Universidad de los Andes

In silico study of spheroids fusion through magnetic field gradients

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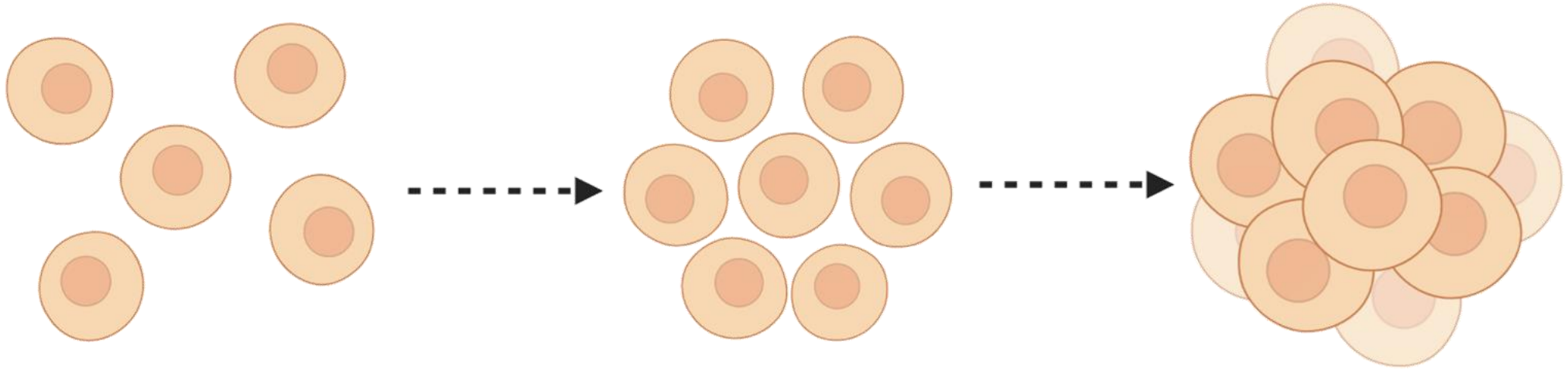
Cell spheroids

Cell attachment is crucial for cell viability and proliferation



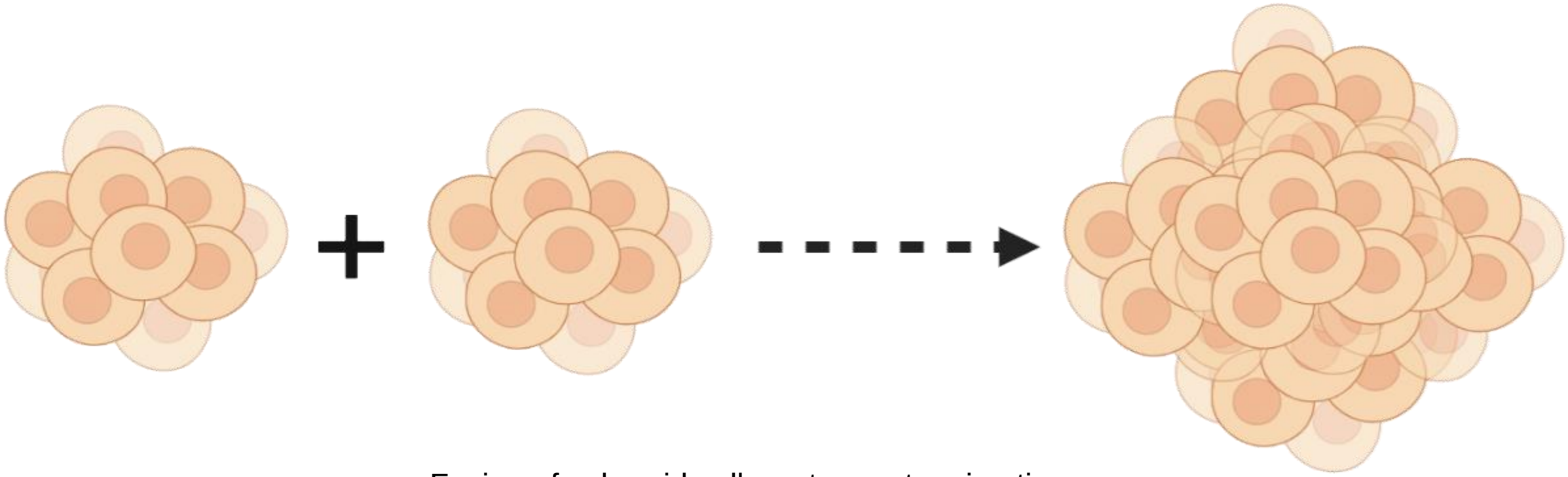
CELL SCATTERING

CELL SPHEROID

Cell-cell adhesion molecules (CAMs) and proteins, such as integrins and cadherins allow for spheroid formation

Rapid formation of cell aggregates and spheroids induced by a “smart” boronic acid copolymer. ACS applied materials & interfaces DOI: 10.1021/acsami.6b07911

