# Multiscale-cell based modeling formalism CPM

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# modeling biotic systems as multilevel systems

Previously:

EMERGENT MESOSCALE ENTITIES:
- discovery and description
- modeling these entities
-variable number of 'entities,
- mean field approximation

Now:

PREDEFINED MULTIPLE LEVEL

- e.g. predefined cells as mesoscale
- multiple timescales of information transfer
- multiple scales of interaction

example of cell movement

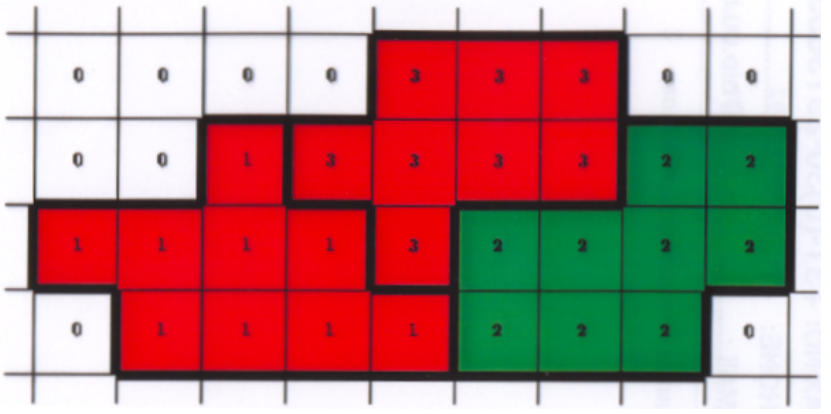
## How to represent a cell?

*cell basic unit in single celled and multi-cellular organisms*

- cell as a dimensionless point: PDE
- cell as occupation of a patch of space: CA
  *NB particle conservation!*
- cell as a "homunculus" IBM
- cell as a ball being moved by external forces (finite element models)
- **Cells are deformable highly viscuous objects,**
  **behaviour determined by internal state (gen expression)**
  **and external interactions operating in subcellular scale**

## How to model? Multilevel model formalism (CPM)

# Glazier-Graner 2-Scale CA model
# CPM




- A 'biotic' cell consists of many lattice sites in same 'state' (= cell identity)
- Cells have a type $\tau$, volume v (and...)
- Between cells: free energy bod $J_{ij}$ where i and j are the types of the cells
- *dynamics*: Free energy minimization with volume conservation:

$$H = \sum \frac{J_{ij}}{2} + \sum J_{im} + \lambda(v - V)^2$$

- Copy state of neighbouring cell with probability:

$$P_{i \to j} = 1 \quad iff \quad \Delta H < -\beta \quad ; \quad P_{i \to j} = e^{-(\Delta H + \beta)/M} \quad iff \quad \Delta H \geq -\beta$$

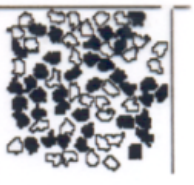
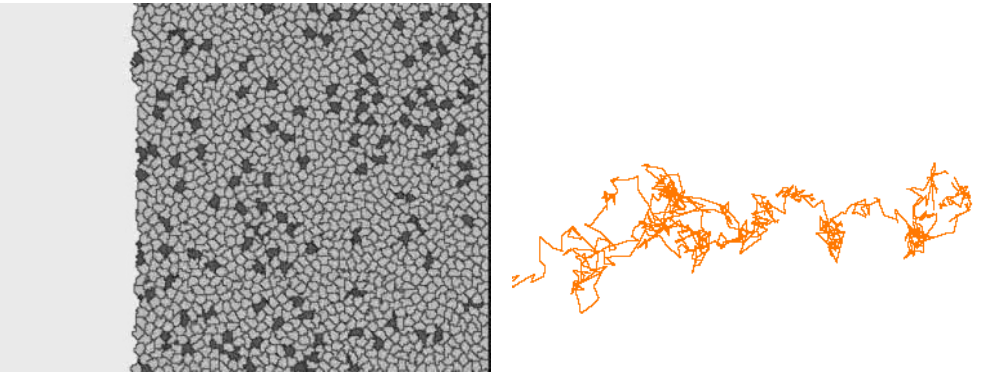
| | |
|---|---|
| Initial configuration |  |
| Cell Sorting<br>$J_{white,white} = J_{grey,grey} < J_{white,grey}$ |  |
| Cell Mixing<br>$J_{white,white} = J_{grey,grey} > J_{white,grey}$ |  |
| Engulfment<br>$J_{white,grey} < J_{white,medium}$<br>$J_{grey,medium} < J_{white,medium}$ |  |
| No cell cell adhesion<br>$J_{cell,cell} > 2J_{cell,medium}$ |  |

