

CPM

**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

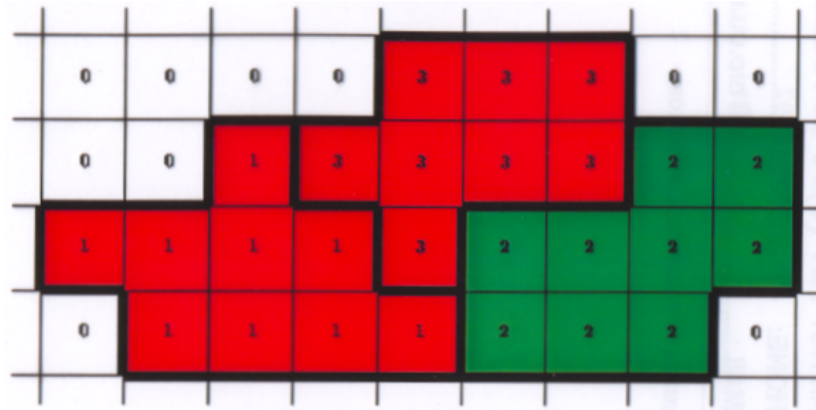
How to represent a cell?

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 viscous 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 τ , volume v (and...)
- Between cells: free energy bond 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:

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



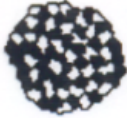


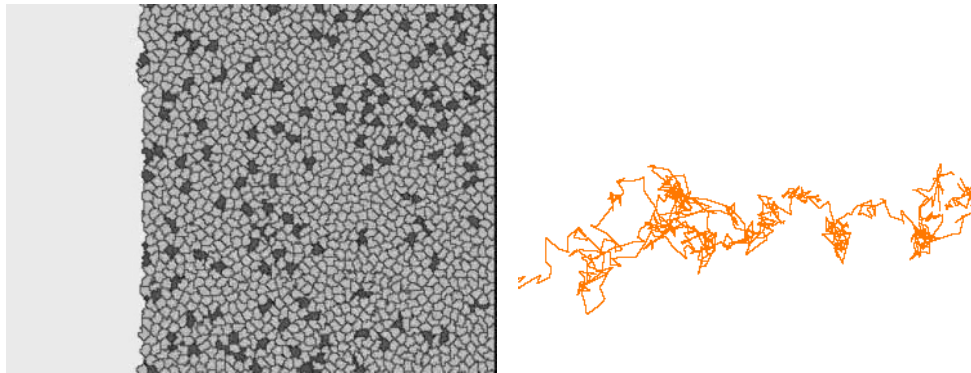
Initial configuration	
Cell Sorting $J_{white,white} = J_{grey,grey} < J_{white,grey}$	
Cell Mixing $J_{white,white} = J_{grey,grey} > J_{white,grey}$	
Engulfment $J_{white,grey} < J_{white,medium}$ $J_{grey,medium} < J_{white,medium}$	
No cell cell adhesion $J_{cell,cell} > 2J_{cell,medium}$	