Spheroids fusion

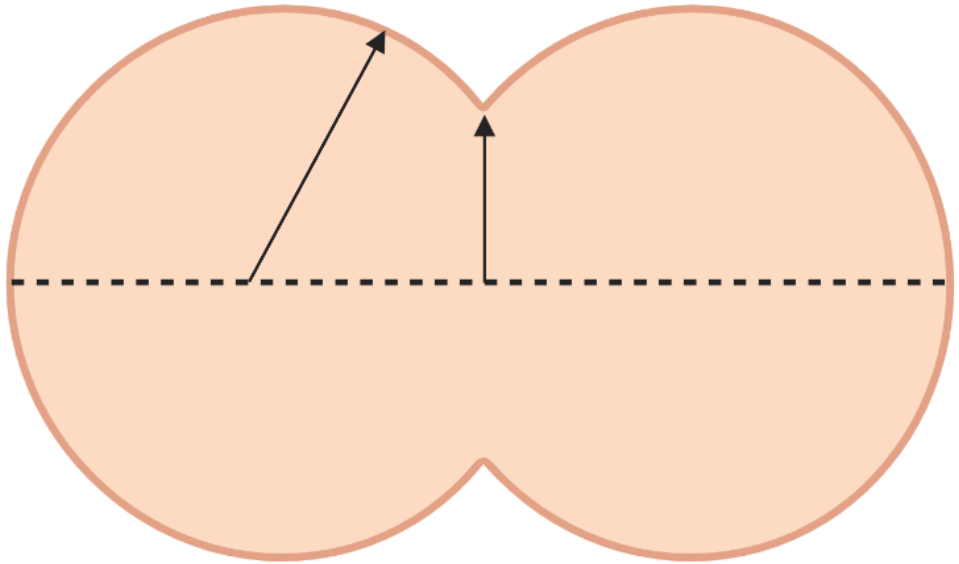


Fusion of spheroids allows to create microtissues

This 3D microenvironment provides a rich microenvironment that better mimics physiological conditions compared with two-dimensional (2D) cell cultures

Rapid formation of cell aggregates and spheroids induced by a “smart” boronic acid copolymer. ACS applied materials & interfaces DOI: 10.1021/acsami.6b07911

Normal fusion process

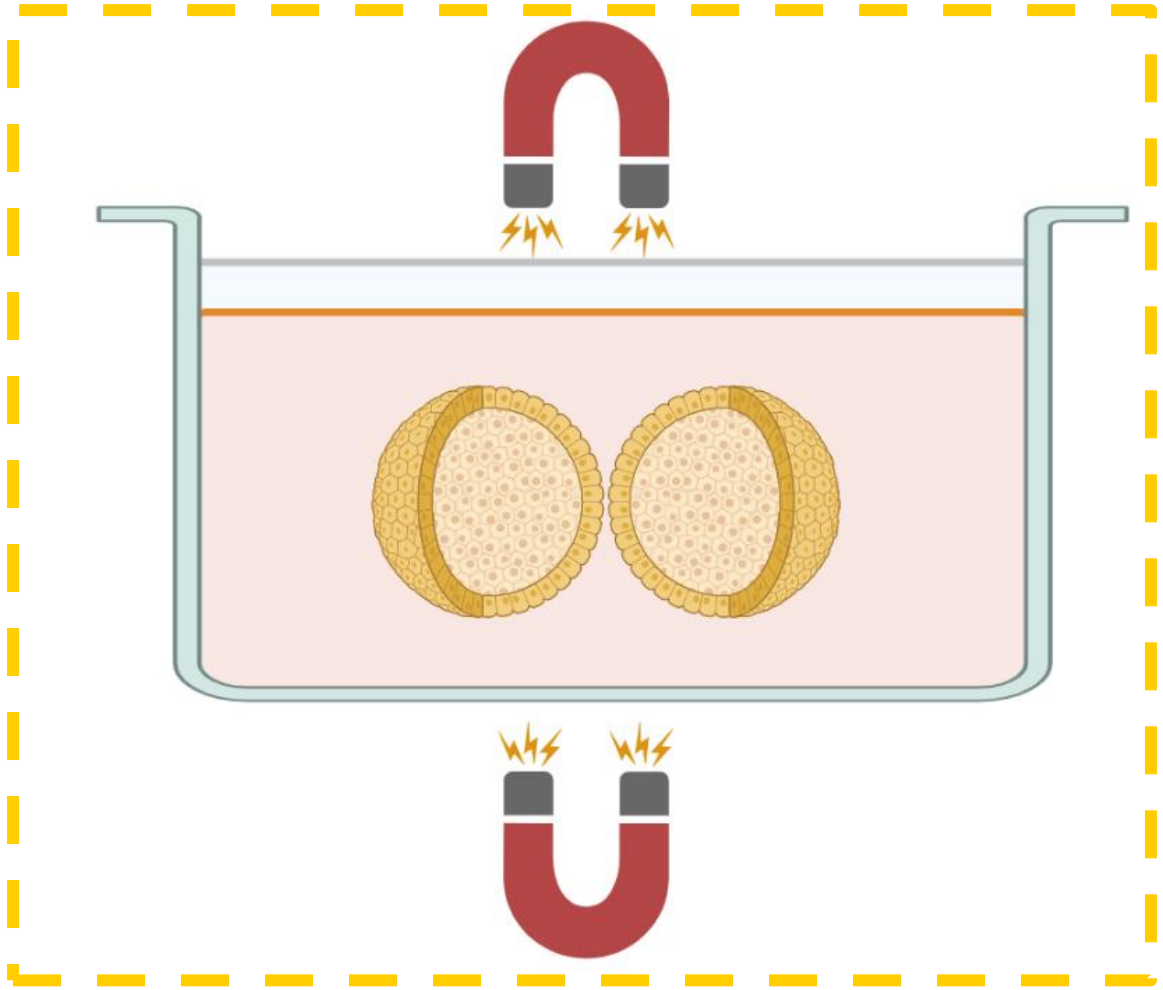


~48 hr

The traditional fusion process takes a long time

Rapid formation of cell aggregates and spheroids induced by a “smart” boronic acid copolymer. ACS applied materials & interfaces DOI: 10.1021/acsami.6b07911

