Continuous Limit of a Chemotaxis Model

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University of Notre Dame

Seminar at Institute of Fundamental Technological Research of the Polish Academy of Sciences, Warzsawa, August 2006

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Outline

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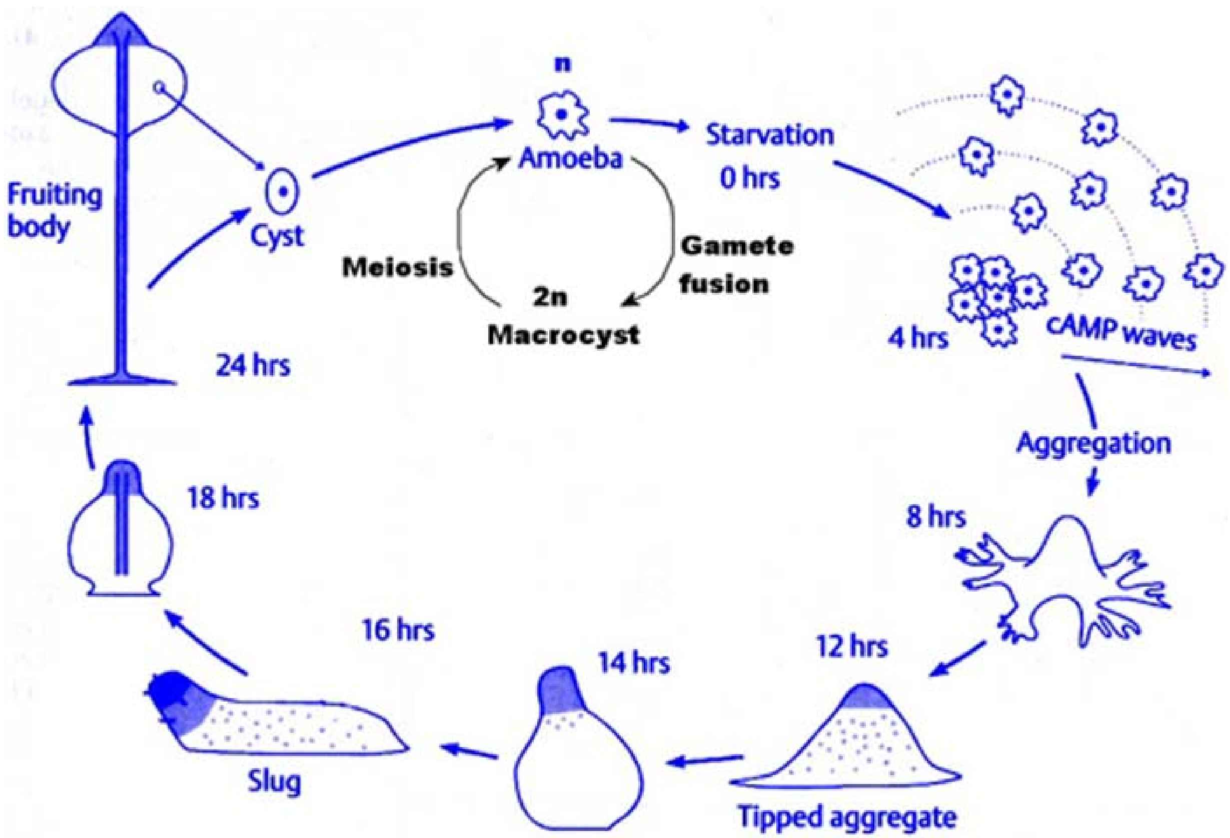
INTRODUCTION: Modeling multicellular behavior

Example 1: Life cycle of slime mold *Dictyostelium discoideum*



http://biology.kenyon.edu/Microbial_Biorealm/eukaryotes/dictyosteliida/dictyosteliida.html

Composite photograph of *Dictyostelium discoideum* life cycle

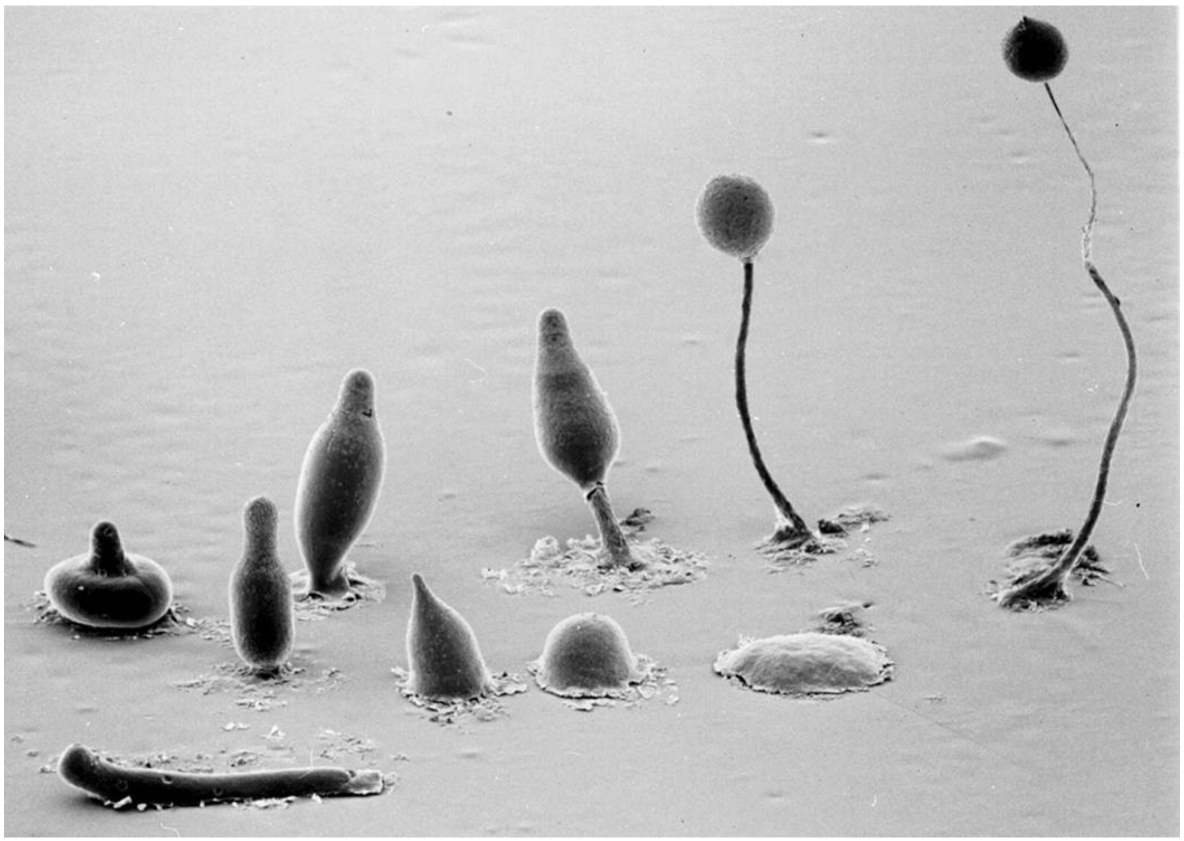
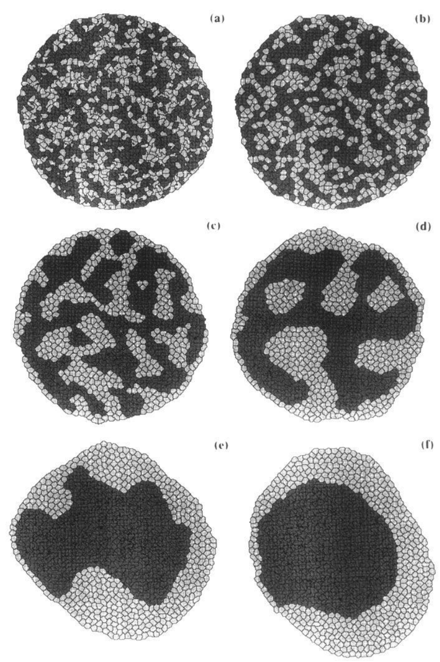


