Theoretical Biophysics
A Computational Approach
Concepts, Models, Methods and Algorithms
Growth, Aggregation and Deposition

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Table of Contents

Introduction

Introduction I

In essence, many of the phenomena associated with growth, aggregation and deposition can be thought of in terms of particles diffusion problems [1, 2]. A particle diffuses through a medium until it gets in contact with either another particle of a cluster of particles. Depending on the model, the particles stick or are reflected a number of times. This simple model, in its variations, is able to reproduce many of the structures one observes.

Beside the control of the growth though diffusion, the process can also be controlled by a reaction limit:

- diffusion limited growth
- reaction limited growth

For both of the above cases there can be

- particle aggregation
- cluster aggregation.

Introduction II

Of course, there can be mixed forms as well.

Assume an object with N elements at positions r_i with unit mass. We define the **radius of gyration** of the object by

$$R_g^2 = \frac{1}{2N^2} \sum_{i,j=1..N} (r_i - r_j)^2 \ . \tag{1}$$

For later purposes we note that an alternative to this approach is to define this radius via the principle moments of the **gyration tensor** S

$$S_{mn} = \frac{1}{N} \sum_{i=1}^{N} r_i^{(m)} r_i^{(n)} \tag{2}$$

where we assume

$$\sum_{i=1}^{N} r_i = 0 \tag{3}$$

$$R_g^2 = \lambda_1^2 + ... + \lambda_d^2 \ . \tag{4}$$

Introduction III

Another possibility is to define the extend of the object by the smallest box that is needed such that object fits into the box

$$R_b = \max_{i,j=1,\ldots,N} |r_i - r_j| \ . \tag{5}$$

We further define the **asphericity**

$$b = \lambda_d^2 - \frac{1}{d-1}(\lambda_1^2 + \ldots + \lambda_{d-1}^2) = \frac{d}{d-1}\lambda_d^2 - \frac{R_g^2}{2} \ . \tag{6}$$

Let R be the radius of the cluster (R_g, R_b) and M be the mass (here the number of occupied lattice sites N) that belongs to cluster, then

$$M = N \propto R^{d_f} \tag{7}$$

describes the relationship between the radius and the mass where we anticipate that the object may not be compact but be fractal with the fractal dimension $d_f < d$ (see later lectures).

Introduction IV

Let n_s be the number of sites at the surface and $h_i(t)$ the distance from a reference distance measuring the height of the surface at time t. Then average height is given by

$$\langle h(t) \rangle = \frac{1}{n_s} \sum_i h_i(t) \; . \tag{8}$$

From this we derive **surface roughness** w

$$w^2(t) = \frac{1}{n_s} \sum_i (h_i(t) - \langle h(t) \rangle)^2 \; . \tag{9}$$

as a function of time t.

Introduction V

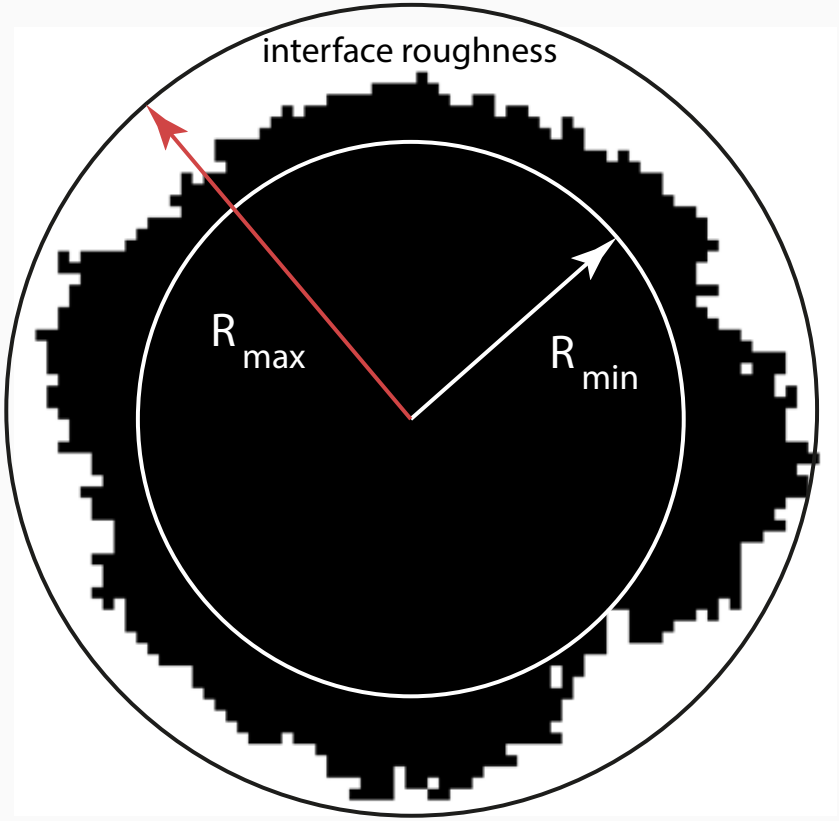

Figure 1: Illustration of interface roughness and parameters.