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

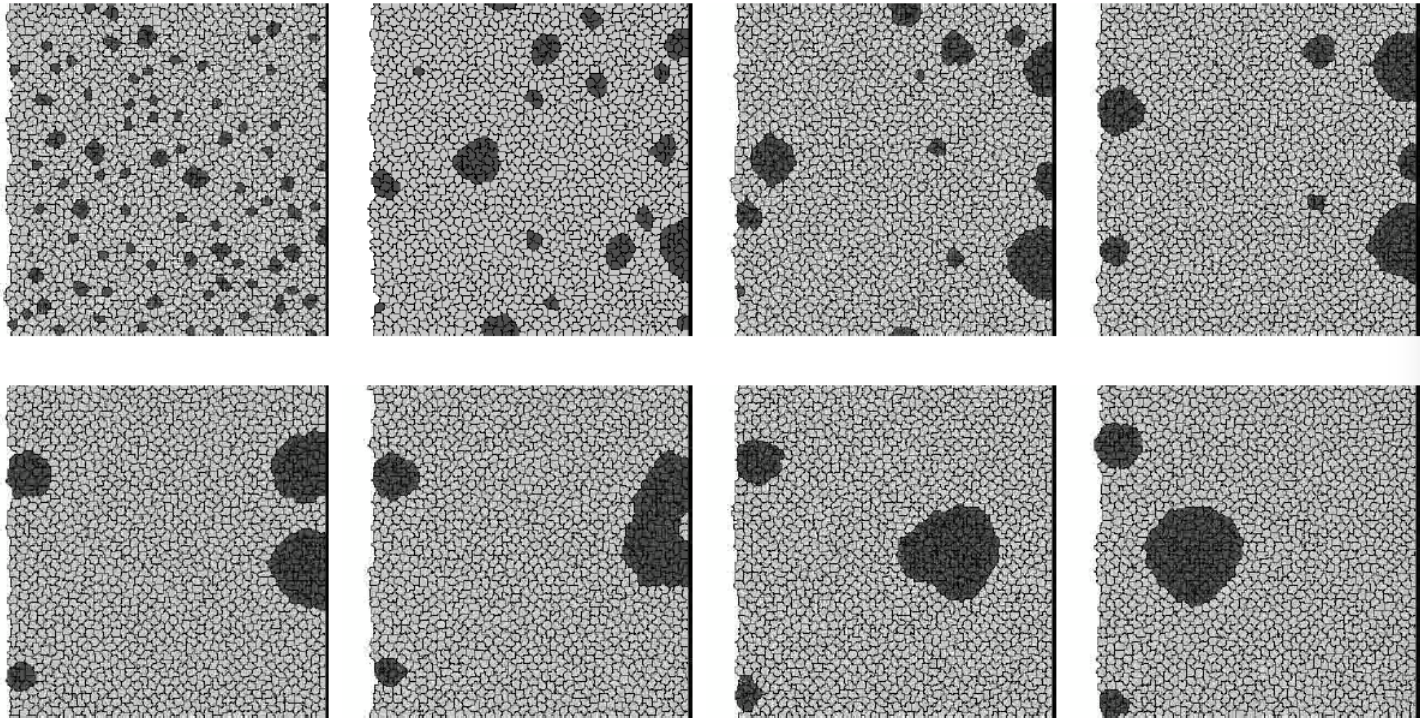
from cells to tissues (and beyond)

- 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 $J_{ll} = 5$ $J_{dl} = 3$ $J_{dd} = 3$

Cells can reverse direction due to clumping forming larger “pseudocell”