Table 2.2: A list of cell sorting behaviours in the Glazier and Graner model

# from cells to tissues (and beyond)

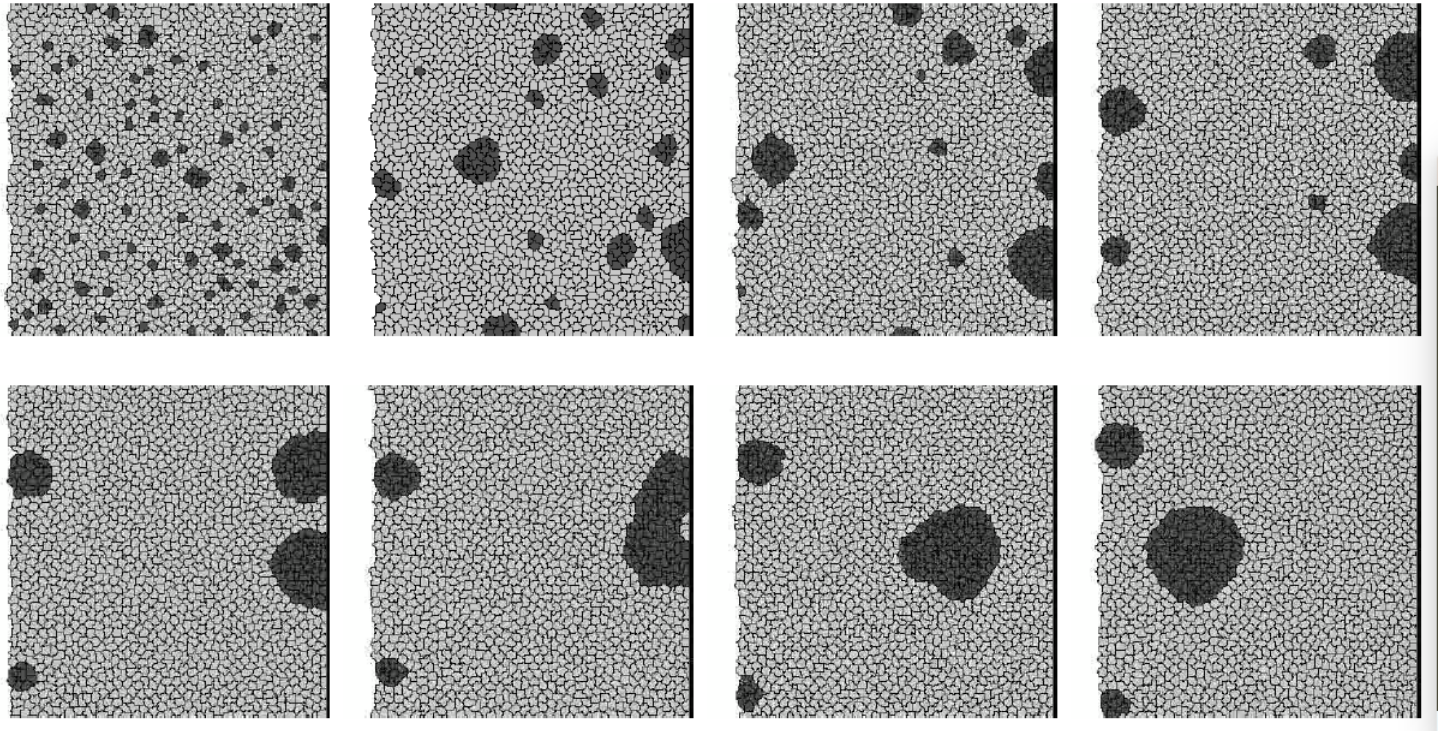
- cell sorting by differential adhesion
- Individual cells 'wiggle' through cell mass



- Same chemotaxis to the right for all cells
- Individual cells can 'move against the flow'
  e.g. by being larger; being in the minority, adhesion
  here: same size $J_{ll} = 5$ $J_{dl} = 3$ $J_{dd} = 3$