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Stochastic Particle based Growth Models

Particle Systems I

We shall start with a lattice like $\Lambda = L^d$ or $\Lambda = \mathbf{Z}_n \times \mathbf{Z}_m$, where n and m are integers, or a graph $\Lambda = G$. We will call a system a **particle systems** if

- each site $s \in \Lambda$ is in one of a finite number q of states, and
- each site can change its state depending on the number of neighbouring sites.

The time evolution of the particle system is described by a **discrete time Markov chain**. Let $s(t)$ be the state of the site s at time t. Then the particle system changes its state $\Lambda(t) \to \Lambda(t+1)$ by the rate $q(s, s')$, where s' denotes one of the possible finite state that s can be in.

Updating rules

- **synchronous**: synchronous updating of a discrete time process which updates all of the sites simultaneously
- **asynchronous**: a site is chosen at random

Growth Models: Eden Cluster I

Eden[3] introduced a stochastic growth model which may be used to study the proliferation of bacteria in a culture medium, propagation of epidemics, chemical reactions, tumor growth etc. In the simplest variant of the model every site on the periphery of the object has an equal probability of being selected as the next growth site.

For simplicity, we assume that the growth takes place on a lattice $\Lambda = L^d$. Once a lattice site s is initially chosen to be the seed, then the nearest neighbour sites are the possible growth sites. Each of the perimeter sites is visited and given the chance to change its state to being occupied. Once a site is occupied, the nearest neighbour sites that are not already part of the cluster are added to the list of perimeter sites. This procedure is iterated.

Growth Models: Eden Cluster II

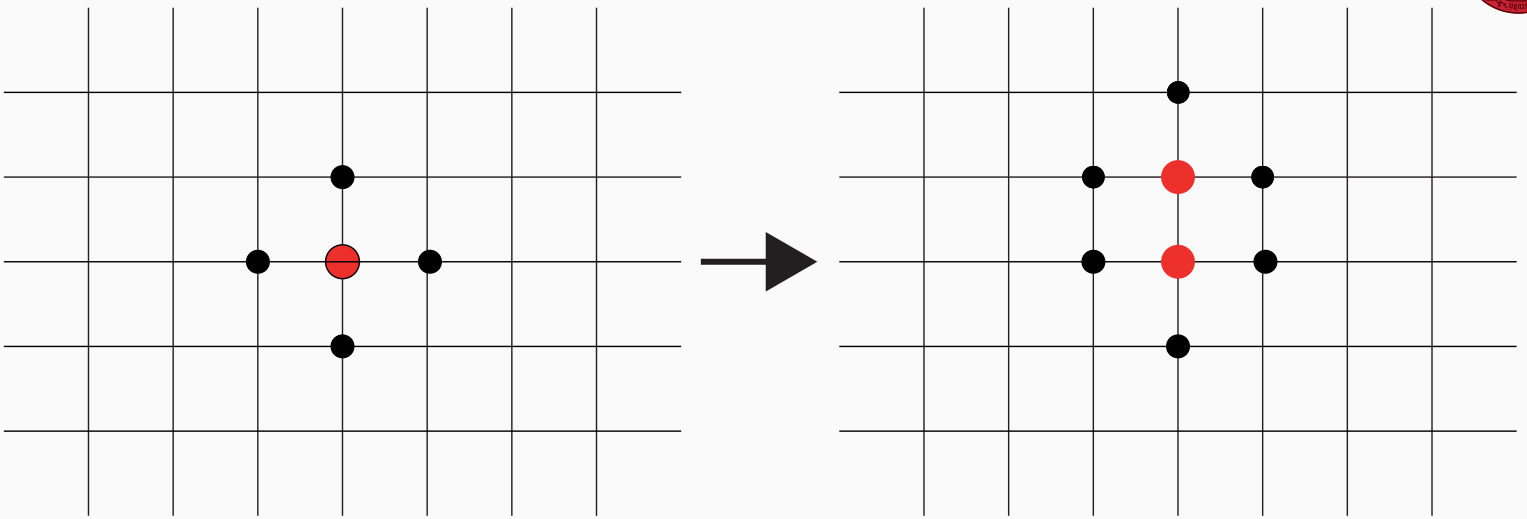

Figure 2: Steps in the Eden cluster growth. The left panel shows and initial occupied (red) site. A site of the perimeter (black) is chosen during the next step and given the chance to change to being occupied. The right panel shows the situation after the perimeter site has changed its state and additional perimeter sites have been added.

Algorithm 1 Basic Algorithm: Growth

choose initial site s
add first site to *perimeter_list*
for *n_cycles* **do**
  len = length of *perimenter_list*
  for *len* **do**
    i iid from $\{0, .., len - 1\}$
    s = select at random one of the nearest neighbours of *perimeter_list*(i)
    if s not in *perimeter_list* and not in *new_sites_list* **then**
      add s to *new_sites_list*
    end if
  end for
  add *new_sites_list* to *perimeter_list*
end for