Proposed model



Magnetite (Fe_3O_4) nanoparticles would generate the magnetic field gradient that is expected to accelerate the fusion process of magnetic spheroids

Mathematical model

Navier -Stokes

$$\rho \frac{\partial u}{\partial t} + \rho(u \cdot \nabla)u = \nabla \cdot [-pI + \mu(\nabla u + \nabla u^T)] + F$$

u = fluid velocity

p =fluid pressure

ρ= fluid density

I = Identity matrix

F = External forces

Gauss' Law

$\nabla B = 0$

$B = \mu_0(H+M)$

$$-\nabla \cdot (\mu_0 \nabla V_m - \mu_0 M) = 0$$

H= Magnetic field intensity

B= Magnetic flux density

M=Magnetization vector

μ_0 = permeability

Vm=Magnetic scalar potential

Phase-field: Interface

$$\phi(x,t) = \begin{cases} 1, & Spheroids \\ -1, & Medium \end{cases}$$

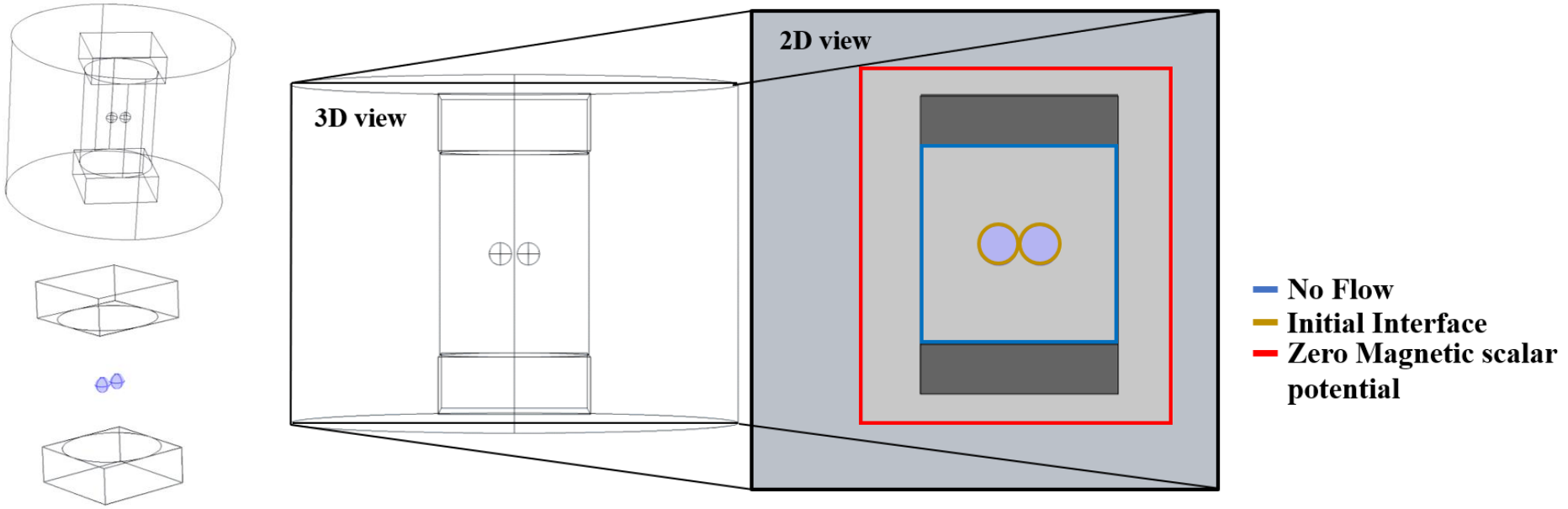
$$\frac{\partial \phi}{\partial t} + u \cdot \nabla \phi = 0$$

$$u = u_n n + u_e$$
$$u_n = a - bk$$

$$k = \frac{1}{|\nabla \phi|}\left(\nabla^2 \phi + \phi \frac{(1-\phi^2)}{w}\right)$$

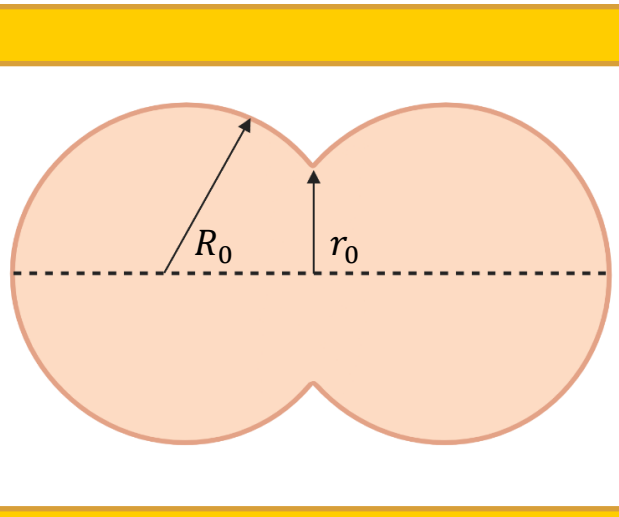
$$\frac{\partial \phi}{\partial t} + a - b\frac{1}{|\nabla \phi|}\left(\nabla^2 \phi + \phi \frac{(1-\phi^2)}{w}\right) n + u_e \cdot \nabla \phi = 0$$