Käfer, Hogeweg & Marée 2006

# Cells can reverse direction due to clumping forming larger "pseudocell"

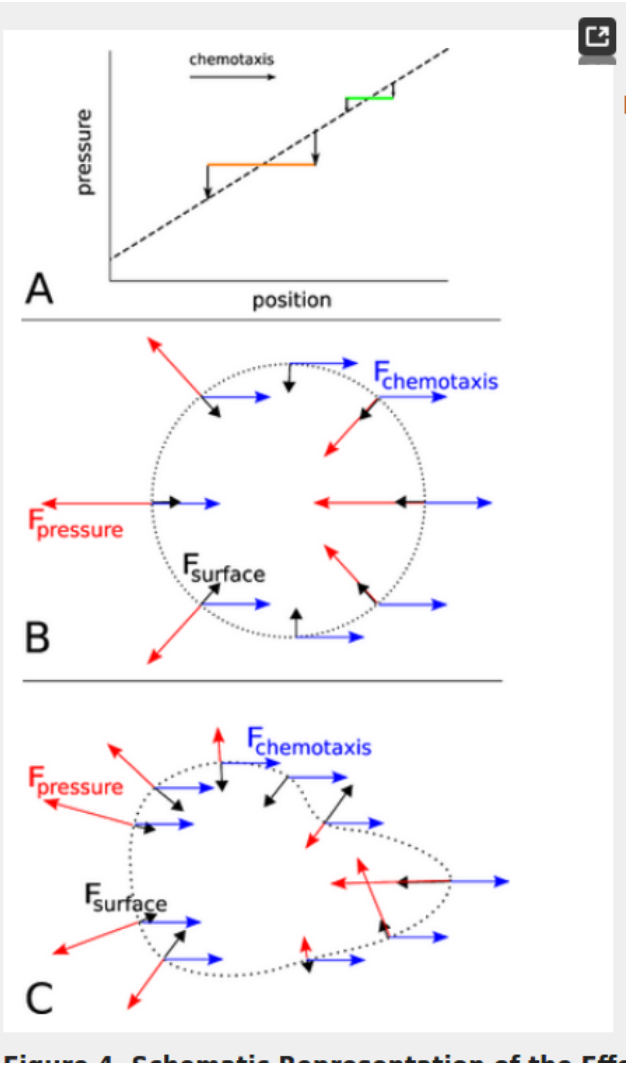


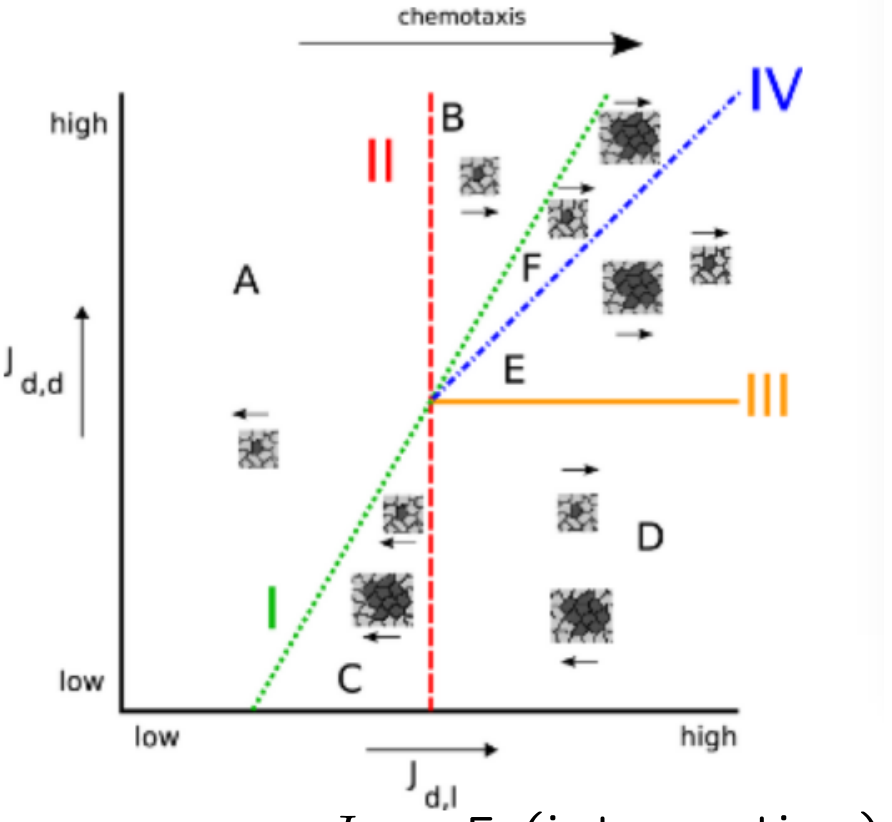
$J_{ll} = 5 \;\; J_{dl} = 8 \;\; J_{dd} = 2$