Growth Models: Eden Cluster

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```
import random
mcs_max = 100
random.seed(4711)

s = (0,0)
perimeter_list = []
new_sites_list = []
perimeter_list.append(s)

for mcs in range(mcs_max):
  for n in range(len(perimeter_list)):
    i = random.randrange(0,len(perimeter_list), 1)
    s = perimeter_list[i]
    d = random.randrange(0,4,1)
    if d == 0:
      sn = (s[0],s[1]-1)
    elif d == 1:
      sn = (s[0],s[1]+1)
    elif d == 2:
      sn = (s[0]-1,s[1])
    elif d == 3:
      sn = (s[0]+1,s[1])
    elif d == 4:
      print "should not happen"
    if sn not in perimeter_list:
      new_sites_list.append(sn)
  perimeter_list.extend(new_sites_list)
  new_sites_list = []
```

Code 1: eden.py

Voter Model I

Let $\Lambda = L^d$ be a lattice. Let f be a function (usually increasing). For each site s of the lattice, a set of neigbours (nearest, next-nearest, etc.) is chosen. Start with a seed which is set to be occupied. Choose at random a site of the lattice. Let *count(s)* be the number of occupied neighbour sites of s. The site s changes its state to occuied with probability $f(count(s))$.

A variation on this that an occupied site becomes occupied at a rate $delta/(1 + count(s))$. A unoccupied site becomes occupied at a rate equal to $1/(1 + count(s))$

Algorithm 2 Basic Algorithm: Leath

choose initial site s
add s to visited list
add neighbours of s to *perimeter_list*
while perimeter_list not empty and *max_sites* not reached **do**
    select site s and delete from *perimenter_list*
    add s to visited sites
    if $p <$ random number **then**
        add s to *sites_list*
        add neighbours of s to *perimeter_list*
    end if
end while

Leath Cluster Model I

Implementation using a **stack**:

Here the *perimeter_list* is a stack where the **pop** operation deletes the element from the stack. Since the **push (append)** put the next perimeter site right at the top of the stack, the growth may proceed 'in preferred direction' as the example in Figure 4 shows. the growth here terminated due to the criterion of 'maximum number of sites reached condition. While in principle the implementation is correct if beside the natural termination criterion no other is used, in practice the implementation is not correct. A *deque* implementation corrects the situation.

Leath Cluster Model


```
def addSiteToList(s,sites_list):
    sites_list.append(s)
    return sites_list

def addNeigboursToList(s,perimeter_list,sites_visited_list):
    sn = (s[0],s[1]-1)
    if (sn not in perimeter_list and sn not in sites_visited_list):
        perimeter_list.append(sn)
    sn = (s[0],s[1]+1)
    if (sn not in perimeter_list and sn not in sites_visited_list):
        perimeter_list.append(sn)
    sn = (s[0]-1,s[1])
    if (sn not in perimeter_list and sn not in sites_visited_list):
        perimeter_list.append(sn)
    sn = (s[0]+1,s[1])
    if (sn not in perimeter_list and sn not in sites_visited_list):
        perimeter_list.append(sn)
    return perimeter_list
```

Code 2: Leath cluster growth algorithm part 1: functions

Leath Cluster Model


```
maxSites = 100000
random.seed(4711)

# Initialize
p  = 0.5
s  = (0,0)
perimeter_list      = []
sites_list          = []
sites_visited_list  = []
addSiteToList(s,sites_list)
addSiteToList(s,sites_visited_list)
addNeigboursToList(s,perimeter_list,sites_list)