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

— — — > chemotaxis

Why? Due to emergent pressure forces and cell shapes

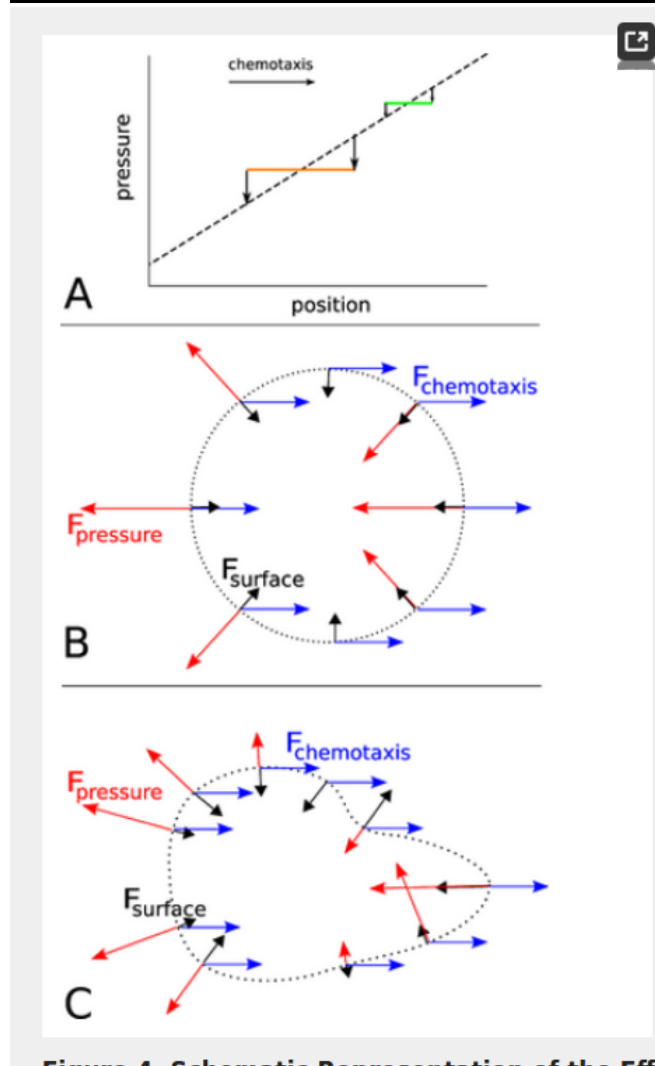
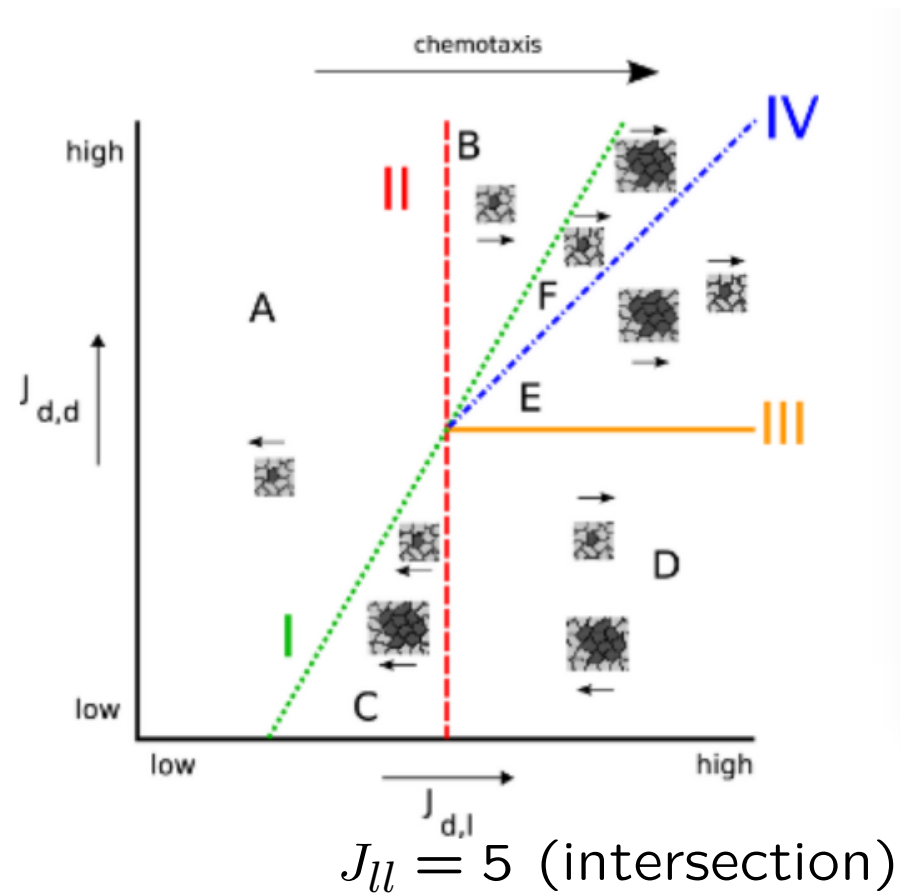
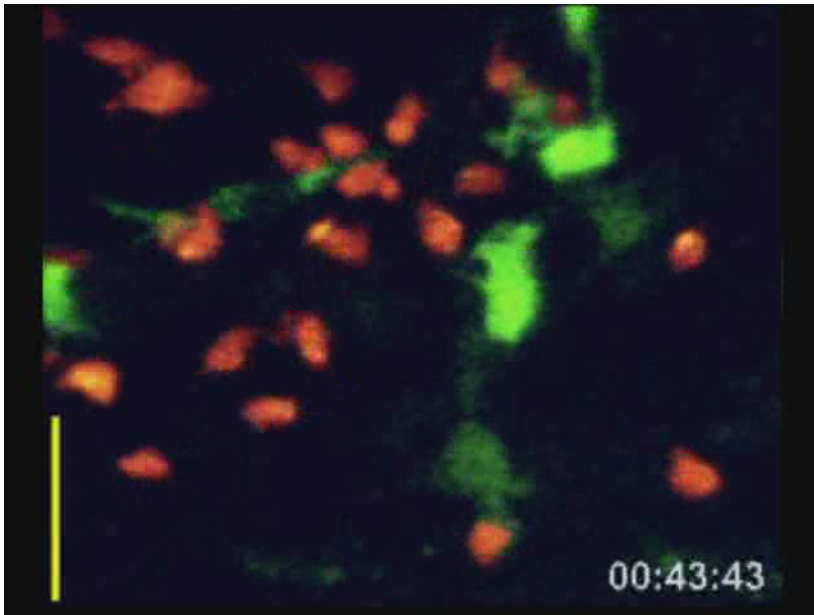
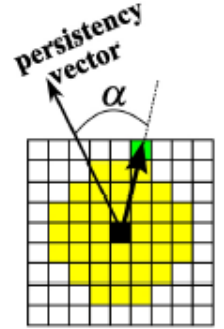