$---->$ chemotaxis

v

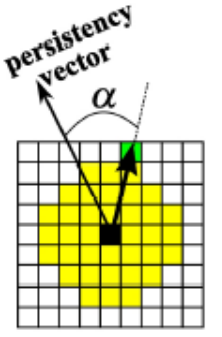
# Why? Due to emergent pressure forces and cell shapes

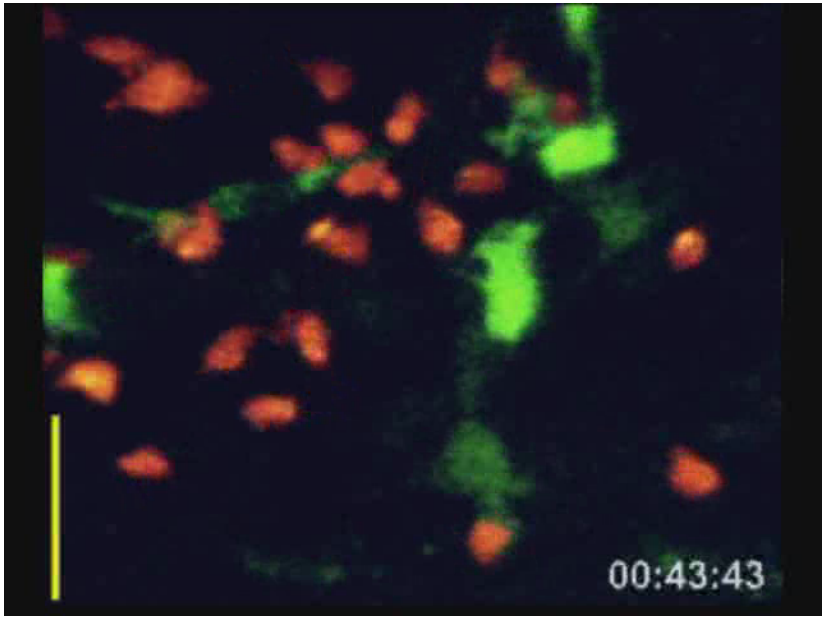


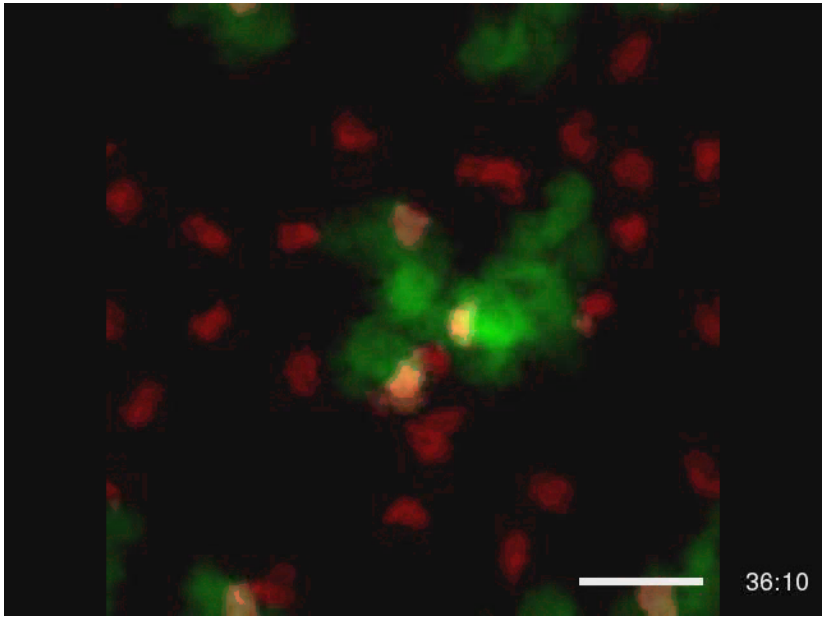

$J_{ll} = 5$ (intersection)