# Main loop
while (len(perimeter_list) > 0 and len(sites_list) < maxSites):

    s = perimeter_list.pop()
    addSiteToList(s,sites_visited_list)
    if (random.random() < p):
       addSiteToList(s,sites_list)
       addNeigboursToList(s,perimeter_list,sites_list)
```

Code 3: Leath cluster growth algorithm part 2

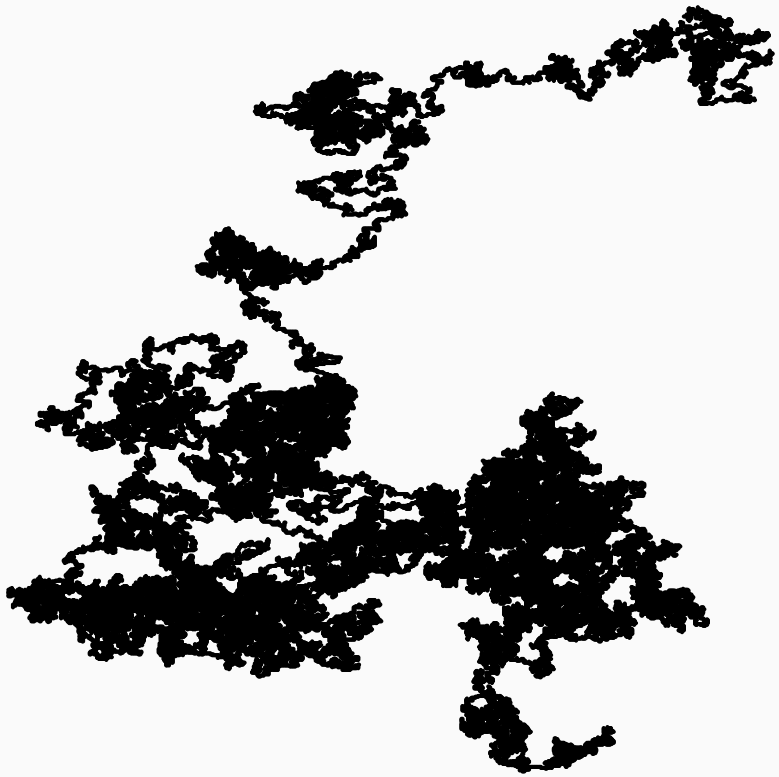


Figure 4: Example using the **stack** algorithm.

Leath Cluster Model

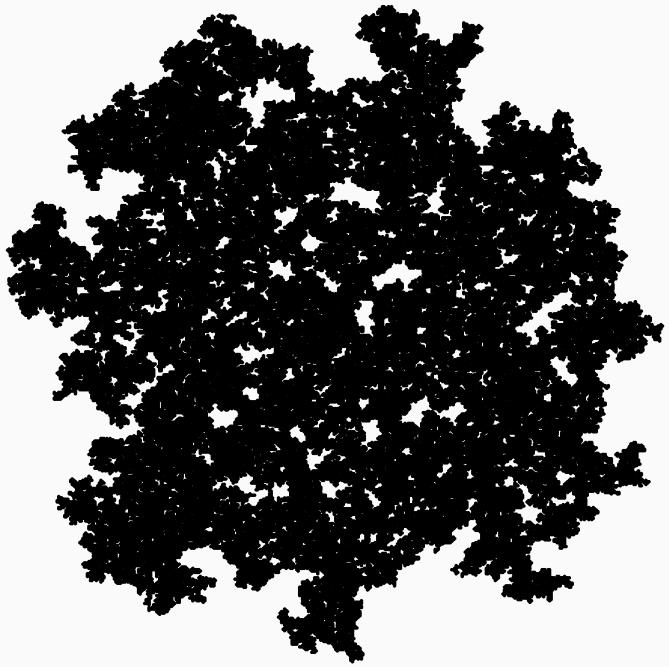
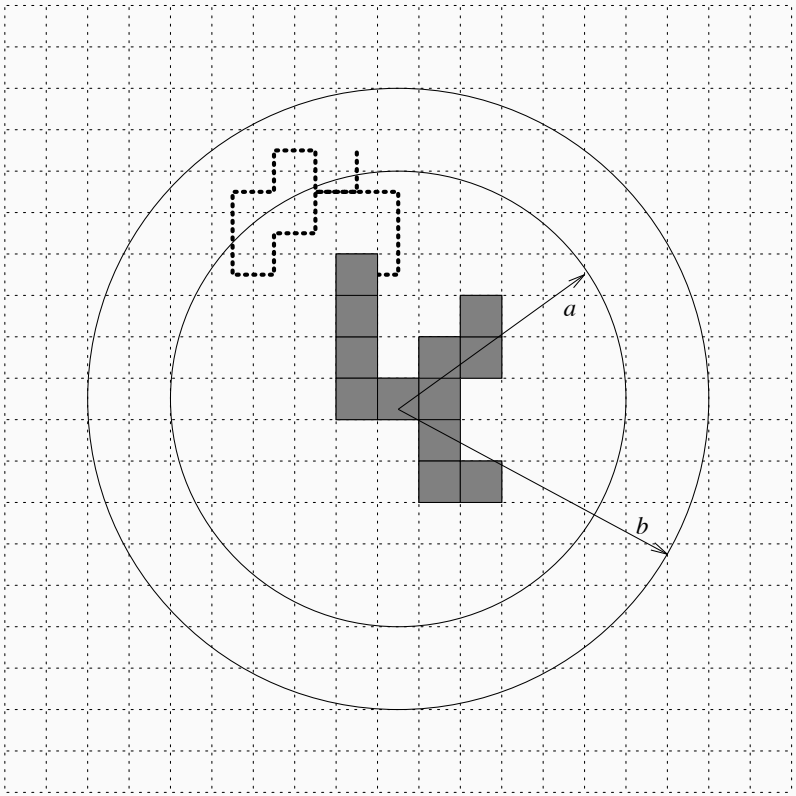


Figure 5: Leath cluster at $p = 0.55$ which is well below the percolation threshold of 0.592746.

Diffusion Limited Aggregation Model

Witten and Sanders [4] proposed a model that also applies to growth of bacterial colonies.



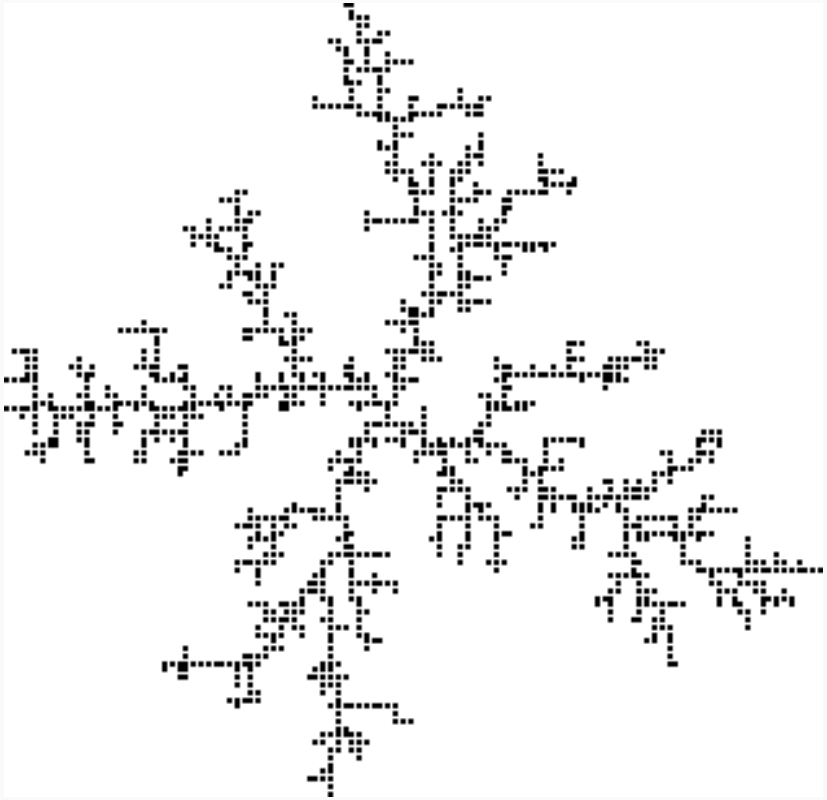


Figure 6: Setup procedure for the injection of a random walker for the diffusion limited aggregation (DLA). The right hand side figure shows an example of a DLA-cluster

Algorithm 3 Basic Algorithm: DLA

choose initial site s
choose a radius R_1 around s
choose a radius R_2 around s such that $R_1 < R_2$
start a random walker at a random position on the circle with radius R_1
while *max_sites* not reached **do**
  while position of random walker within R_2 **do**
    advance the random walker one step
    if random walker is nearest neighbour of an occupied site **then**
      add site to list of occupied sites
      start a new random walker at a random position on the circle with radius R_1
    else if site is outside of R_2 **then**
      start a new random walker at a random position on the circle with radius R_1
    end if
    compute distance d of the nearest occupied site to R_1
    if $d < d_c$ **then**
      increase R_1 and R_2
    end if
  end while
end while

Diffusion Limited Aggregation Model