Figure 4. Schematic Representation of the Effects of Chemotaxis and Pressure Forces on Cell Migration.

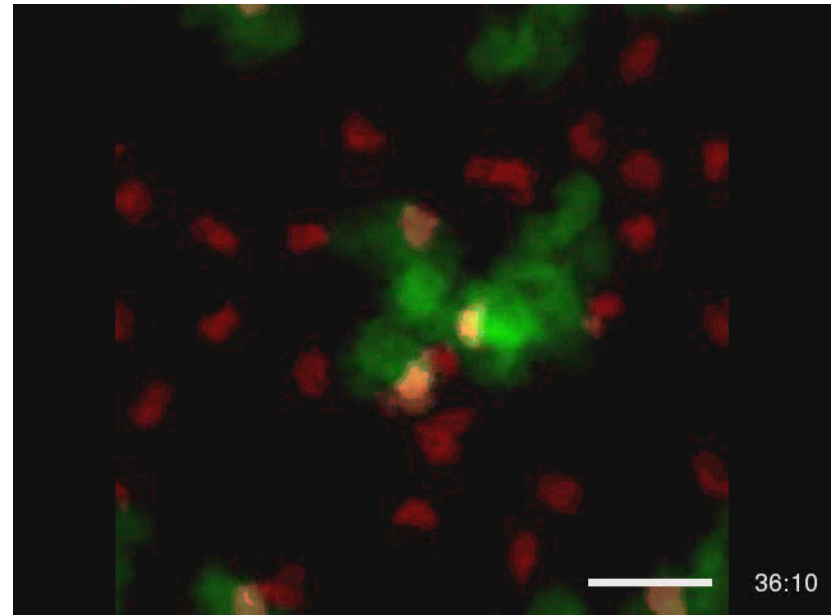


$$J_{ll} = 5 \text{ (intersection)}$$

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



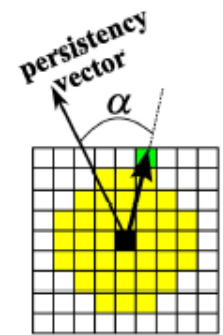
in vitro (Miller et al)



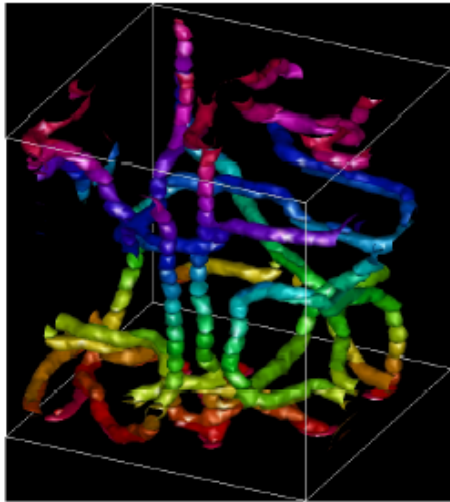
in silico (Beltman et al)