Photo by Mark Grimson and Larry Blanton, Texas Tech University

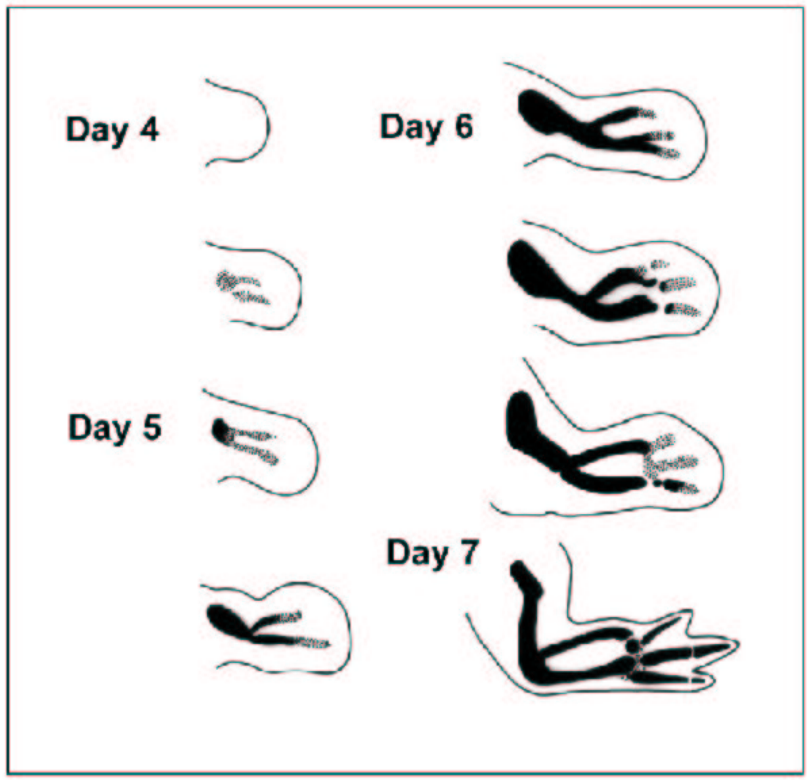
Example 2: Cell Sorting

Randomly mixed differentiated cells can sort out



Simulation by James Glazier and F. Graner

Example 3: Organogenesis in early development: Precartilage condensation



Stuart A. Newman, NYMC

Basic “Ingredients” for pattern formation in multicellular systems

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4. cellular secretion and absorption of extracellular scaffolding

Goals of Mathematical Modeling

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- to predict previously unidentified phenomena
- to guide experiments

Why Modeling?

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- simplify overwhelming complexity by forcing a hierarchy of importance
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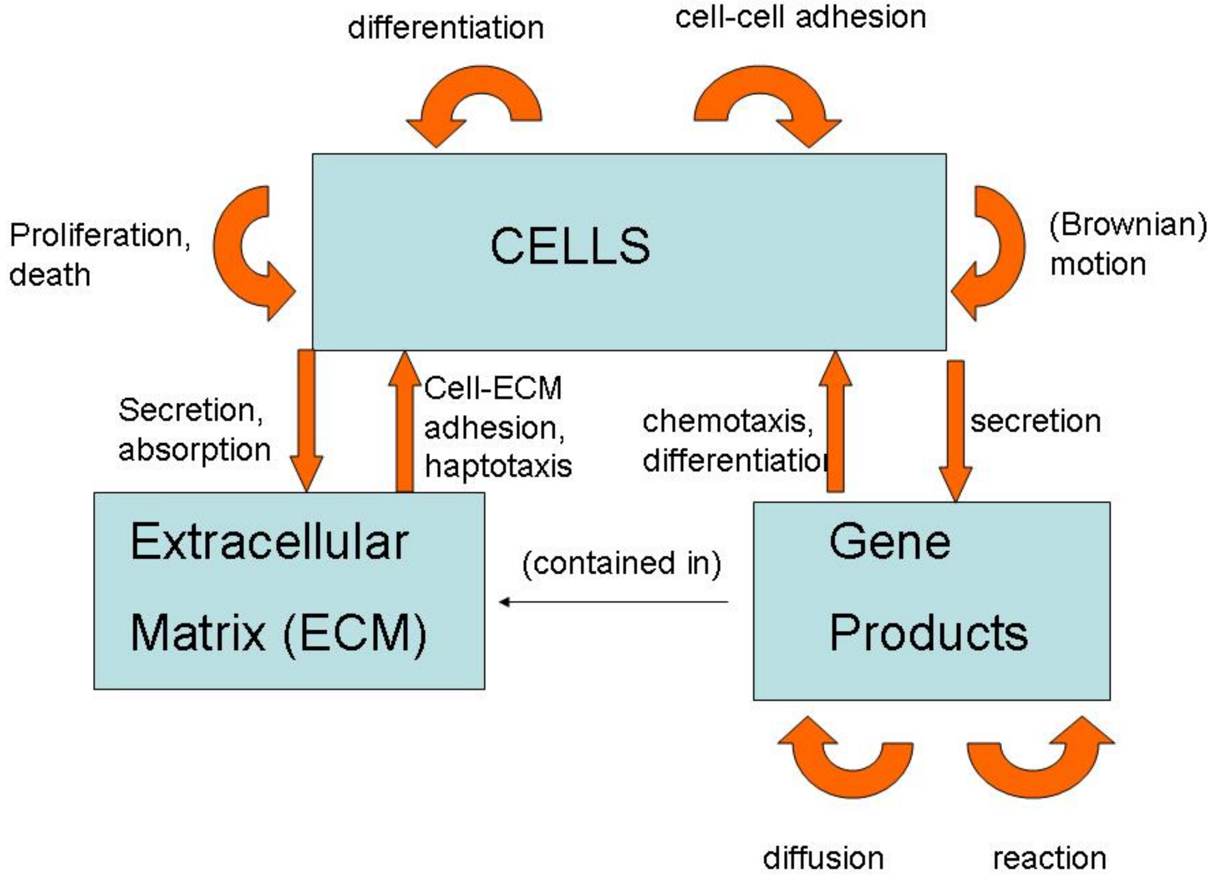
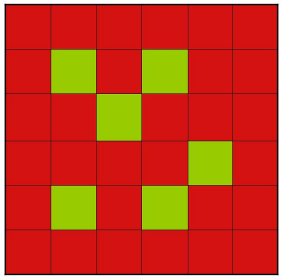
- failure of models can identify missing components

Model modules



Discrete vs. continuous models



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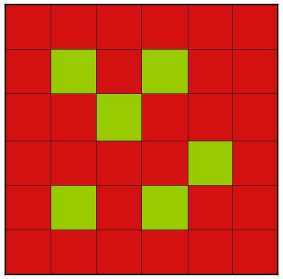
Discrete vs. continuous models



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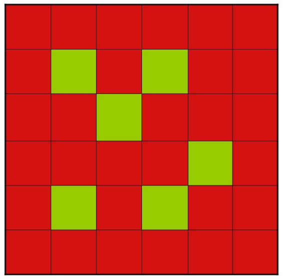

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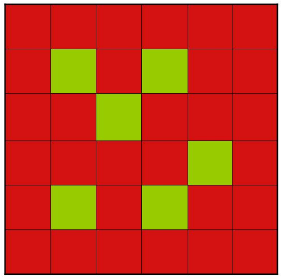

- **discrete models:**
  represent cells as (collections of) lattice sites
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- **continuous models:**
  represent cells via cell density $\rho(x,t)$ (continuous variable of space x and time t)

Continuous Models

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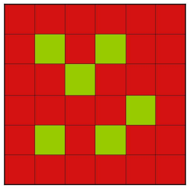
- $\mathbf{J}_{\text{diffusion}} = -\mathbf{D}\nabla\rho$ Brownian motion (Fickian diffusion)
- $\mathbf{J}_{\text{chemotaxis}} = \chi\nabla\mathbf{c}(\mathbf{x},\mathbf{t})$ chemotaxis up the gradients of a chemical $c(x,t)$

Discrete models

Discrete models

- Cellular Automata Models

Discrete models



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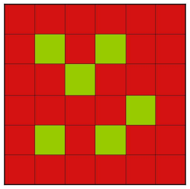

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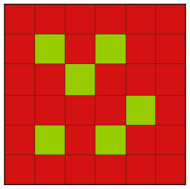

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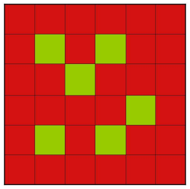

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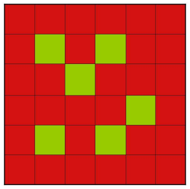

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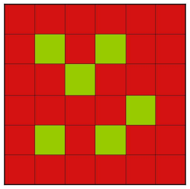

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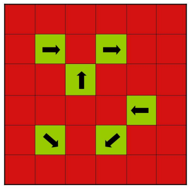

- Lattice-gas Cellular Automata
  every occupied lattice site has a (discretized) velocity

