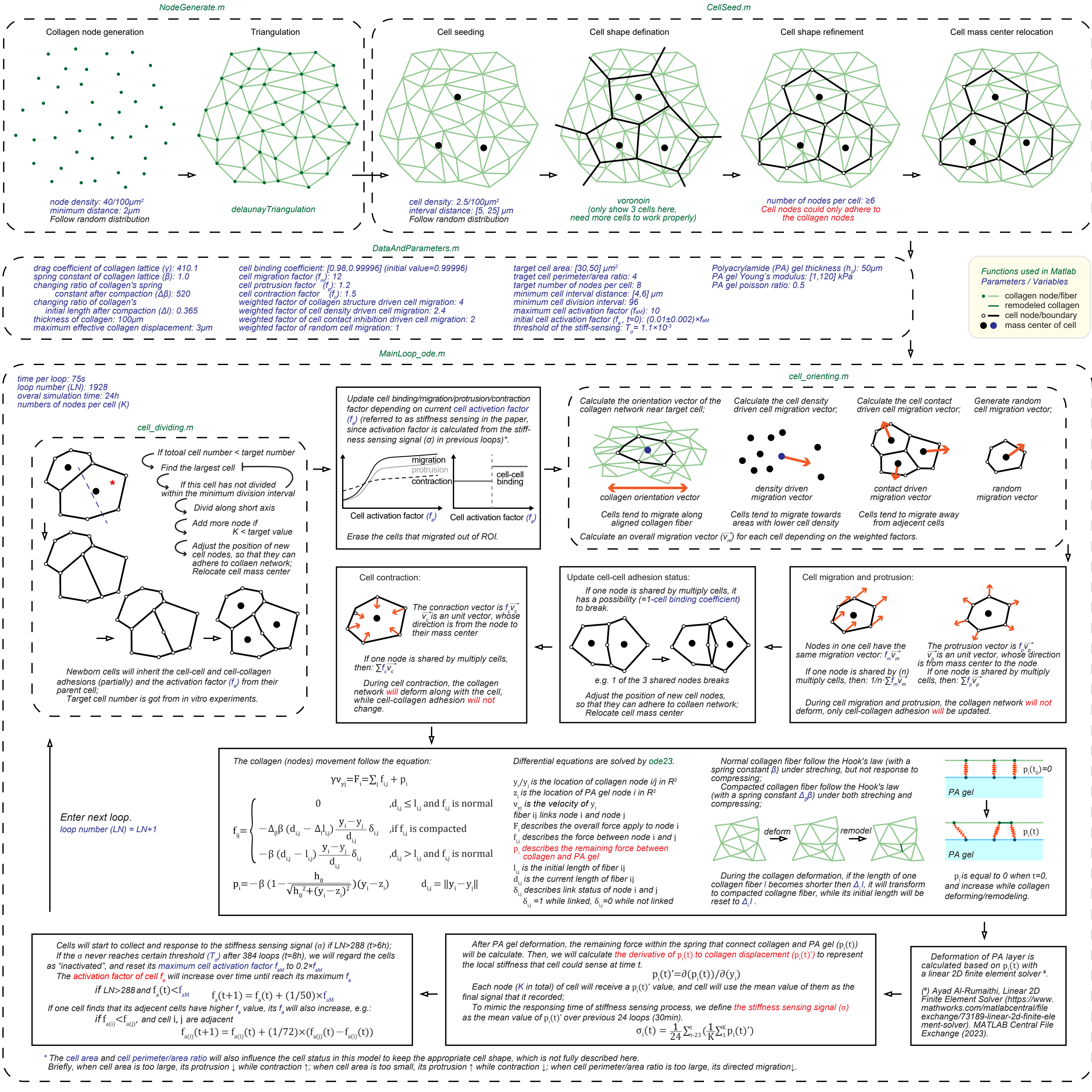
NodeGenerate.m
CellSeed.m
Collagen node generation
Triangulation
Cell seeding
Cell shape defination
Cell shape refinement
Cell mass center relocation
node density: 40/100μm²
minimum distance: 2μm
Follow random distribution
delaunayTriangulation
cell density: 2.5/100μm²
interval distance: [5, 25] μm
Follow random distribution
voronoin
(only show 3 cells here,
need more cells to work properly)
number of nodes per cell: ≥6
Cell nodes could only adhere to
the collagen nodes
DataAndParameters.m
drag coefficient of collagen lattice (γ): 410.1
spring constant of collagen lattice (β): 1.0
changing ratio of collagen's spring
constant after compaction (Δβ): 520
changing ratio of collagen's
initial length after compaction (Δl): 0.365
thickness of collagen: 100μm
maximum effective collagen displacement: 3μm
cell binding coefficient: [0.98,0.99996] (initial value=0.99996)
cell migration factor (fm): 12
cell protrusion factor (fp): 1.2
cell contraction factor (fc): 1.5
weighted factor of collagen structure driven cell migration: 4
weighted factor of cell density driven cell migration: 2.4
weighted factor of cell contact inhibition driven cell migration: 2
weighted factor of random cell migration: 1
target cell area: [30,50] μm²
traget cell perimeter/area ratio: 4
target number of nodes per cell: 8
minimum cell interval distance: [4,6] μm
minimum cell division interval: 96
maximum cell activation factor (faM): 10
initial cell activation factor (fa, t=0): (0.01±0.002)×faM
threshold of the stiff-sensing: Tσ= 1.1×10⁻³
Polyacrylamide (PA) gel thickness (h0): 50μm
PA gel Young's modulus: [1,120] kPa
PA gel poisson ratio: 0.5
Functions used in Matlab
Parameters / Variables
collagen node/fiber
remodeled collagen
cell node/boundary
mass center of cell
MainLoop_ode.m
time per loop: 75s
loop number (LN): 1928
overal simulation time: 24h
numbers of nodes per cell (K)
cell_dividing.m
If totoal cell number < target number
Find the largest cell
If this cell has not divided
within the minimum division interval
Divid along short axis
Add more node if
K < target value
Adjust the position of new
cell nodes, so that they can
adhere to collaen network;
Relocate cell mass center