Cell movement in empty Lymphnode

Beltman et al 2007

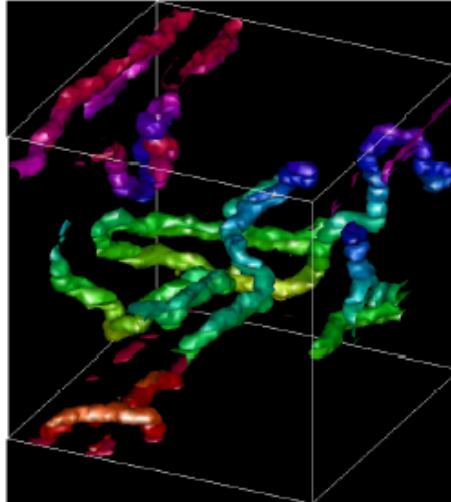


Cell track of individual lone cell

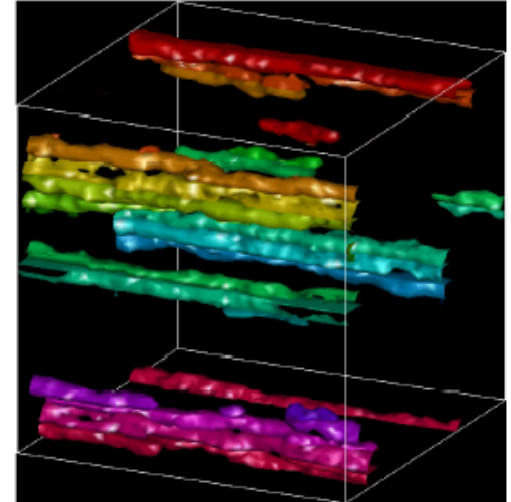


b

Cell track of 5 cells in an environment with many cells



c



d

Chemotaxis in lymphnodes? *beware of modeling artifacts*

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

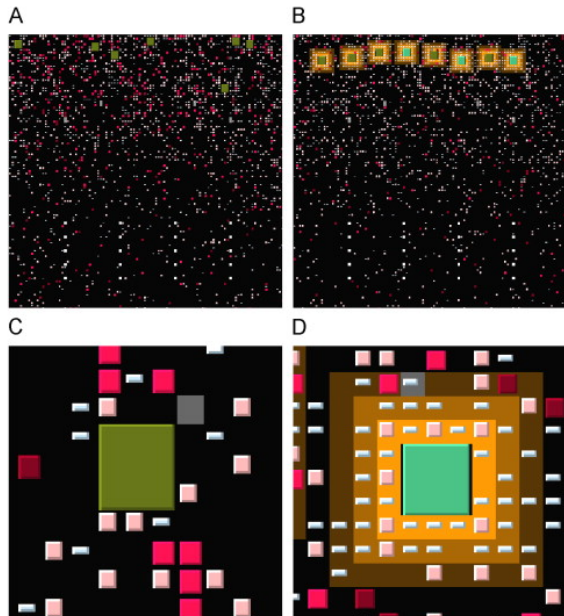
Our [CA modeling results] suggest that, within a LN T-zone, a random search strategy is optimal for a rare cognate T cell to find its DC match and maximize production of activated T cells "

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

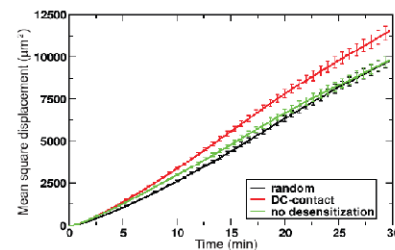
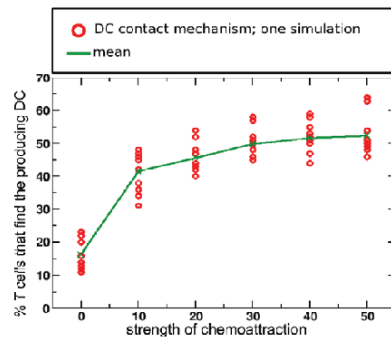
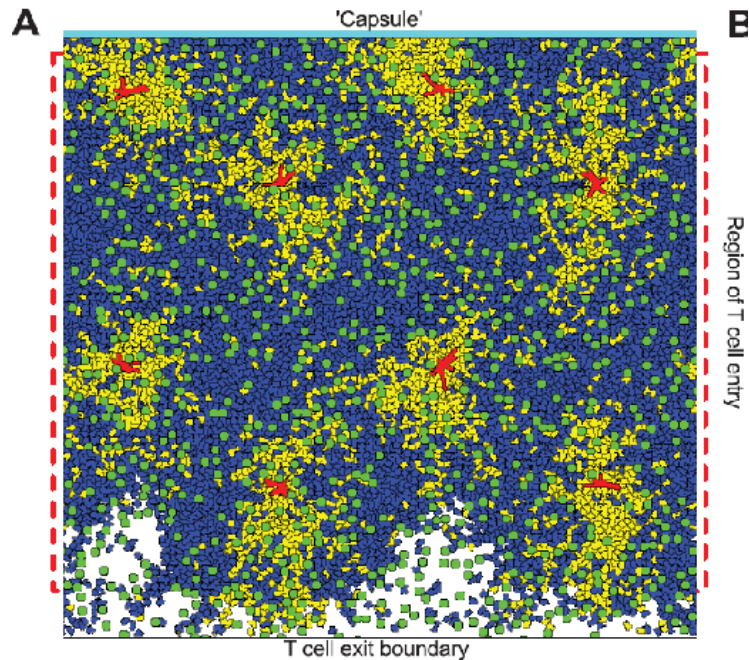