Cellular Potts Model

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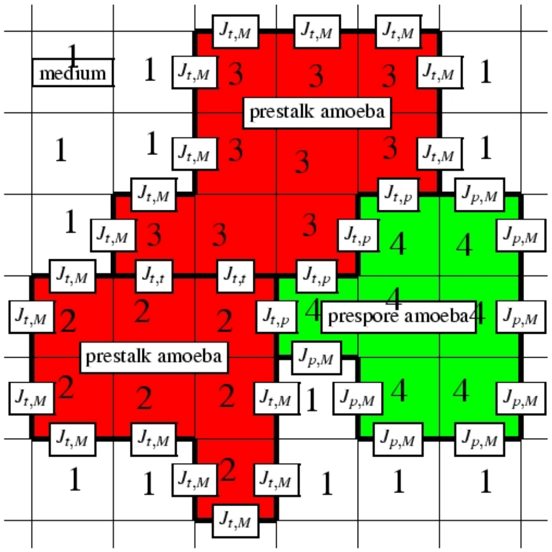
(Incomplete) List of Applications:

- Glazier/Graner(early 90s): testing Steinberg's differential adhesion hypothesis
- Marée et al. (late 1990s+): fruiting body formation of Dictyostelium discoideum
- COMPUCELL group (2000s): modeling chondrogenesis in vertebrate embryos
- Turner/Sherratt (1990s): tumor growth
- ETC

Cellular Potts Model: Set-up



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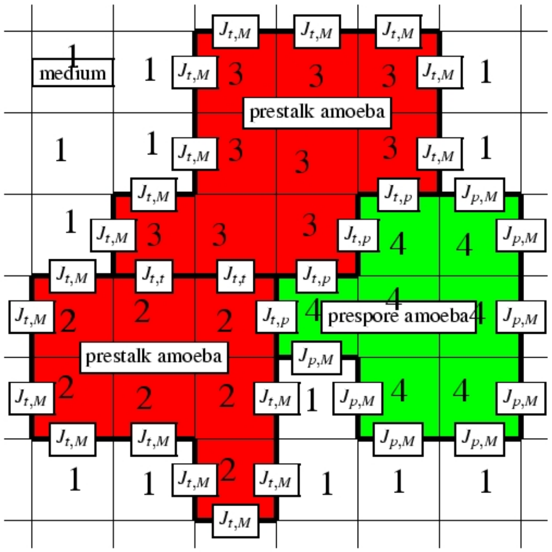

Hamiltonian (energy)= interaction energy + volume constraint energy + surface constraint energy+chemical energy

$$E = \sum_{\text{sites } i,j} J_{\tau(\sigma_i),\tau(\sigma_j)} + c_V \sum_{\text{cells } \sigma_i} (V_i - V_{target})^2$$

$$+ c_S \sum_{\text{cells } \sigma_i} (S_i - S_{target})^2 + \sum_{\text{cells } \sigma_i} \mu_{\sigma_i} C_i$$

Cellular Potts Model: Metropolis Monte Carlo Algorithm

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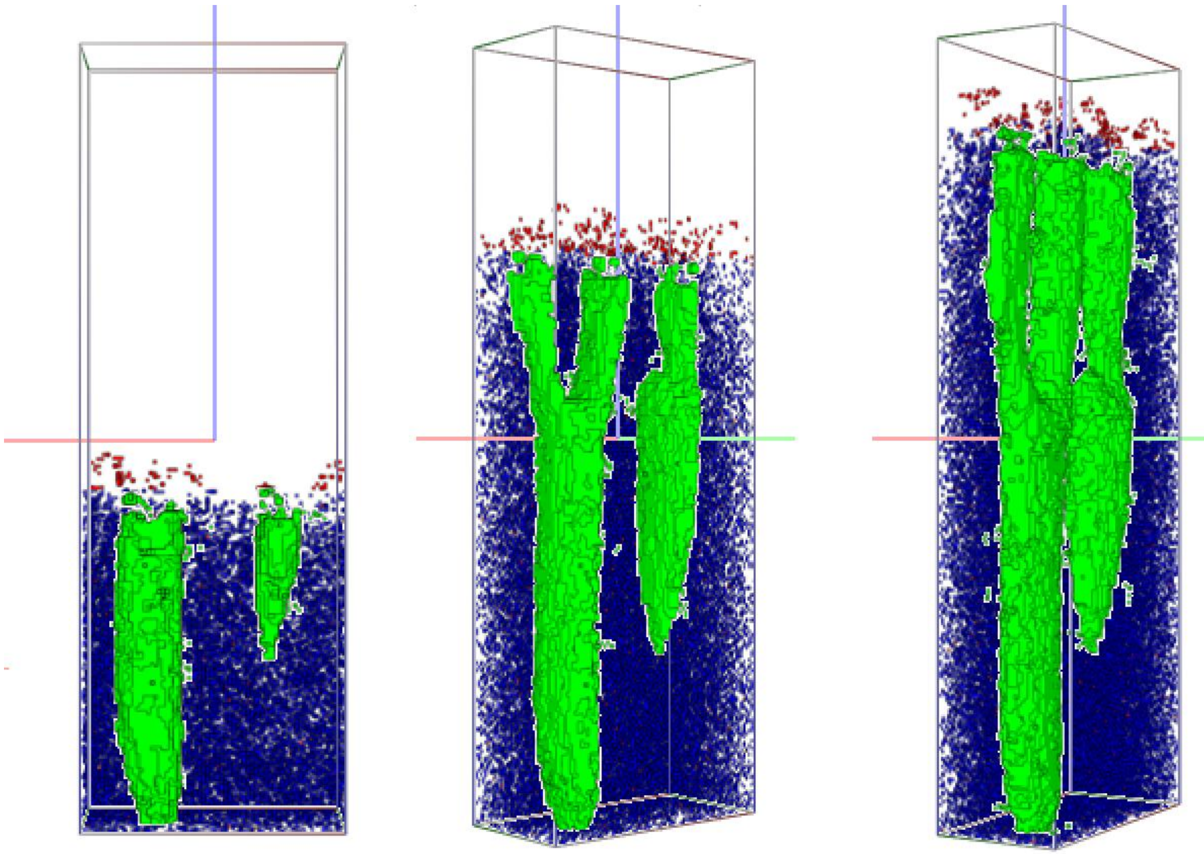
2. Choose a random cell index σ'
3. Decide if the index σ of the site i should be “flipped” to σ':

$$\text{Prob}(\sigma \to \sigma') = \begin{cases} 1 & \Delta E < 0 \\ \exp(-\beta \Delta E) & \Delta E \geq 0 \end{cases}.$$

(Here $\Delta E = E_{after} - E_{before}$ and $\beta \ldots 1/$temperature.)

Example 1



Picture of Chondrogenesis Simulation with CPM (COMPUCELL group)

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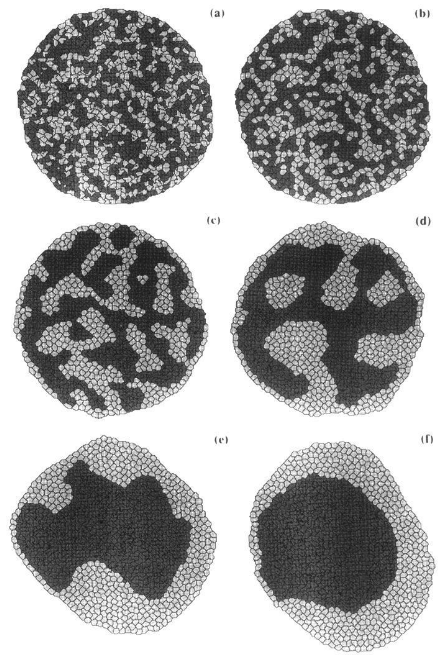

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THE GENERAL PROBLEM OF THE CONTINUOUS LIMIT OF A DISCRETE MODEL

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Turner, Sherratt, Painter, Savill (2004) Derivation of diffusion equation for 1-D Potts without chemical energy

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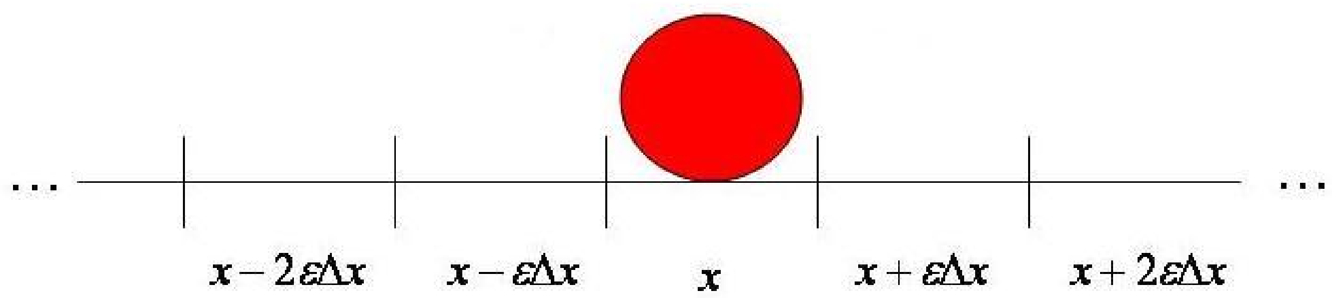
- Theoretical interest: Consistency of different models