Geometry

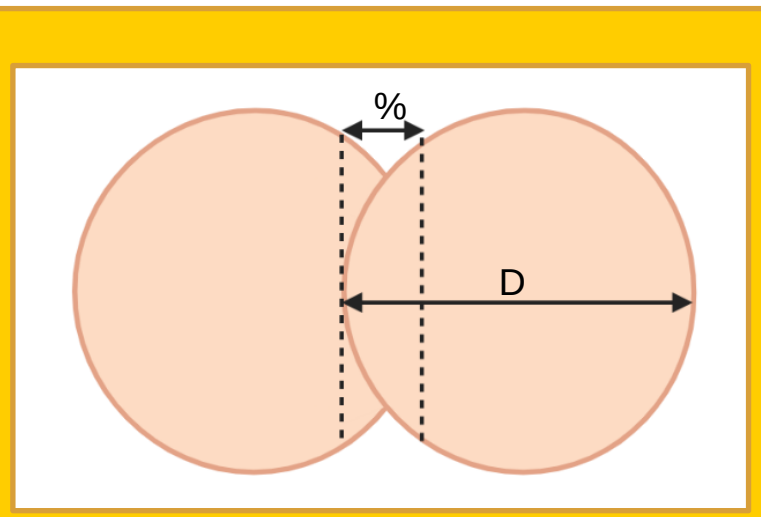


a) 3D view Geometry spheroids, magnets, and environment configuration, and **b)** 2D Geometry spheroids, magnets, and environment as projected from the 3D geometry.