RANDOM

CHEMOTAXIS

(3D)

CPM model of Vroomans et al

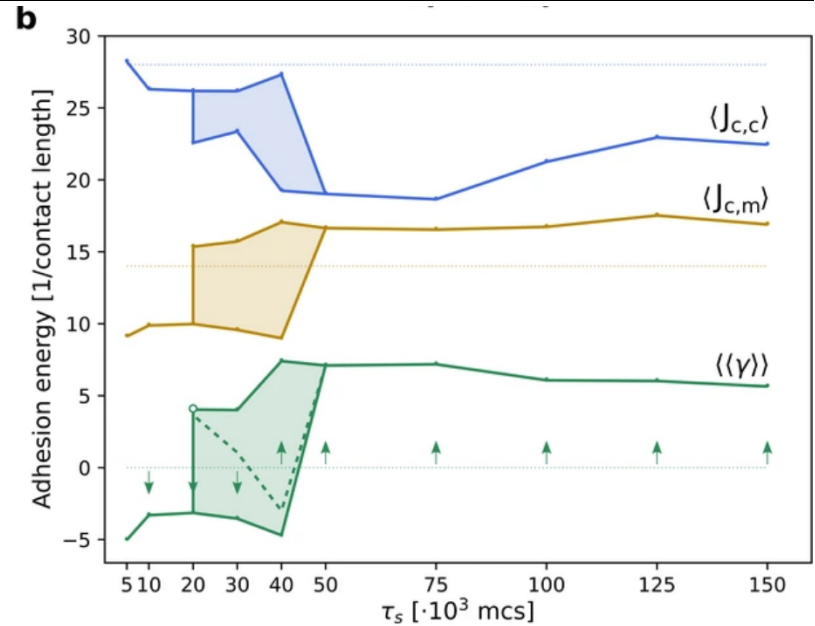
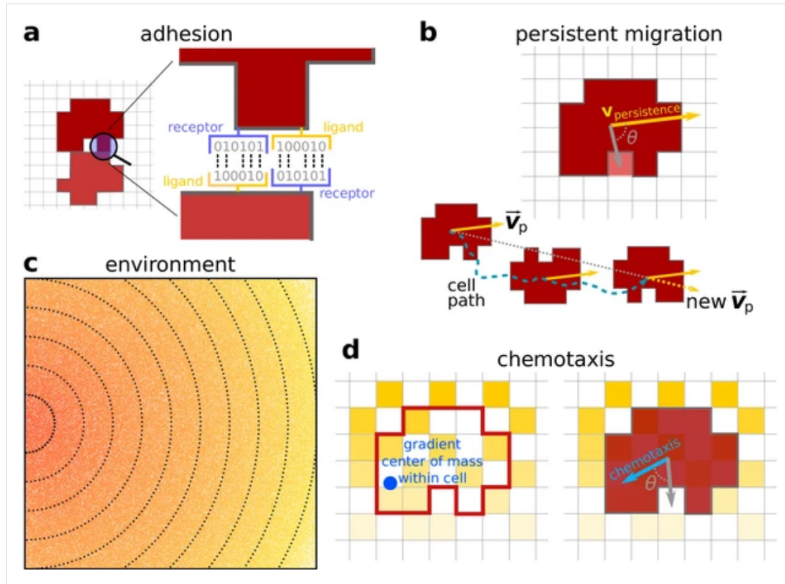


(2D)

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 (τ)

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) reaction diffusion systems
ddc	map lattices
ddd	CA
ccd	individual oriented models off lattice particle systems / event-based
dcc	meta-population models
c/dc (d+c)	hybrid models

note: translations