Basic Technique



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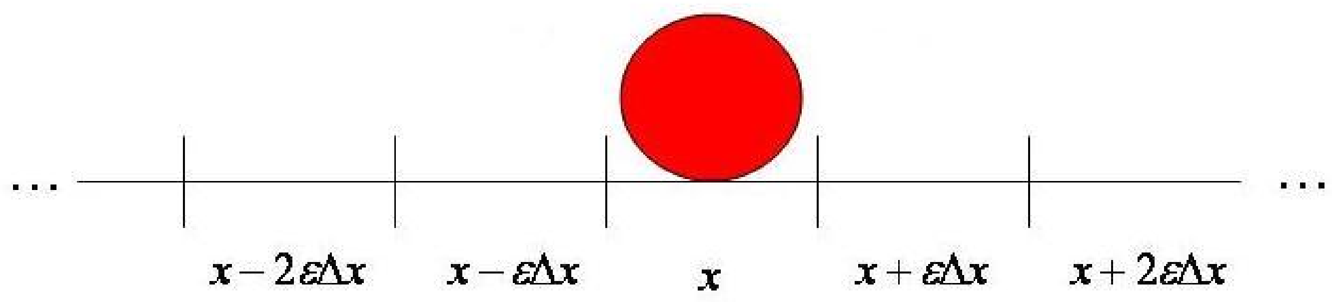

$\Delta x \cdots$ constant spatial interval; $\Delta t \cdots$ constant time interval
Scaling with small ϵ: $\quad \epsilon\Delta x, \quad \epsilon^2\Delta t$

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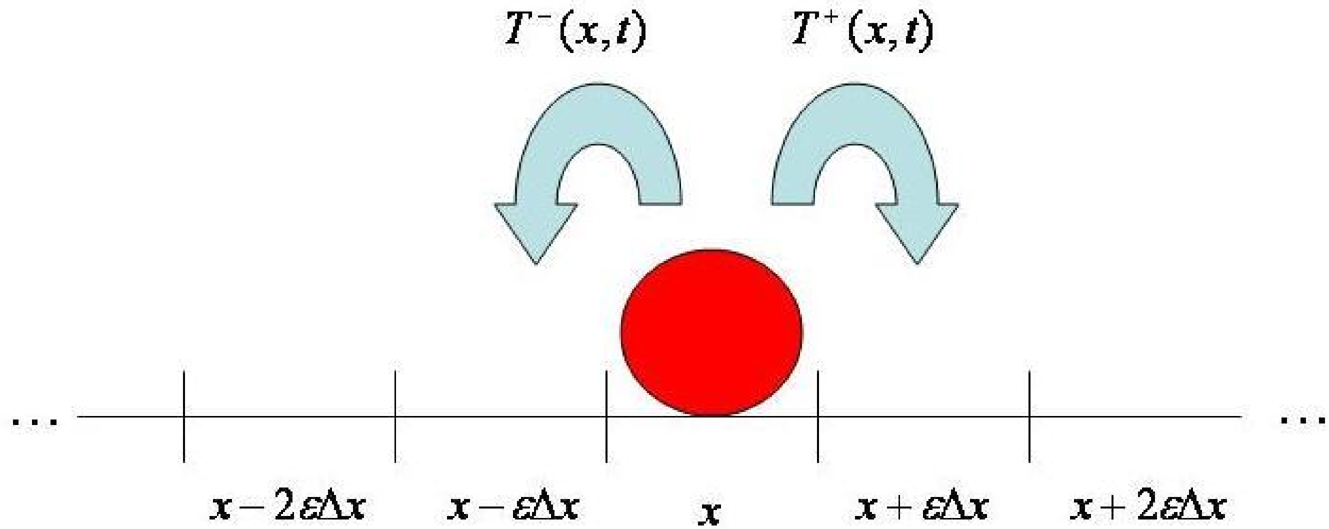

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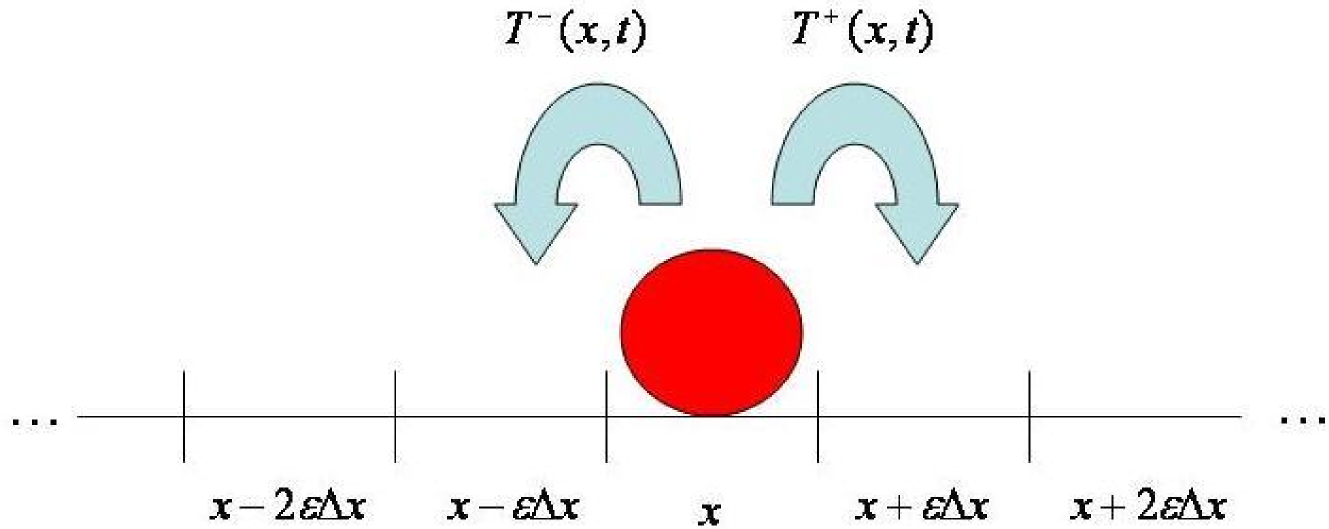

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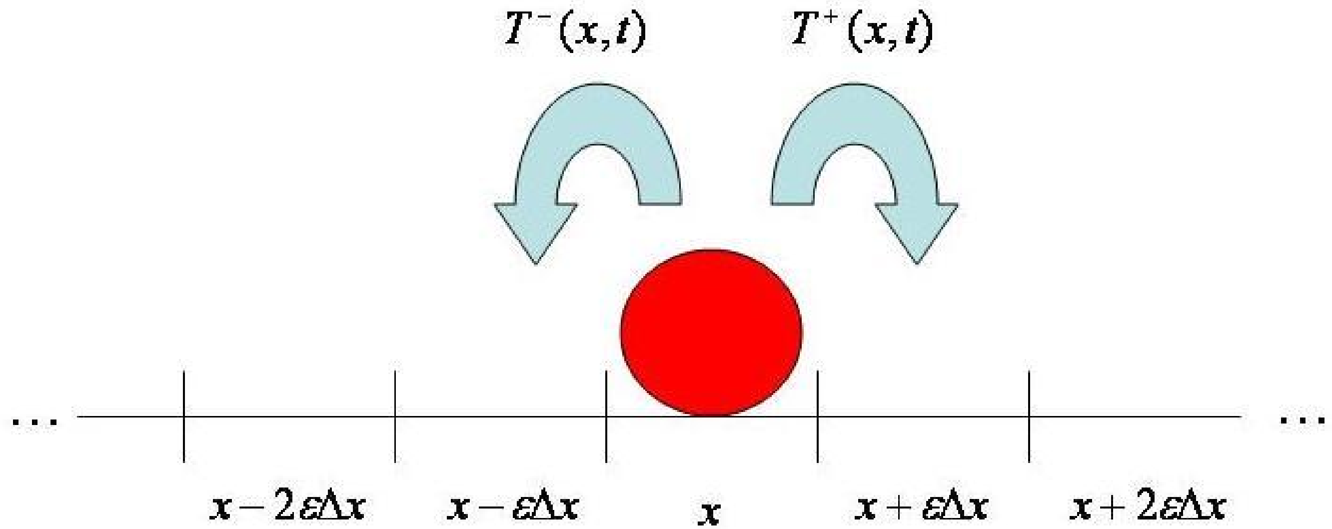

