a\nabla^2 s \right]$$

$$= -\nabla \cdot J_a$$

$$= D_1 \nabla \cdot \left[(1-s)\nabla a + a \nabla s \right]$$

$$J_a = -D_1 \left[(1-s)\nabla a + a \nabla s \right]$$

$$D_1 = \lim_{\Delta, \tau \to 0} \left[\frac{P_1 \Delta^2}{4\tau} \right]$$

similar algebra leads to

$$\frac{\partial b}{\partial t} = D_2 \nabla \cdot \left[(1-s)\nabla b + b \nabla s \right]$$

1D

$$\frac{\partial a}{\partial t} = D_1 \frac{\partial}{\partial x} \left[(1-s)\frac{\partial a}{\partial x} + a \frac{\partial s}{\partial x} \right] \quad (1)$$

$$\frac{\partial b}{\partial t} = D_2 \frac{\partial}{\partial x} \left[(1-s)\frac{\partial b}{\partial x} + b \frac{\partial s}{\partial x} \right] \quad (2)$$

special case $D_1 = D_2 = D$, sum (1) + (2)

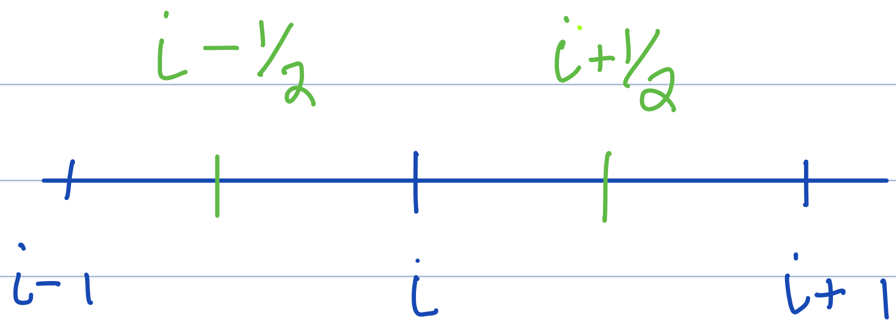
$$\frac{\partial s}{\partial t} = D \frac{\partial}{\partial x} \left[(1-s)\frac{\partial s}{\partial x} + s \frac{\partial s}{\partial x} \right]$$

$$= D \frac{\partial^2 s}{\partial x^2}$$

linear diffusion!

numerical solution

$$\frac{\partial a}{\partial t} = -\frac{\partial J_a}{\partial x}, \qquad J_a = -D\left[(1-s)\frac{\partial a}{\partial x} + a\frac{\partial s}{\partial x}\right]$$



$$\frac{da_i}{dt} = -\frac{1}{\delta}\left[J_{i+\frac{1}{2}} - J_{i-1/2}\right]$$

$$J_{i+\frac{1}{2}} = -D\left[\left(1 - s_{i+\frac{1}{2}}\right)\left.\frac{\partial a}{\partial x}\right|_{i+\frac{1}{2}} + a_{i+1/2}\left.\frac{\partial s}{\partial x}\right|_{i+1/2}\right]$$

$$s_{i\pm\frac{1}{2}} = \frac{1}{2}\left(s_i + s_{i\pm 1/2}\right)$$

$$a_{i\pm 1/2} = \frac{1}{2}\left(a_i + a_{i\pm 1/2}\right)$$

$$J_{i+1/2} = -D\left[\frac{(2-s_i-s_{i+1})}{2}\,\frac{(a_{i+1}-a_i)}{\delta} + \frac{(a_i+a_{i+1})}{2}\,\frac{(s_{i+1}-s_i)}{\delta}\right]$$

$$\frac{da_i}{dt} = \frac{D_1}{2\delta^2}\Big[(2-s_i-s_{i+1})(a_{i+1}-a_i)+(a_i+a_{i+1})(s_{i+1}-s_i)$$

$$-(2-s_i-s_{i-1})(a_i-a_{i-1})+(a_i+a_{i-1})(s_i-s_{i-1})\Big]$$

$$\frac{db_i}{dt} = \frac{D_2}{2\delta^2}\Big[(2-s_i-s_{i+1})(b_{i+1}-b_i)+(b_i+b_{i+1})(s_{i+1}-s_i)$$

$$-(2-s_i-s_{i-1})(b_i-b_{i-1})+(b_i+b_{i-1})(s_i-s_{i-1})\Big]$$

adjust $\frac{da_1}{dt}$, $\frac{da_I}{dt}$, $\frac{db_i}{dt}$, $\frac{db_I}{dt}$, to impose

no flux at the boundaries and explore consequences in Julia.