Newborn cells will inherit the cell-cell and cell-collagen
adhesions (partially) and the activation factor (fa) from their
parent cell;
Target cell number is got from in vitro experiments.
Update cell binding/migration/protrusion/contraction
factor depending on current cell activation factor
(fa) (referred to as stiffness sensing in the paper,
since activation factor is calculated from the stiff-
ness sensing signal (σ) in previous loops)*.
migration
protrusion
contraction
cell-cell
binding
Cell activation factor (fa)
Cell activation factor (fa)
Erase the cells that migrated out of ROI.
cell_orienting.m
Calculate the orientation vector of the
collagen network near target cell;
Calculate the cell density
driven cell migration vector;
Calculate the cell contact
driven cell migration vector;
Generate random
cell migration vector;
collagen orientation vector
density driven
migration vector
contact driven
migration vector
random
migration vector
Cells tend to migrate along
aligned collagen fiber
Cells tend to migrate towards
areas with lower cell density
Cells tend to migrate away
from adjecent cells
Calculate an overall migration vector (vm) for each cell depending on the weighted factors.
Cell contraction:
The conraction vector is fc vc
vc is an unit vector, whose
direction is from the node to
their mass center
If one node is shared by multiply cells,
then: ∑fc vc
During cell contraction, the collagen
network will deform along with the cell,
while cell-collagen adhesion will not
change.
Update cell-cell adhesion status:
If one node is shared by multiply cells, it
has a possibility (=1-cell binding coefficient)
to break.
e.g. 1 of the 3 shared nodes breaks
Adjust the position of new cell nodes,
so that they can adhere to collaen network;
Relocate cell mass center
Cell migration and protrusion:
Nodes in one cell have the
same migration vector: fm vm
If one node is shared by (n)
multiply cells, then: 1/n·∑fm vm
The protrusion vector is fp vp
vp is an unit vector, whose direction
is from mass center to the node
If one node is shared by multiply
cells, then: ∑fp vp
During cell migration and protrusion, the collagen network will not
deform, only cell-collagen adhesion will be updated.