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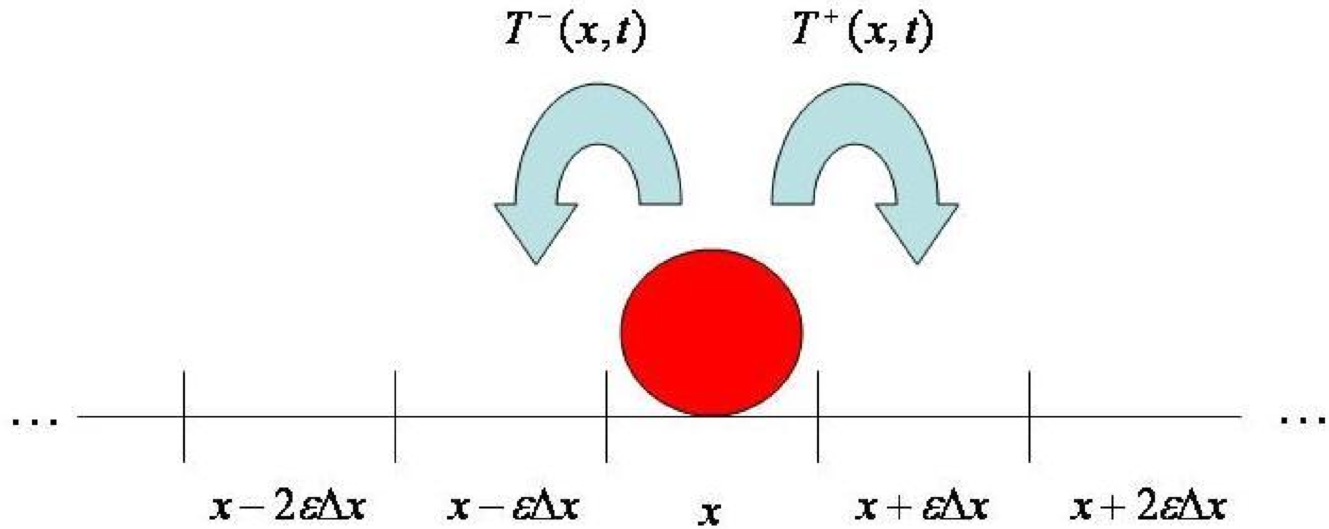

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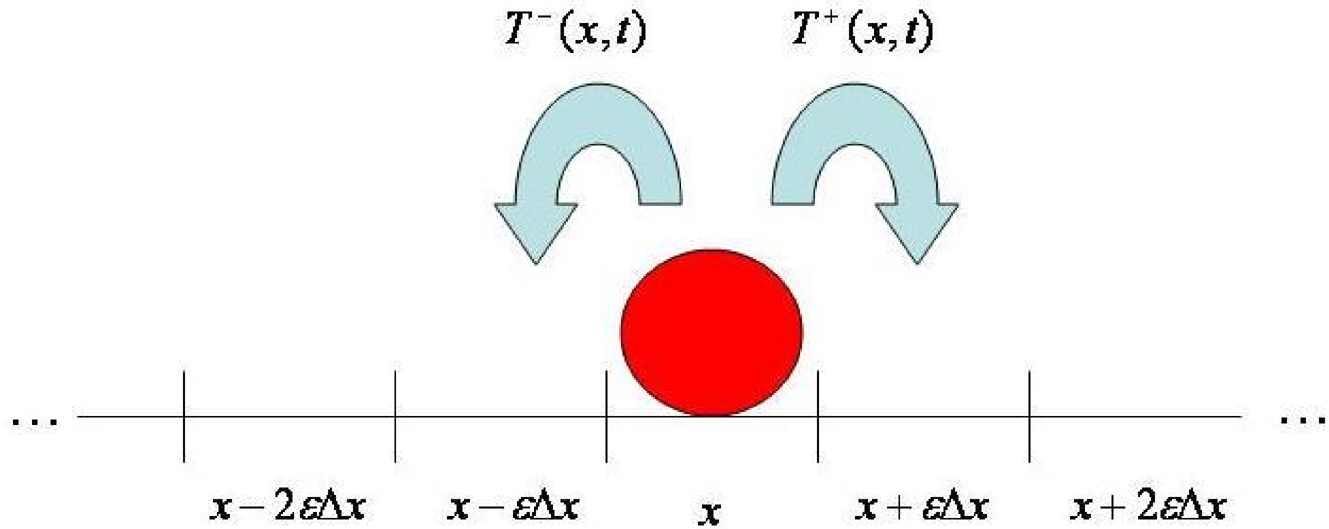

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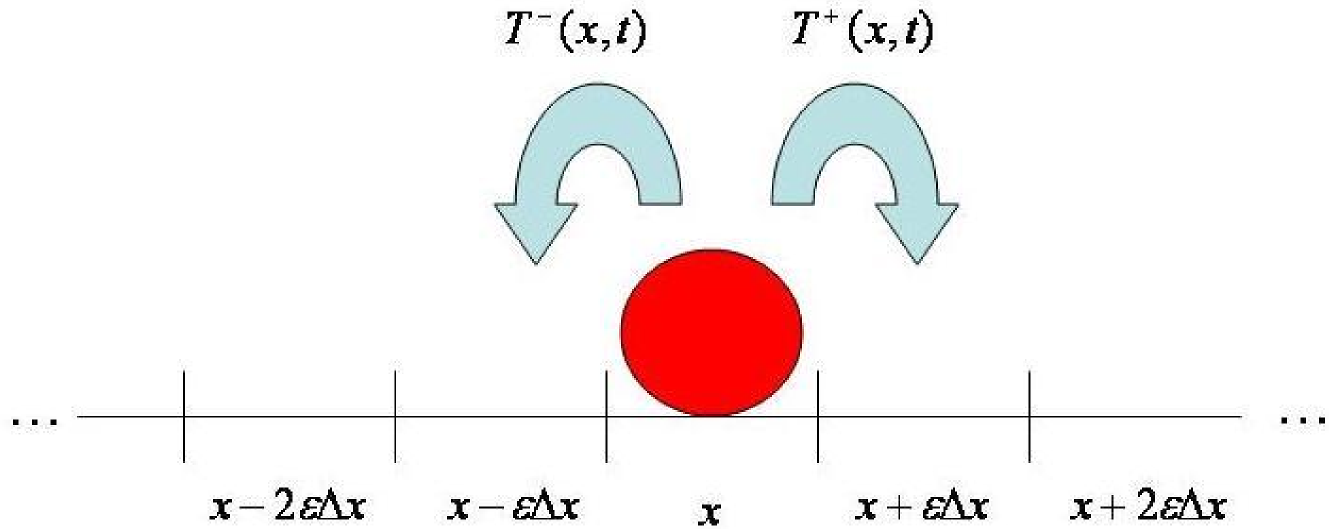

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Taylor expansion in ε, throw away terms $\mathcal{O}(\varepsilon^3)$

Example

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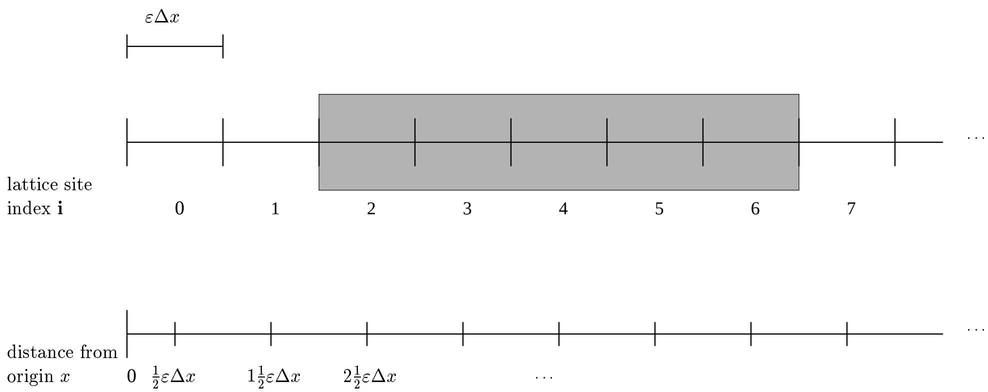
Diffusion equation, $D = T \Delta x^2 / \Delta t$

CONTINUOUS LIMIT FOR A CPM CHEMOTAXIS MODEL

Chemotaxis 1 D Cellular Potts Model



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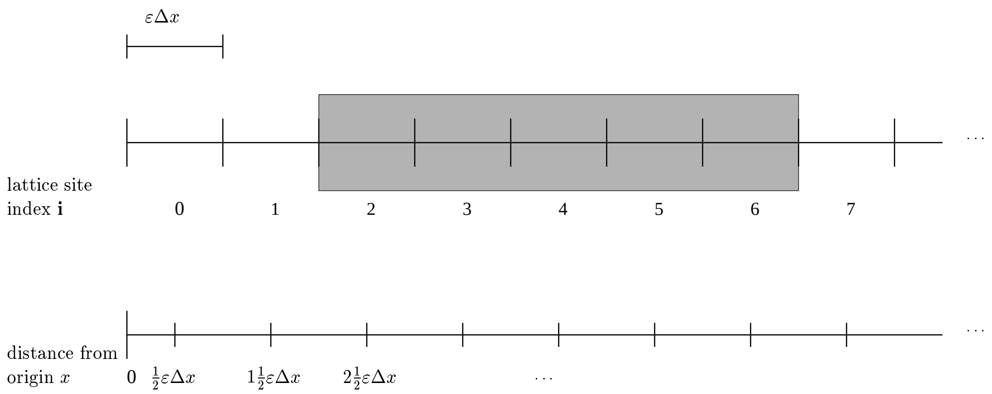