# Cell movement in Lymphnode: stop and go ( Beltman et al 2007)



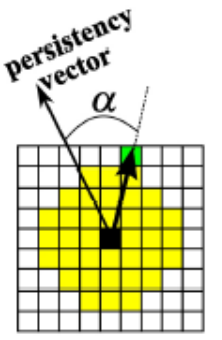



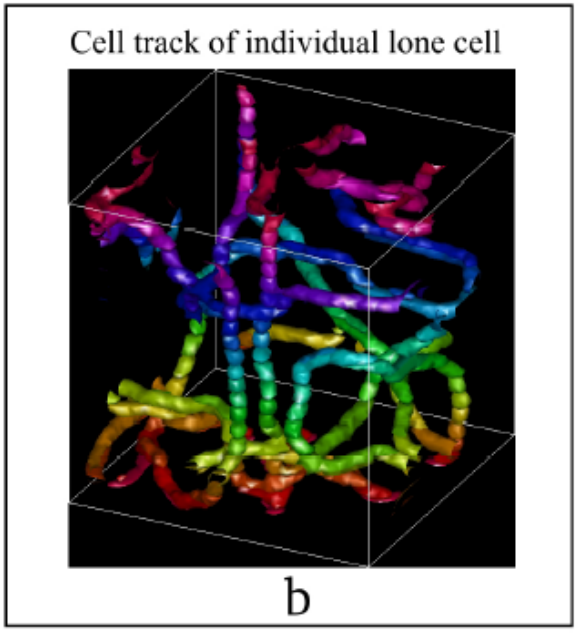

in vitro (Miller et al)

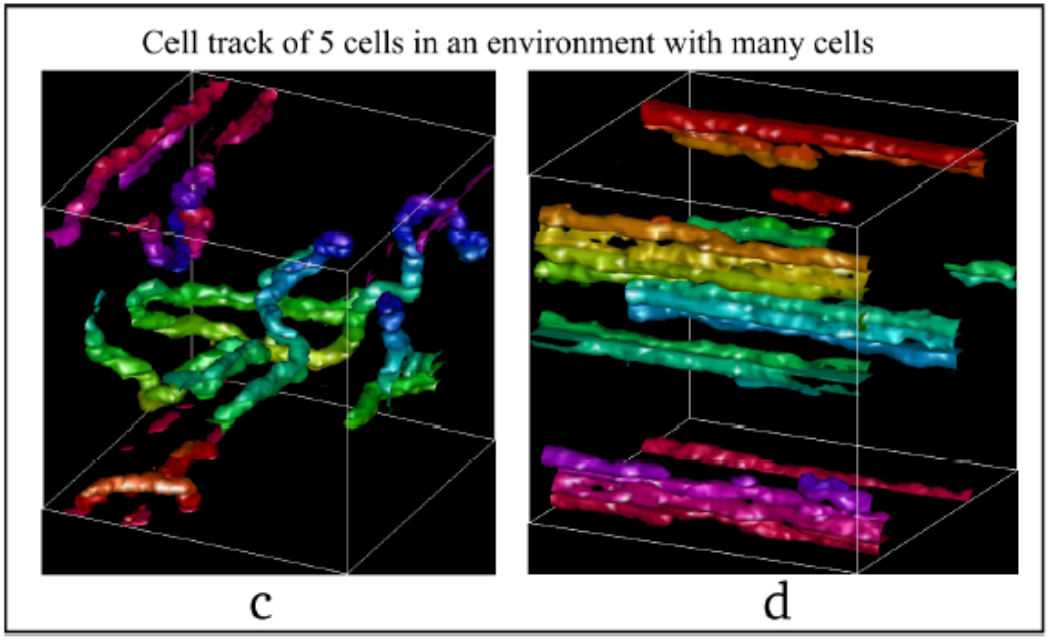



in silico (Beltman et al)

# Cell movement in emty Lymphnode
# Beltman et al 2007



## Chemotaxis in lymphnodes?

*beware of modeling artifacts*

Weak chemotaxis hard to detect by cell tracking. Augment by modeling: what would the effect of chemotoxis be?

2 models: opposite conclusions

Riggs et al JTB 2008:" A comparison of random vs. chemotaxis-driven contacts of T cells with dendritic cells during repertoire scanning" .