Enter next loop.
loop number (LN) = LN+1
The collagen (nodes) movement follow the equation:
$\gamma v_{yi} = F_i = \sum_j f_{i,j} + p_i$
$f_{ij} = \begin{cases} 0 & ,d_{i,j} \le l_{i,j} \text{ and } f_{i,j} \text{ is normal} \\ -\Delta_\beta \beta\,(d_{i,j} - \Delta_l l_{i,j}) \dfrac{y_i - y_j}{d_{i,j}} \delta_{i,j} & ,\text{if } f_{i,j} \text{ is compacted} \\ -\beta\,(d_{i,j} - l_{i,j}) \dfrac{y_i - y_j}{d_{i,j}} \delta_{i,j} & ,d_{i,j} > l_{i,j} \text{ and } f_{i,j} \text{ is normal} \end{cases}$
$p_i = -\beta\,(1 - \dfrac{h_0}{\sqrt{h_0^2 + (y_i - z_i)^2}})(y_i - z_i) \qquad d_{i,j} = \|y_i - y_j\|$
Differential equations are solved by ode23.
yi/yj is the location of collagen node i/j in R²
zi is the location of PA gel node i in R²
vyi is the velocity of yi
fiber ij links node i and node j
Fi describes the overall force apply to node i
fi,j describes the force between node i and j
pi describes the remaining force between
collagen and PA gel
li,j is the initial length of fiber ij
di,j is the current length of fiber ij
δi,j describes link status of node i and j
δi,j =1 while linked, δi,j =0 while not linked
Normal collagen fiber follow the Hook's law (with a
spring constant β) under streching, but not response to
compressing;
Compacted collagen fiber follow the Hook's law
(with a spring constant Δββ) under both streching and
compressing;
deform
remodel
During the collagen deformation, if the length of one
collagen fiber l becomes shorter then Δl l, it will transform
to compacted collagne fiber, while its initial length will be
reset to Δl l .
pi(t0)=0
PA gel
pi(t)
PA gel
pi is equal to 0 when t=0,
and increase while collagen
deforming/remodeling.
Cells will start to collect and response to the stiffness sensing signal (σ) if LN>288 (t>6h);
If the σ never reaches certain threshold (Tσ) after 384 loops (t=8h), we will regard the cells
as "inactivated", and reset its maximum cell activation factor faM to 0.2×faM
The activation factor of cell fa will increase over time until reach its maximum fa
if LN>288 and fa(t)<faM $f_a(t+1) = f_a(t) + (1/50)\times f_{aM}$
If one cell finds that its adjecent cells have higher fa value, its fa will also increase, e.g.:
if fa(i)<fa(j), and cell i, j are adjacent
$f_{a(i)}(t+1) = f_{a(i)}(t) + (1/72)\times(f_{a(j)}(t) - f_{a(i)}(t))$
After PA gel deformation, the remaining force within the spring that connect collagen and PA gel (pi(t))
will be calculate. Then, we will calculate the derivative of pi(t) to collagen displacement (pi(t)') to represent
the local stiffness that cell could sense at time t.
$p_i(t)' = \partial(p_i(t))/\partial(y_i)$
Each node (K in total) of cell will receive a pi(t)' value, and cell will use the mean value of them as the
final signal that it recorded;
To mimic the responsing time of stiffness sensing process, we define the stiffness sensing signal (σ)
as the mean value of pi(t)' over previous 24 loops (30min).
$\sigma_i(t) = \frac{1}{24}\sum_{t-23}^{t}(\frac{1}{K}\sum_1^K p_i(t)')$
Deformation of PA layer is
calculated based on pi(t) with
a linear 2D finite element solver #.
(#) Ayad Al-Rumaithi, Linear 2D
Finite Element Solver (https://www.
mathworks.com/matlabcentral/file
exchange/73189-linear-2d-finite-ele
ment-solver). MATLAB Central File
Exchange (2023).
* The cell area and cell perimeter/area ratio will also influence the cell status in this model to keep the appropriate cell shape, which is not fully described here.
Briefly, when cell area is too large, its protrusion ↓ while contraction ↑; when cell area is too small, its protrusion ↑ while contraction ↓; when cell perimeter/area ratio is too large, its directed migration↓.