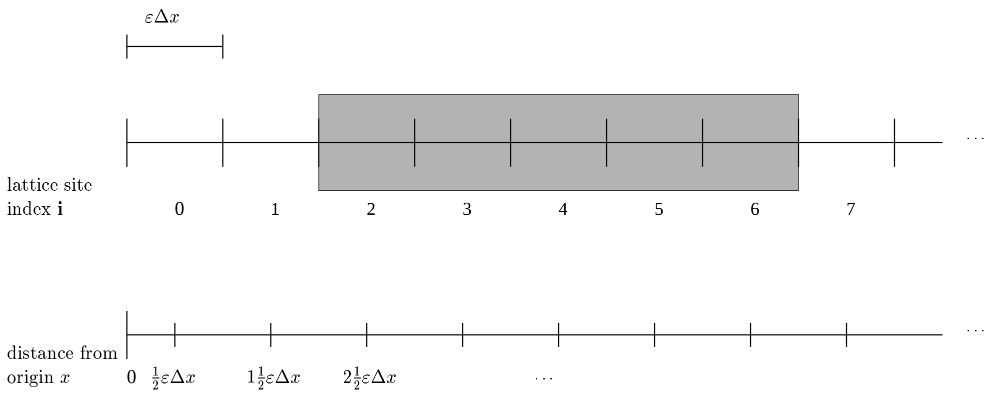
$$E = E(x_{CM}, L) = J_{cm}(2L + 2\Delta x) + \lambda(L - L_T)^2 + \mu c(x_{CM})L$$

$c(x) \cdots$ external chemical field

$L \cdots$ cell length

$x_{CM} \cdots$ center of mass

Chemotaxis 1 D Cellular Potts Model



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Potts parameters:

$L_T \cdots$ target length, $\lambda \cdots$ cell length constraint parameter, $\mu \cdots$ chemical energy parameter, $J_{cm} \cdots$ cell-medium interaction energy parameter

Result 1: “Full” PDE

Let $p(x, L, t)$ be the probability distribution for the cell location and cell length.

Up to $\mathcal{O}(\varepsilon)$, one gets the following PDE:

$$\partial_t P(x, L, t) = D(\partial_x^2 + 4\partial_L^2)P + 8D\beta\lambda\partial_L(\tilde{L}P) + D\beta L\mu\partial_x\Big[Pc'(x)\Big]$$

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where:

$D = \frac{(\Delta x)^2}{8\,\Delta t} + \mathcal{O}(\varepsilon)$,

$\tilde{L} = L - L_m(x), \qquad L_m(x) = \frac{2J_{cm} + \mu\, c(x)}{2\lambda}$

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For “reasonable” parameter ranges ($\sqrt{\beta\lambda}[L_T - L_m(x)] >> 0$), approximation:

$\chi(x) = \frac{(\Delta x)^2}{8\,\Delta t}\beta\mu\,(L_T - L_m(x)) + \mathcal{O}(\varepsilon)$

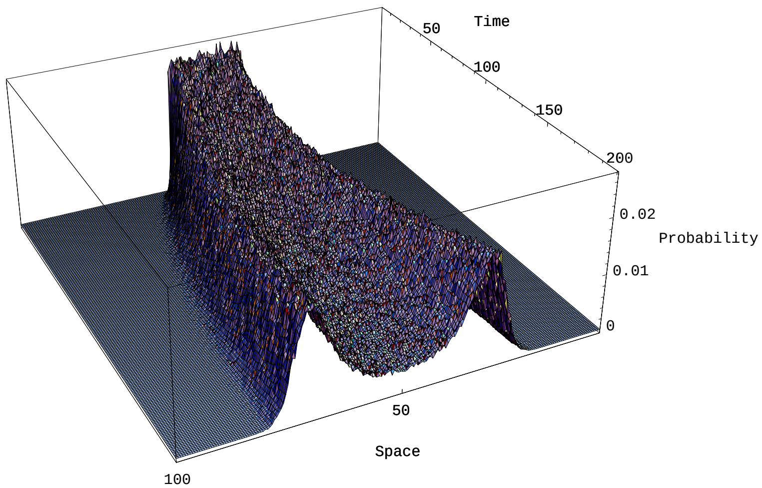
Derivation of Keller-Segel model

If the cells also secrete the chemical, we get the Keller-Segel model

$$\frac{\partial c}{\partial t} = D_c \cdot \partial_x^2 c + k_c\, p - k_d p$$
$$\frac{\partial p}{\partial t} = D \cdot \partial_x^2 p + \partial_x(\chi(x) \cdot p\, \partial_x c)$$