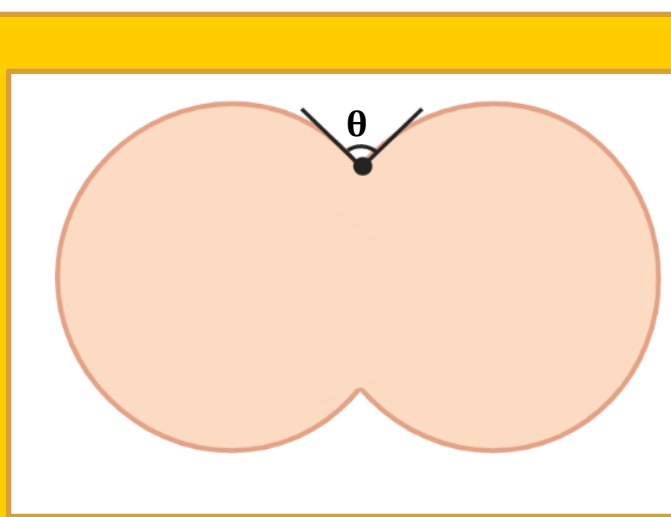
Evaluation of the models



$\left(\frac{r_0}{R_0}\right)^2$ **Fusion neck**

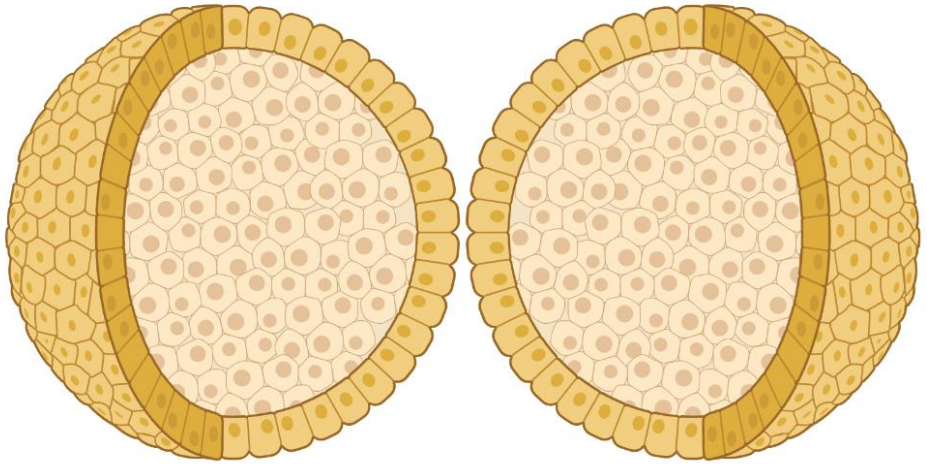


Percent of envelopment

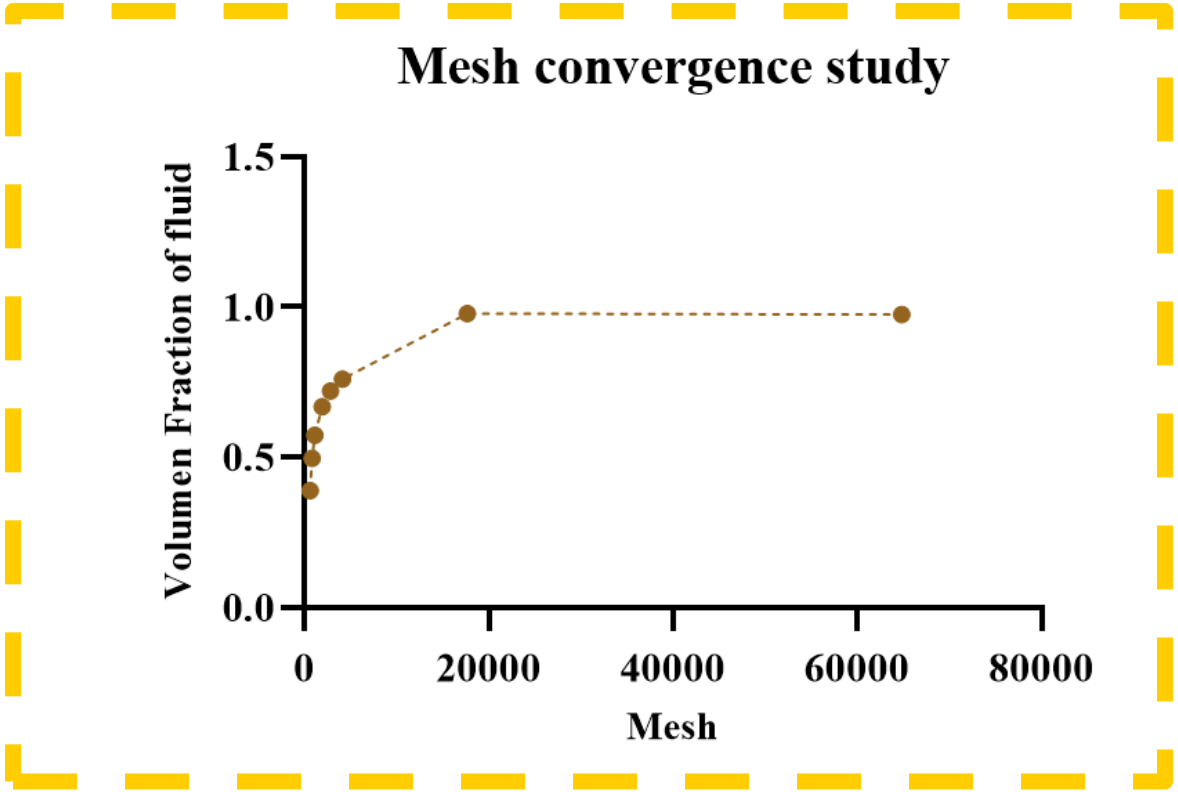


Fusion angle

RESULTS AND DISCUSSION



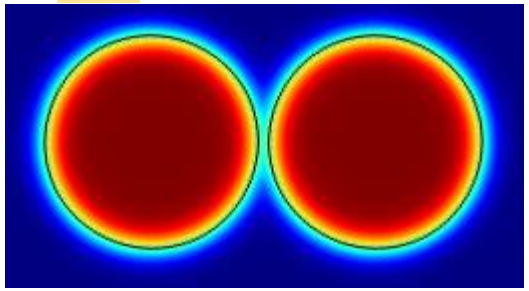
Mesh convergence 2D base model without magnetic field



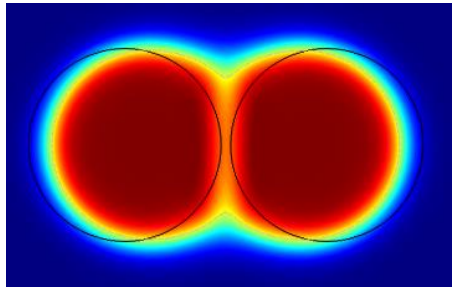
Mesh convergence with 17664 domain elements