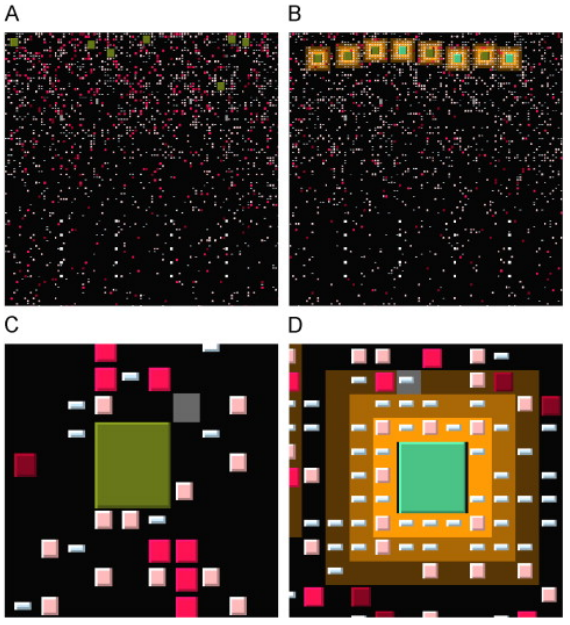
*Our [CA modeling results] suggest that, within a LN T-zone, a random search strategy is optimal for a rare cognate T cell to find its DC match and maximize production of activated T cells "*

Vroomans et al 2012: "Chemotactic Migration of T Cells towards Dendritic Cells Promotes the Detection of Rare Antigens"

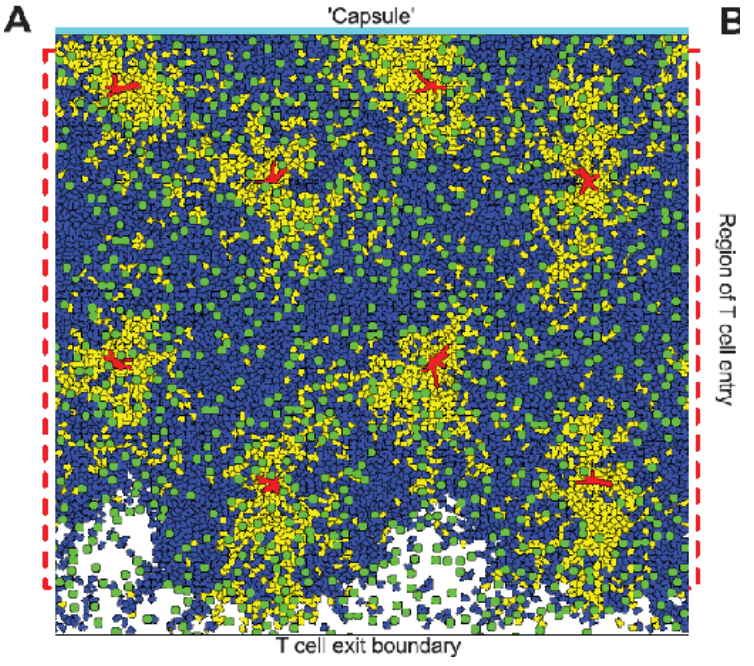
*Our [CPM] simulations show that chemoattraction of T cells enhances the DC scanning efficiency, leading to an increased probability that rare antigen-specific T cells find DCs carrying cognate antigen.*

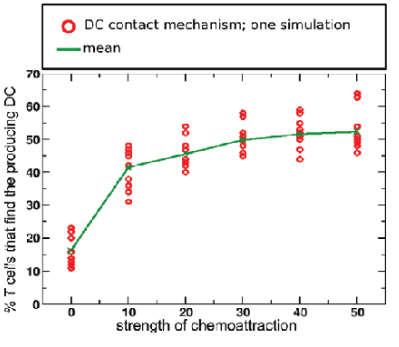
**Models incorporate very similar biological assumptions**
**Difference in modeling formalism**