NUMERICAL VALIDATION

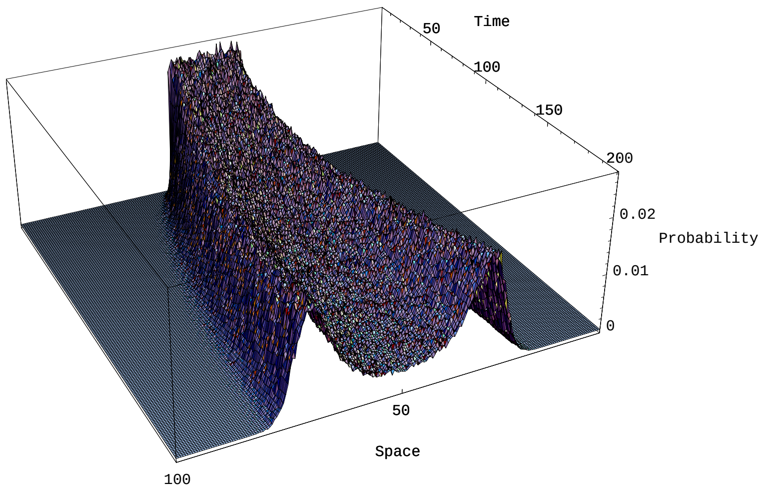
Set up

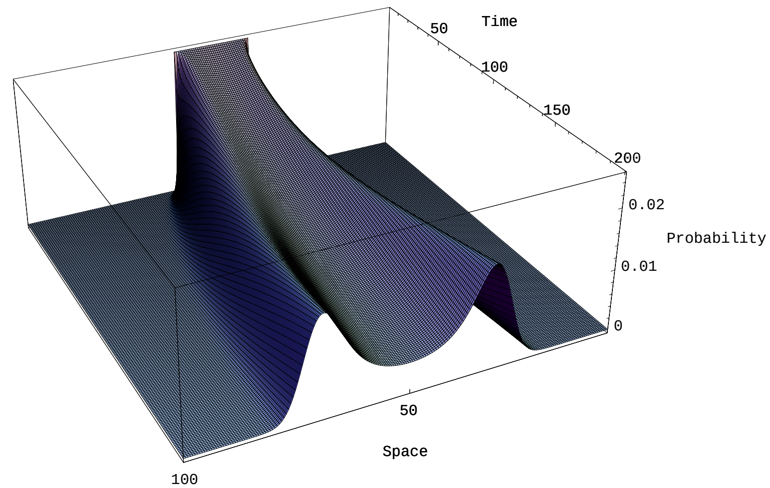


Potts Monte Carlo

typically 200,000 single cell runs

Set up

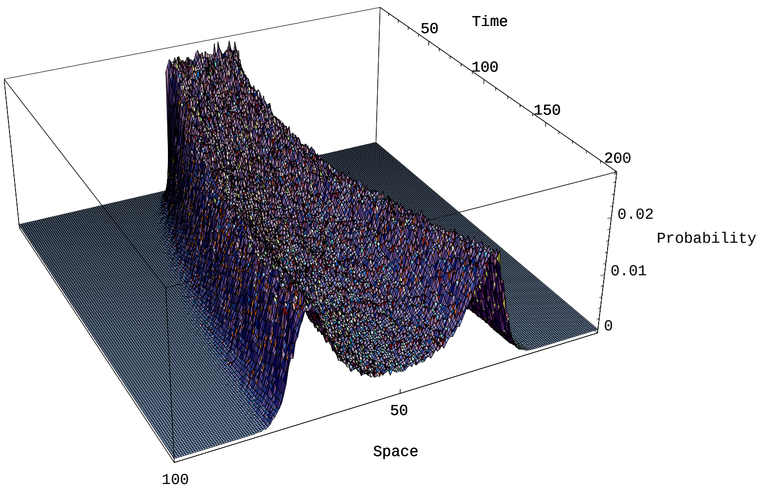




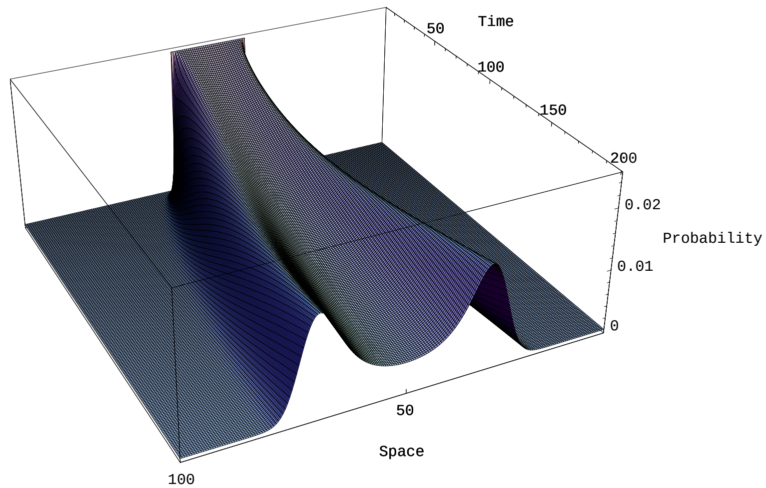
Potts Monte Carlo
typically 200,000 single cell runs

Numerical solution of chemotaxis PDE

Set up



Potts Monte Carlo



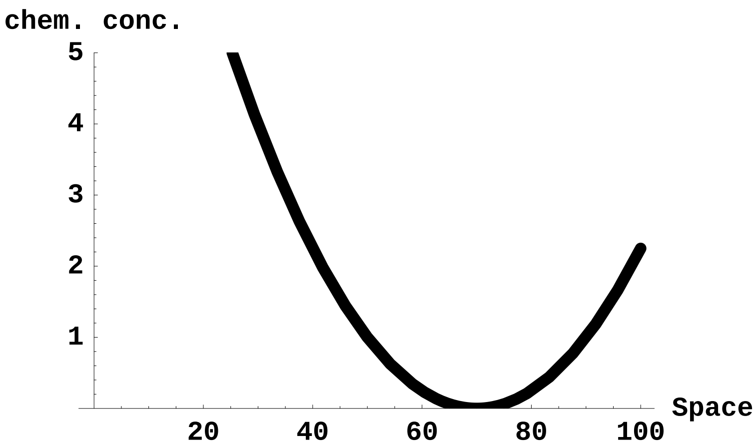
Numerical solution of chemotaxis PDE

typically 200,000 single cell runs

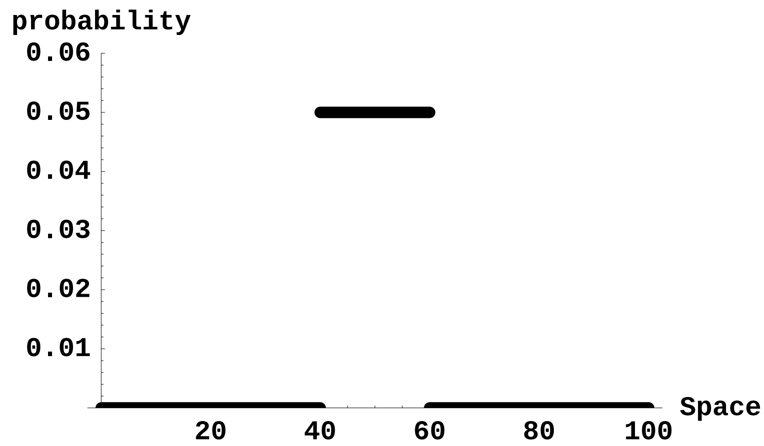
$100/\varepsilon$ lattice sites; $200/\varepsilon^2$ time steps
(For plots renormed to 100 Potts lattice sites;
Time $t = 0 \cdots 200$; $\Delta x = \Delta t = 1$.)

Test 1

Parameters $\lambda = 4, L_T = 5, J_{cm} = 2, \beta = 15,$
$\mu = 0.1$ (Chemorepellant)

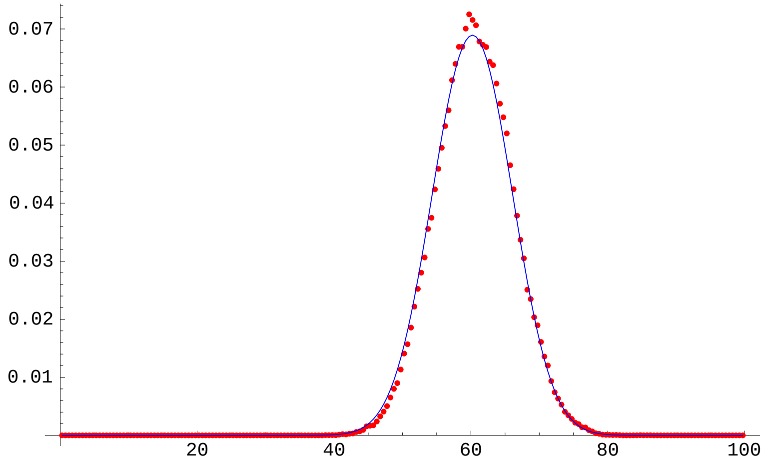


Chemical Concentration



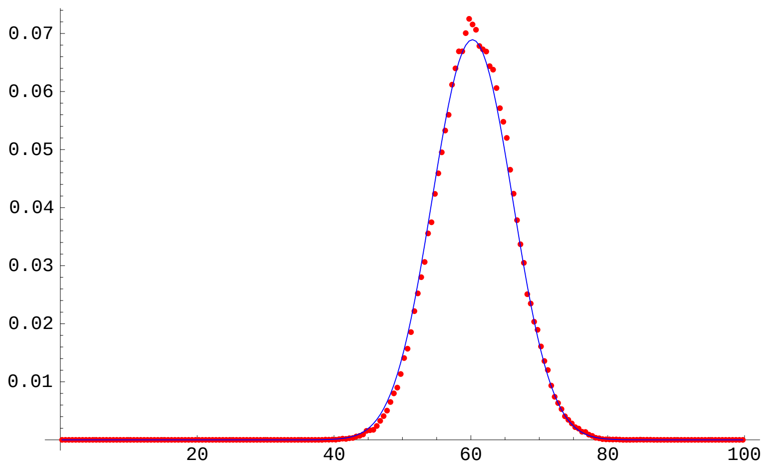
Initial Distribution of the Celll Centers