```
while (sites < max_sites):
    w  = start_rw_on_circle(r1,midx,midy)
    while (check_inside_disk(w,r2,midx,midy)):
        w  = advance_random_walk(w)
        if ( nearest_neighour_of_occupied_site(w,grid) ):
            grid[w[0]][w[1]] = 1
            sites           += 1
            cm = center_of_mass(grid,cols,rows)
            r1 = cluster_radius(cm) + d
            r2 = r1 + dx
            w  = start_rw_on_circle(r1,midx,midy)
```

Code 4: Diffusion-Limited Aggregation

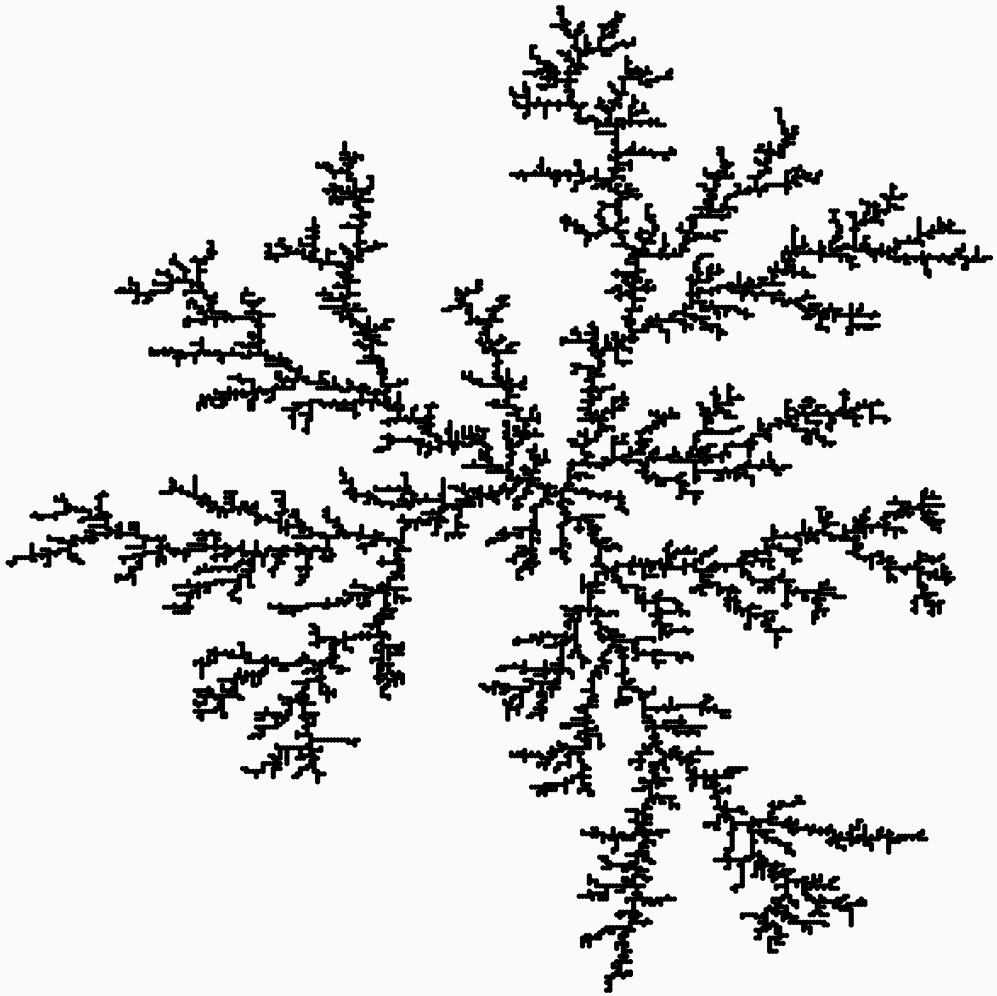


Figure 7: DLA-cluster with 10000 occupied sites.

Diffusion Limited Aggregation Model I

$$C(r, r') =< n(r)n(r + r') > \propto r^{d-d_f} \tag{10}$$

Fractal dimension for $d = 2$ $d_f = 1.66$.

Deposition

Figure 8

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Particle-Continuous Mixture Models

Particle-Continuous Mixture Models I

As an example, we study the thrombus formation using a mixture model coupling the discrete Potts model of platelet and blood cell aggregation to continuous PDEs describing the hydrodynamics of blood flow and the kinetics of coagulation reactions [6]. The basic ideas are demonstrated in Figures 9 and 10. The model consists of a list of biological cells, a list of generalized cells, a set of chemical diffusants and a description of their biological and physical behaviours and interactions embodied in the effective energy, with auxiliary equations to describe absorption and secretion of diffusants and extracellular materials, state changes within the cell, mitosis, cell death and the behaviour of extracellular diffusants.

- **Platelets**
  Platelets can exist in three states: a quiescent (resting) state; an initial activated state; and a final activated state. The concentration of resting platelets is assumed to be constant. The platelets in the two latter states generate molecules to promote coagulation and activation of the neighbouring resting platelets.
- **Coagulation factors**
  Coagulation occurs on the surface of individual activated platelets in blood.

- **Fibrin**
  Thrombin is considered as the final product of the coagulation system, which converts fibrinogen in the blood into fibrin.
- **Blood cells**
  A significant percentage of the volume of blood contains erythrocytes that are responsible for the transport of oxygen throughout the body, and leucocytes that mediate inflammatory responses.
- **Blood plasma**
  The blood plasma is treated as an incompressible fluid with constant viscosity.

The blood plasma is treated as an incompressible fluid with constant viscosity.