2D Fusion model

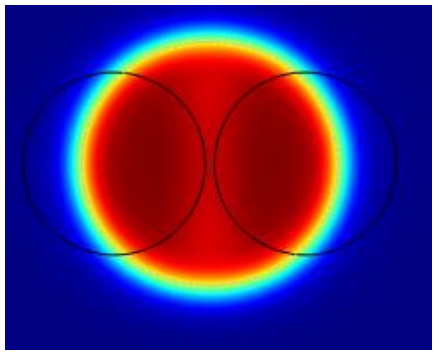
t=0d Volume fraction



t=2d Volume fraction

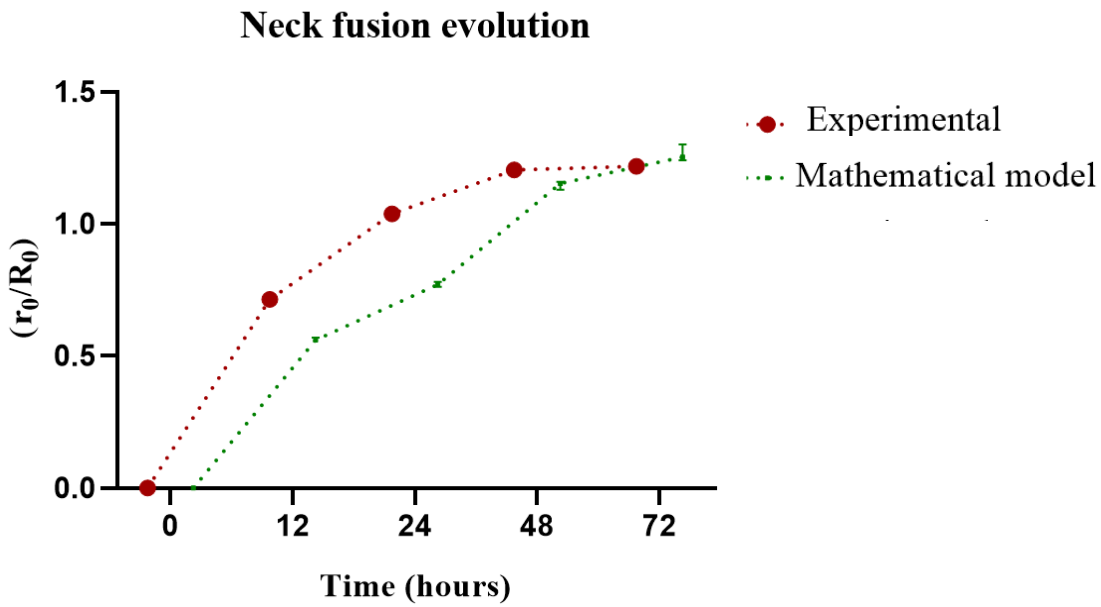


t=4d Volume fraction



Evaluation of the 2D model without magnetic field

$\left(\frac{r_0}{R_0}\right)^2$ Fusion neck



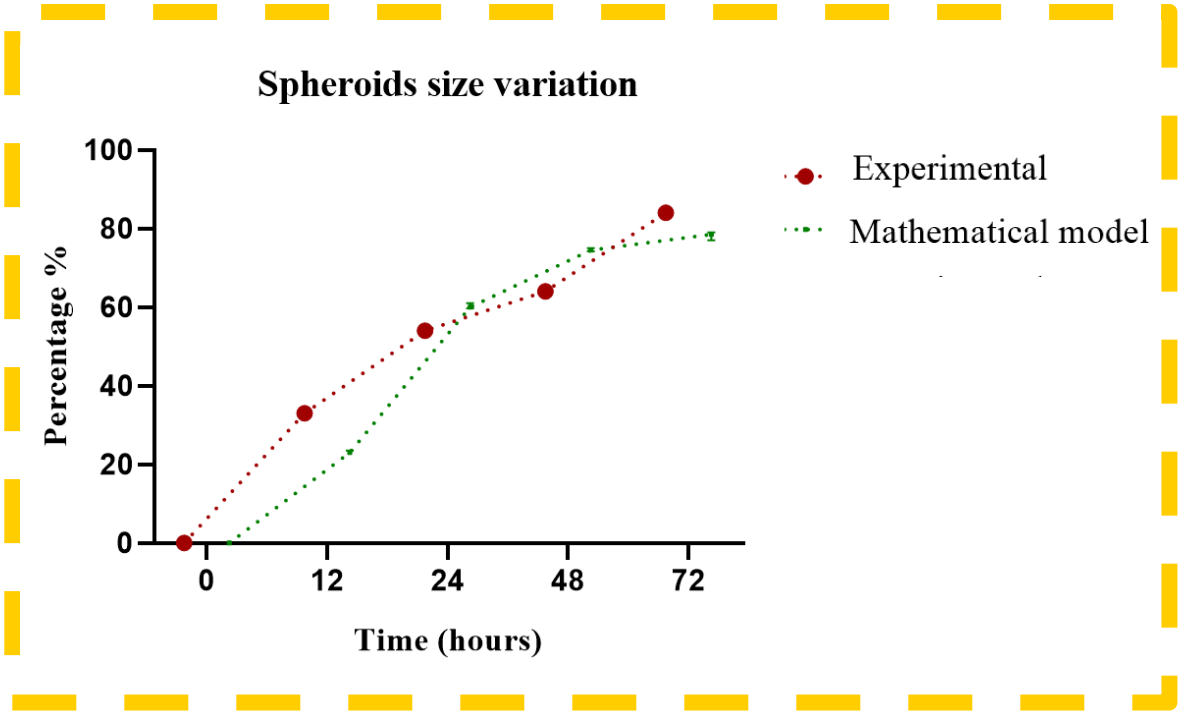
$$\sum_{i=1}^{n} \frac{|Experimental - Matematical|}{Experimental}$$

13,981%

Tissue spheroid fusion-based in vitro screening assays for analysis of tissue maturation DOI:10.1002/term.291