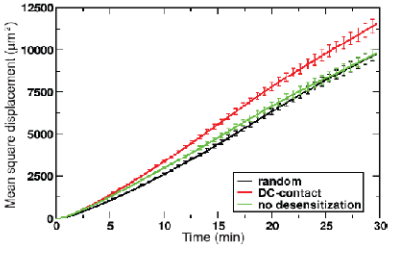
CA model of Riggs et al




CPM model of Vroomans et al



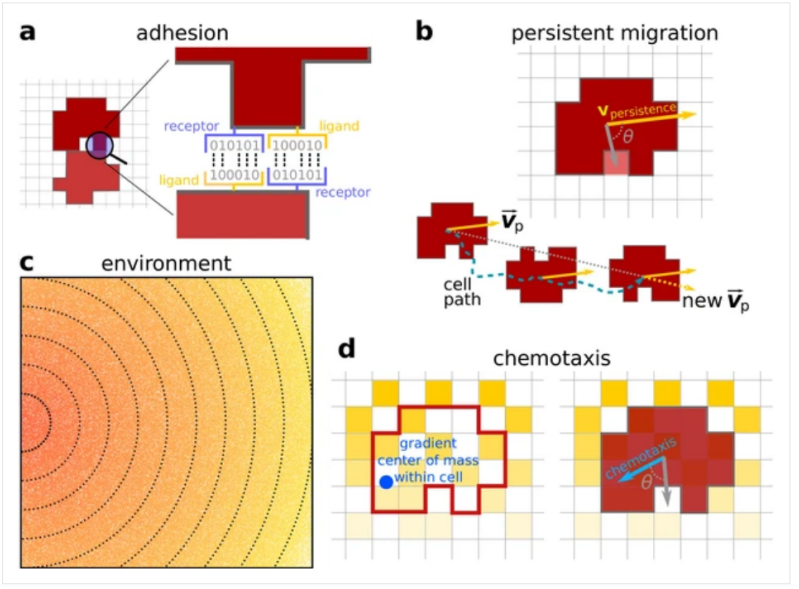

RANDOM CHEMOTAXIS

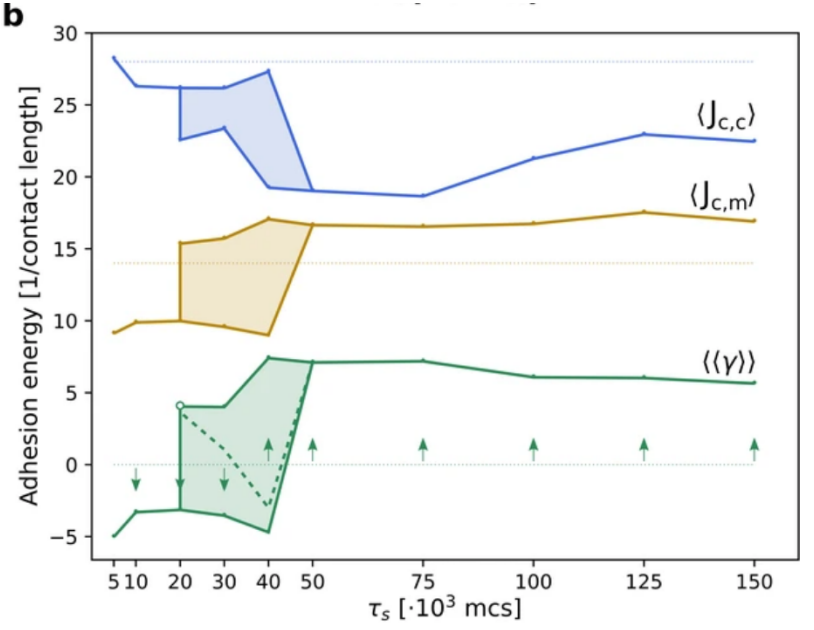
(3D) (2D)

Vroomans: sensitive T cells (blue), insensitive T cells (yellow), DCs (red), reticular

network (green)

# Evolution of multicellularity (Colizzi et al 2020)




Adhesion defined by complementary matching of receptor and ligand.

Chemoattractant diffuses from food resource;

Location of foodsource changes periodically ($\tau$)

Reproduction chance dependent on distance to food at end of season
mutations of receptor and ligand.

# Spatial modeling formalisms

| **space / time / var.** | **formalism** |
|---|---|
| ccc (ddc) | partial differential equations (PDE)<br>reaction diffusion systems |
| ddc | map lattices |
| ddd | CA |
| ccd | individual oriented models<br>off lattice particle systems / event-based |
| dcc | meta-population models |
| c/dc (d+c) | hybrid models |

note: translations