$$\rho \left(\frac{\partial \mathbf{v}}{\partial t} + \mathbf{v} \cdot \nabla \mathbf{v} \right) = -\nabla P + \mu \nabla^2 \mathbf{v} + \rho \mathbf{f} \tag{11}$$

$$\nabla \cdot \mathbf{v} = 0 \tag{12}$$

with $\mathbf{v}$ the flow velocity, ρ the density of the blood plasma and P the pressure. The viscosity μ is assumed to be constant. $\mathbf{f}$ is the force density due to cohesion of

activated platelets, which generates elastic stresses that influence motion of the blood plasma.

The system is partitioned into cells where we assume that a cell has the same velocity value as the blood flow. The average flow velocity for a cell i is

$$V_i = \sum_k v_K / Vol_i \tag{13}$$

where v_k is the flow velocity at site k and Vol_i is the volume of cell i. The flow energy change for cell i caused by state change is

$$\Delta E_{\text{flow}(i)} = -K_{e2} V_i \Delta d_i \tag{14}$$

where Δd_i is the change of the centre of mass of cell i caused by the state change and K_{e2} is the flow energy constant.

To describe coagulation within the plasma, we use a rate equation approach for species (i)

$$d[C_j] = \sum_i k_{ij}[C_j]dt \tag{15}$$

where $[C_i]$ is the concentration of species i and $k_{ij}, i, j = 1, ..., n$ are the corresponding rates.

The thrombin concentration (θ) dynamics is modelled by

$$\frac{\partial \theta}{\partial t} + \mathbf{u}\nabla\theta = D_\theta \nabla^2 \theta + \sum_{i=1}^{N} \Delta\theta_i \tag{16}$$

where $\Delta\theta_i$ is the thrombin generated by the i activated platelet, D_θ is the diffusion coefficient and N is the number of cells in a discretization (c.f. Figure 10).

The production of fibrin is modelled by

$$\frac{\partial \psi}{\partial t} = \kappa\theta \ . \tag{17}$$

The effective energy of the system mixes energies

$$E = E_{\text{adhesion}} + E_{\text{area}} \ . \tag{18}$$

To model the adhesion we consider Potts spins $s_i = (1, 2, \ldots, q)$, interacting via the Hamiltonian

$$-\beta H = K \sum_{<i,j>} \delta_{s_i, s_j} \ . \tag{19}$$

Here, this translates into

$$E_{\text{adhesion}} = \sum_{(i,j,k)(i',j',k')} J_{\tau(\sigma)\tau'(\sigma')}(1 - \delta(\sigma(i,j,k)\sigma(i',j',k'))) \tag{20}$$

where $J_{\tau,\tau'}$ the binding energy per unit length. Cell of type τ have a prescribed target area $a_{\text{target}}(\sigma, \tau)$.

$$E_{\text{area}} = \sum_{\sigma} \lambda(a(\sigma, \tau - a_{\text{target}}(\sigma, \tau)) \tag{21}$$

where ψ is the concentration of fibrin and κ the corresponding rate.

The flow force applied to a cell i is taken to be the integral of blood pressure along a cell membrane

$$\mathbf{F}_i = \sum_k p_k \mathbf{n}_k S_k \ . \tag{22}$$