Evaluation of the 2D model without magnetic field

Percent of envelopment



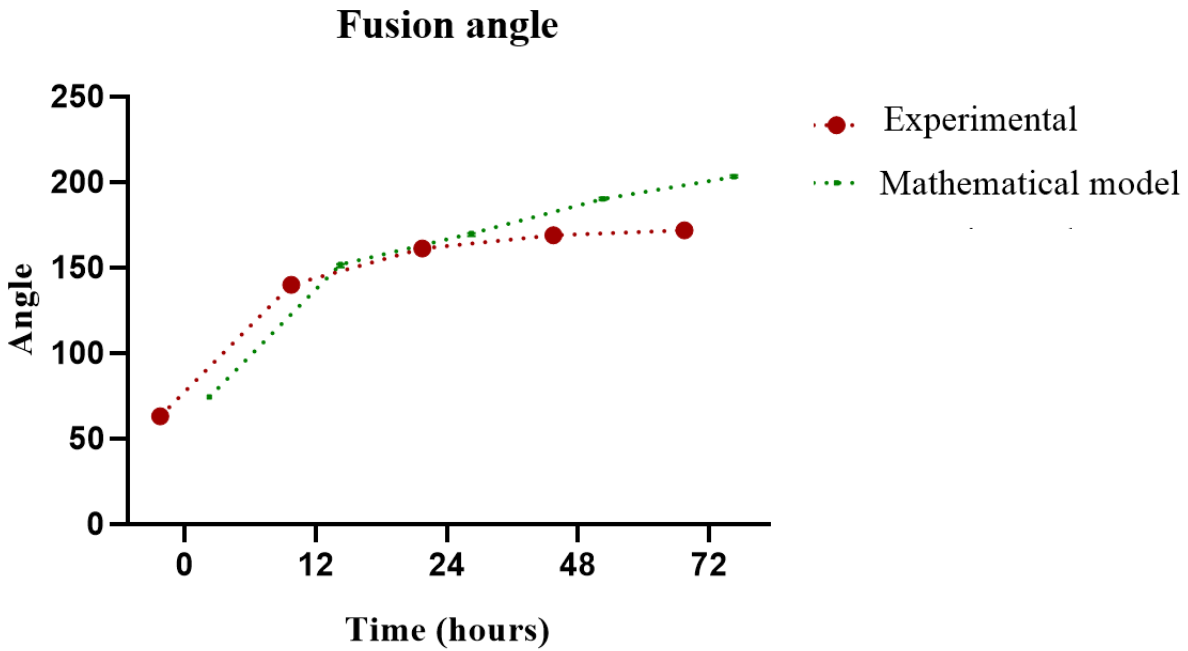
$$\sum_{i=1}^{n} \frac{|Experimental - Matematical|}{Experimental}$$

16,1385%

Tissue spheroid fusion-based in vitro screening assays for analysis of tissue maturation DOI:10.1002/term.291

Evaluation of the 2D model without magnetic field

Fusion angle



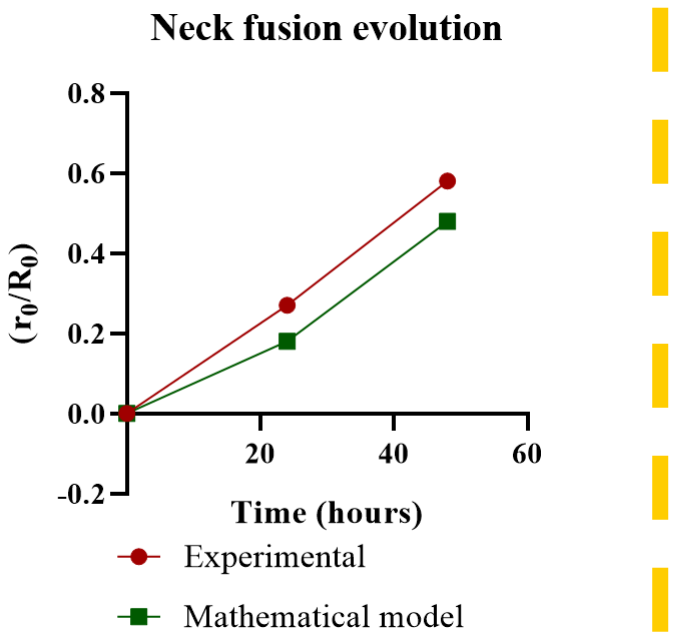
$$\sum_{i=1}^{n} \frac{|Experimental - Matematical|}{Experimental}$$

12,4827%

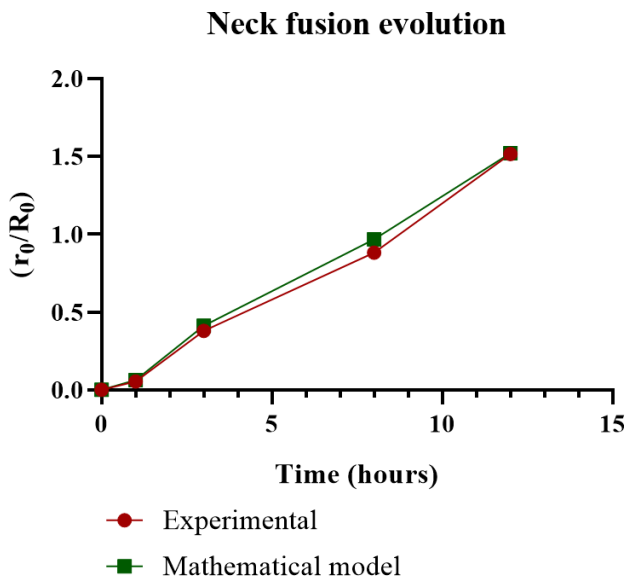
Tissue spheroid fusion-based in vitro screening assays for analysis of tissue maturation DOI:10.1002/term.291