Test 1: Comparisons for time $t = 200$

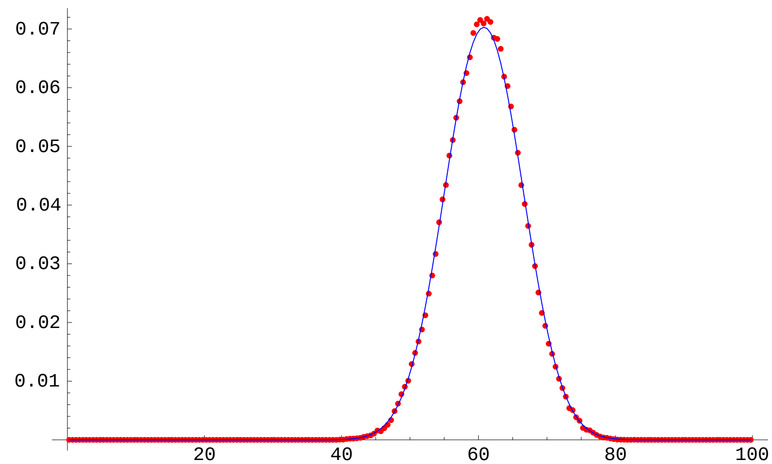


$\varepsilon = 0.02, p-$val$= 4.33 \cdot 10^{-135}$

Test 1: Comparisons for time $t = 200$

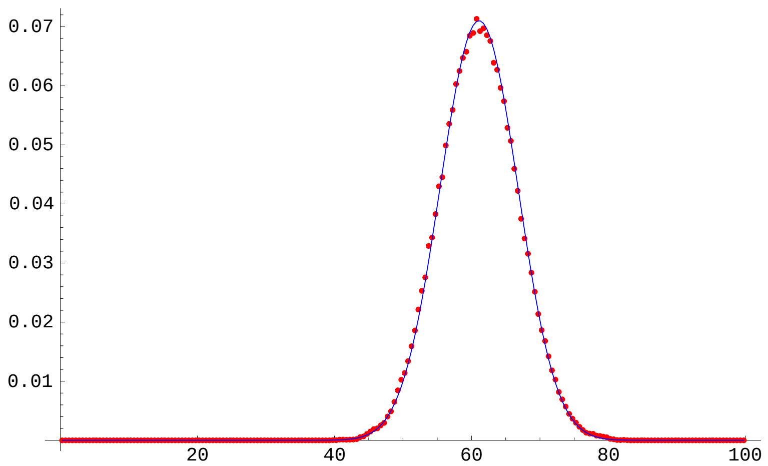


$\varepsilon = 0.02, p-$val$= 4.33 \cdot 10^{-135}$



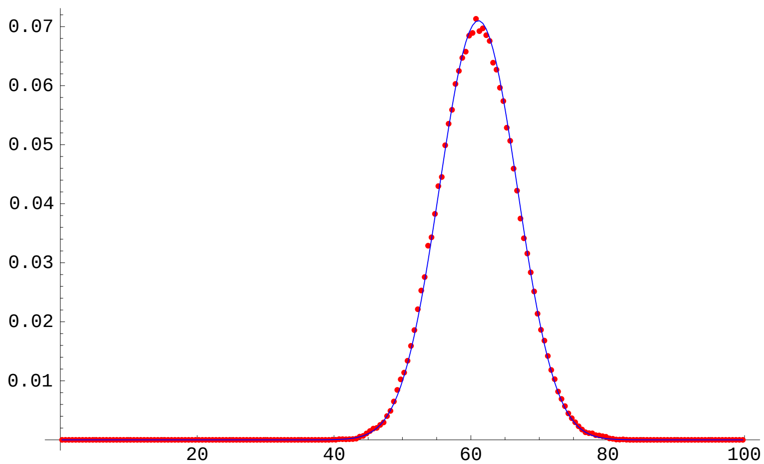
$\varepsilon = 0.01, p-$val$= 1.47 \cdot 10^{-14}$

Test 1: Comparisons for time $t = 200$ cont'd

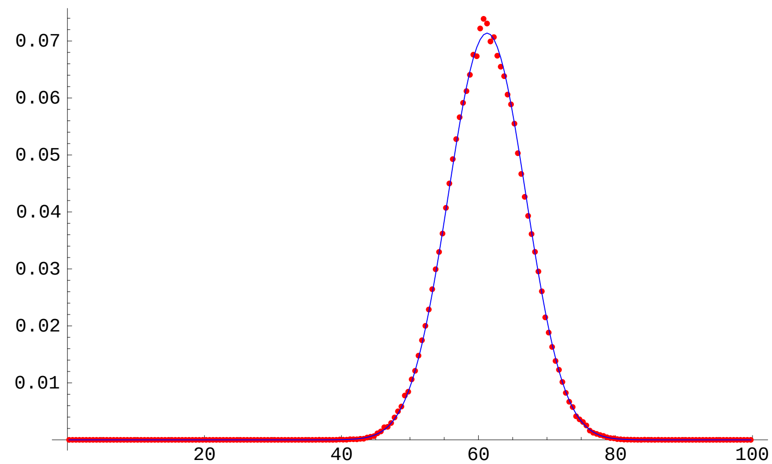


$\varepsilon = 0.005$, $p-$val$= 3.75 \cdot 10^{-10}$

Test 1: Comparisons for time $t = 200$ cont'd



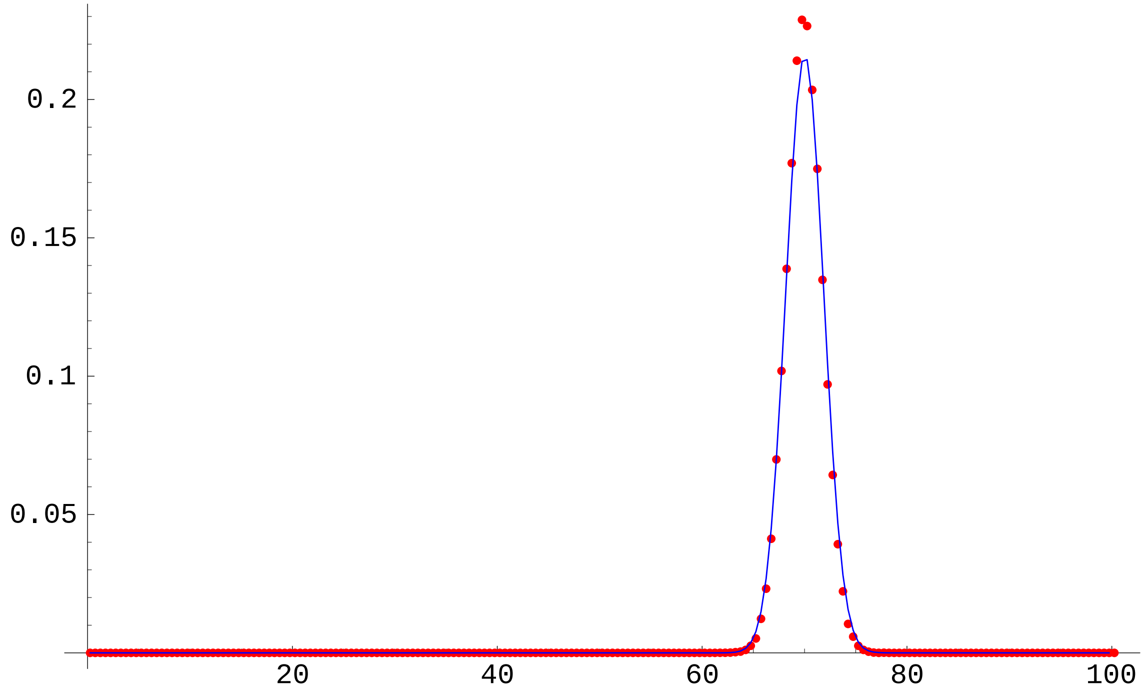
$\varepsilon = 0.005, p-$val$= 3.75{\cdot}10^{-10}$



$\varepsilon = 0.0025, p-$val$= 2.58{\cdot}10^{-4}$

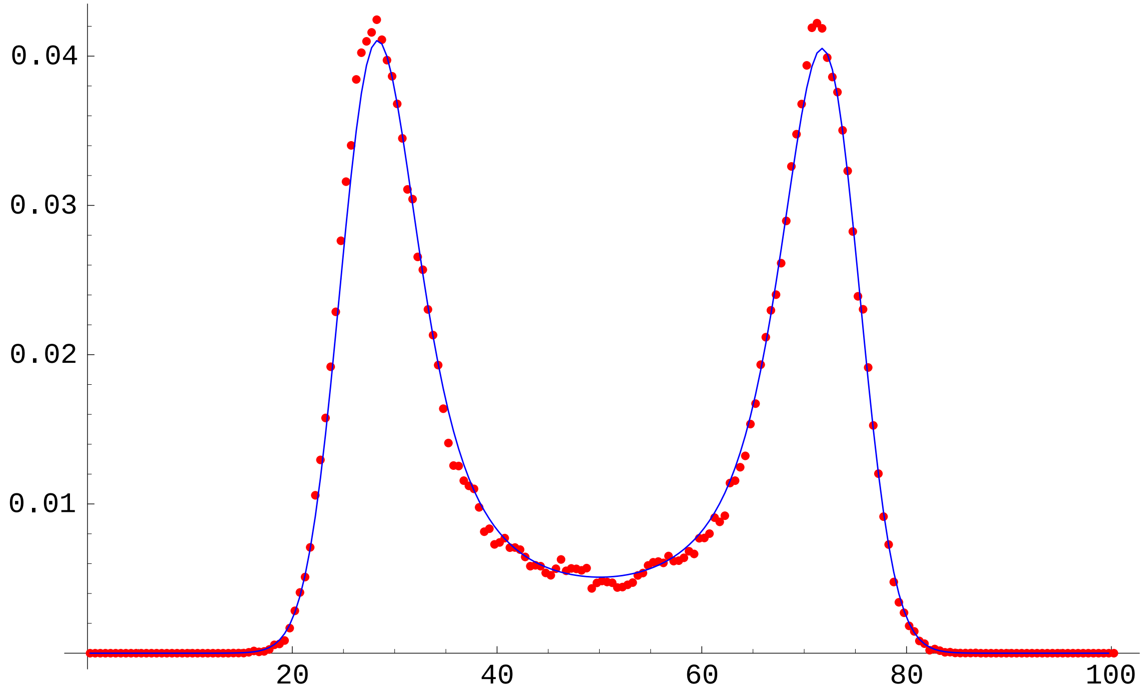
Test 2

Same as Test 1, but $\beta = 150$



Test 3

Same as Test 1, but “double well” chemical potential



Test 4

$\mu = -0.1$ (Chemoattractant)