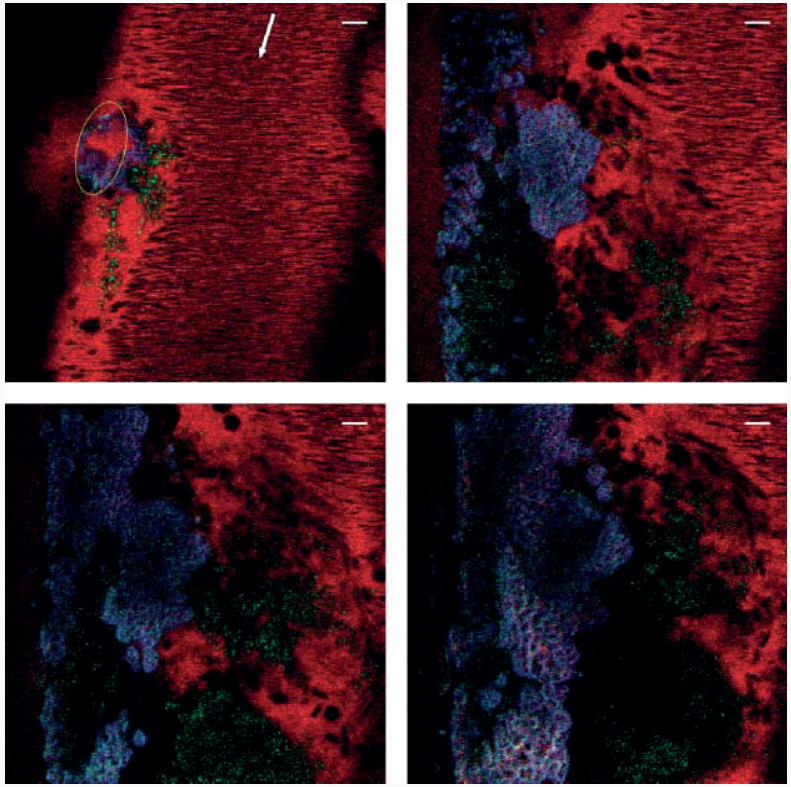
where k denotes the interface segment of cell i. p_i is the pressure applied to the blood?cell interface segment$k$. $\mathbf{n}_k$ is the membrane length of the blood?cell interface segment k.

The flow energy change for the cell i is taken to be

$$\Delta E_{\text{flow}(i)} = -K_{\text{el}} \mathbf{F}_i \Delta \mathbf{d}_i \tag{23}$$

where $\Delta \mathbf{d}_i$ is the change in the position of the centre of mass of cell i caused by the state change and K_{el} is a flow energy constant.

Particle-Continuous Mixture Models VII



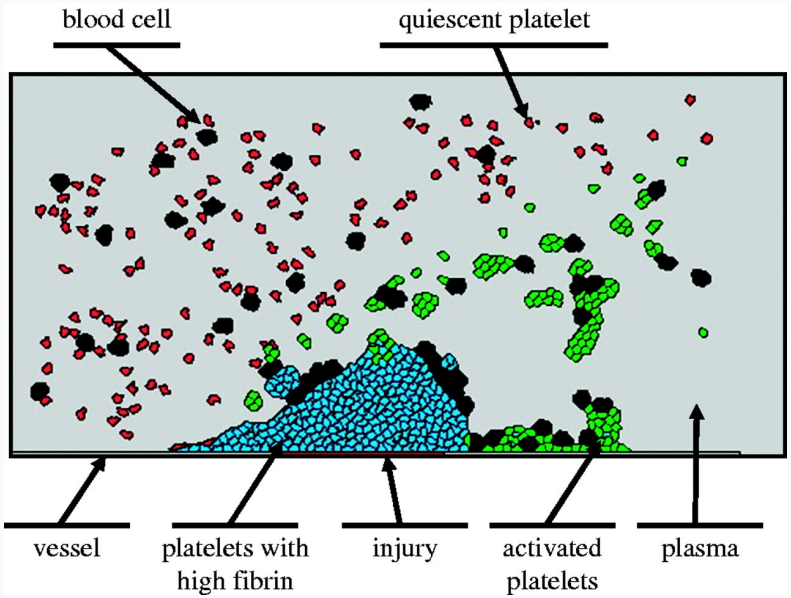


Figure 9: The left panel shows intravital confocal images of a developing venous thrombus. The right panel shows the modelling approach. Images taken from [6].

Particle-Continuous Mixture Models VIII

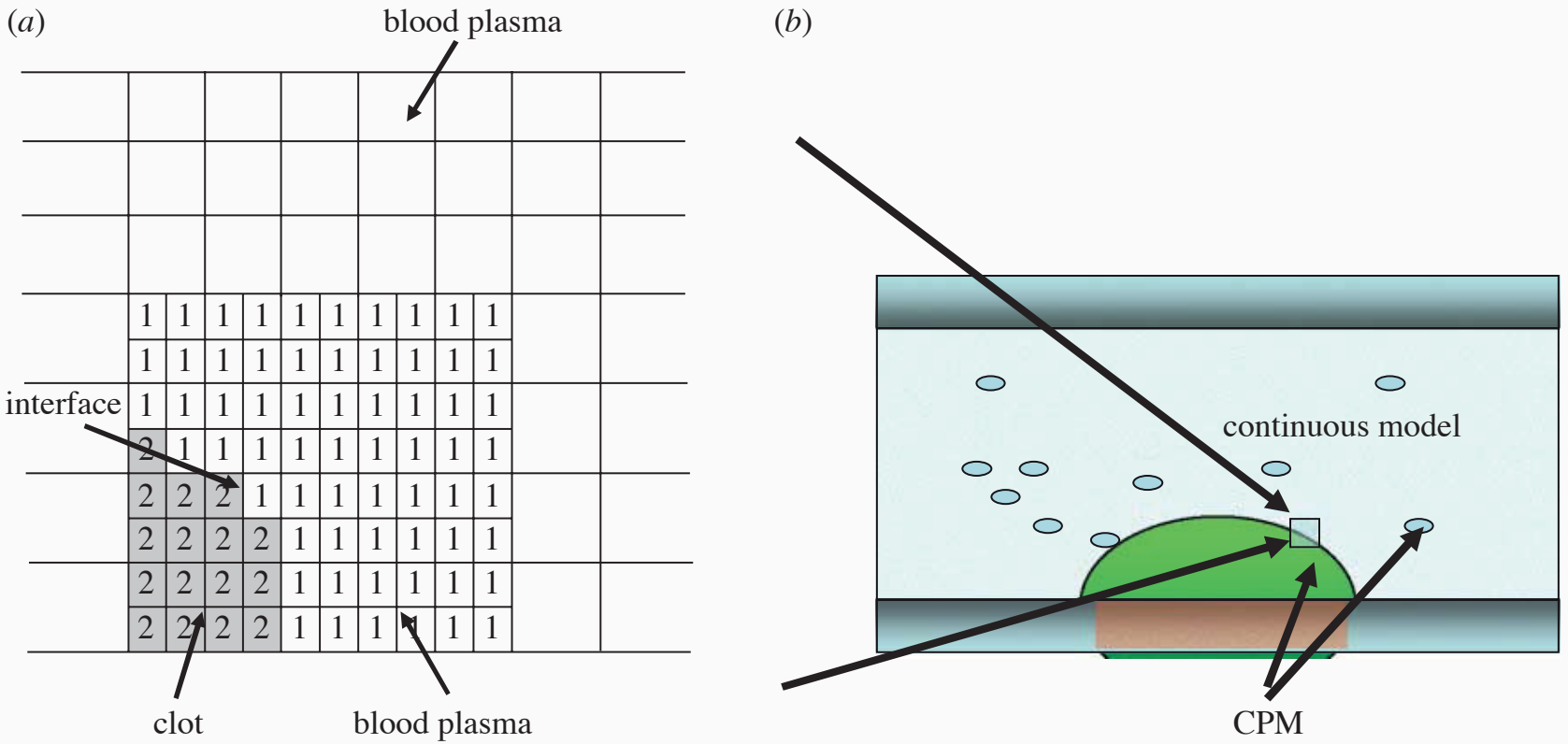


Figure 10: The modelling approach. Images taken from [6].

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Excercises

Excercises I

Exercise 1: **Richardson's Model [15]**

In the Richardson's model occupied sites remain occupied. Unoccupied sites change state to occupied at time $t+1$ with probability p if at least one neighbor was occupied at time n. Show numerically that the asymptotic shape of the object (in $d=2$) has a straight edge if $p > p_c$, where p_c is a critical value. Determine p_c.

Exercise 2: **Williams and Bjerknes Tumor Growth Model [16]**

This model generalizes the Eden model as a stochastic model for the spread of cancer cells (skin cancer). At each time step a site can become either ill with probability α or healthy with probability β. Thus the ratio $\kappa = \alpha/\beta$ determines the behaviour with $\kappa = \infty$ recovering the Eden model. Rewrite the above Eden model algorithm to incorporate the modification.

Exercise 3: **DLA with reaction-controlled absoption**

Assume a DLA model. Let P be the probability for a particle to react with the nearest-neighbour site that is occupied. Modify the above program to incorporate the changed absorption.

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Exercise 4: **Continuum Model of DLA**

In the continuum model of DLA each particle is assumed to have a radius a. At every step the random walker is performing a gaussian random walk with steps size $\leq a$. The particles sticks to the aggregate is the distance to the nearest particle is $\leq a$. Modify the above program to incorporate the changed absorption. Show that

$$d = 2 \quad d_f = 1.71 \tag{24}$$

$$d = 3 \quad d_f = 2.5 \tag{25}$$

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Index

Index I

Index II