Model validation with other materials

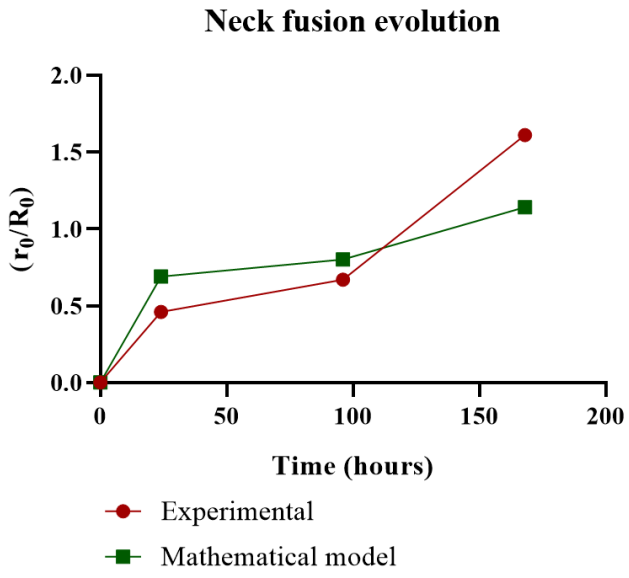
$\left(\frac{r_0}{R_0}\right)^2$ Fusion neck



Cardiomyocytes and fibroblasts



Vascular smooth muscle cells and endothelial cells lining

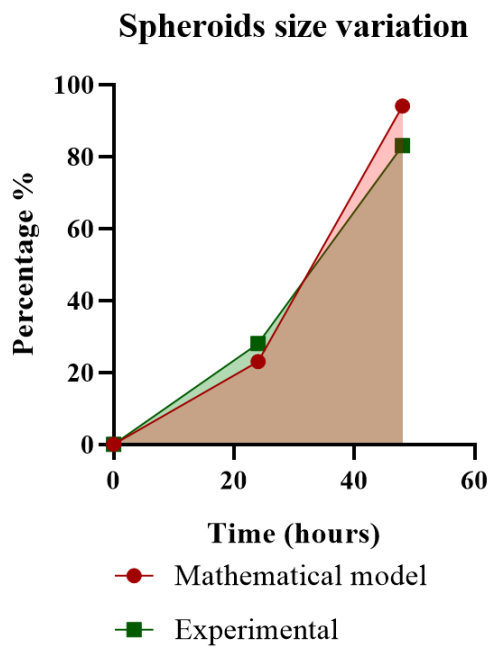


Normal human fibroblast

3D bioprinting of high cell-density heterogeneoustissue models through spheroid fusion within self-healing hydrogels DOI: 0.1038/s41467-021-21029-2
Fusion of Uniluminal Vascular Spheroids: A Model for Assembly of Blood Vessels DOI: 10.1002/dvdy.22161
Controlling Cell Position in Complex Heterotypic 3DMicrotissues by Tissue Fusion DOI: 10.1002/bit.22162

Model validation with other materials

Percent of envelopment



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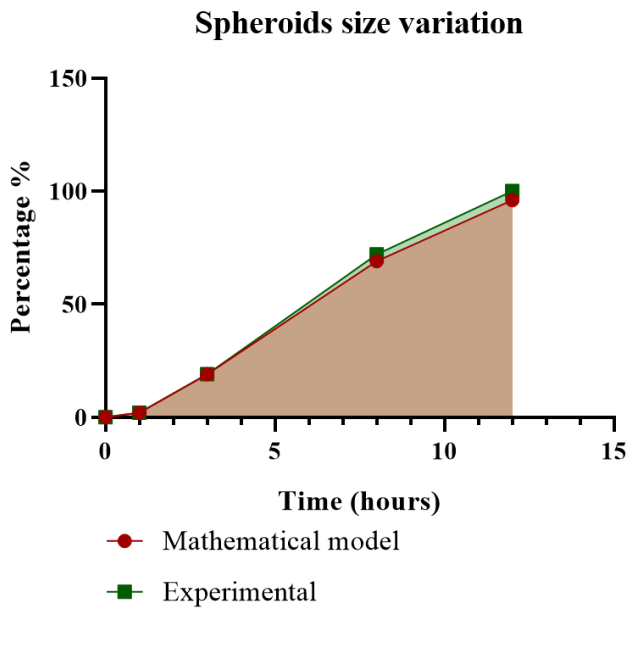

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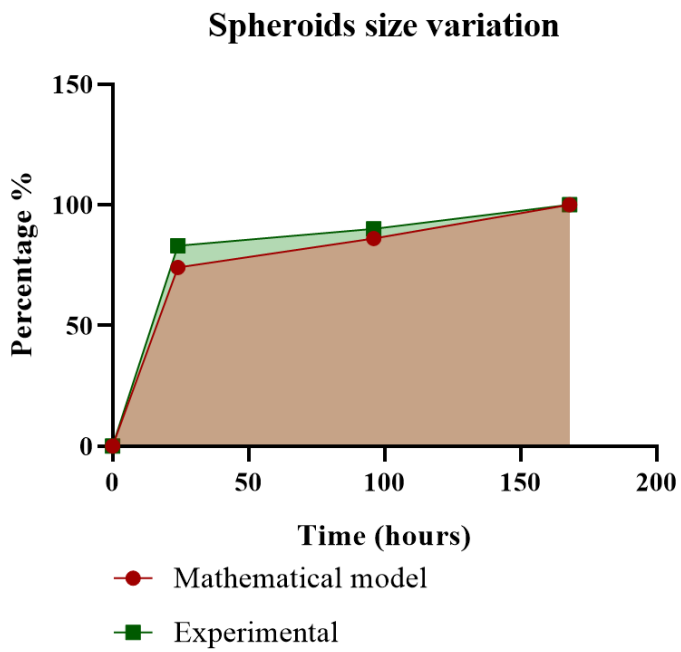

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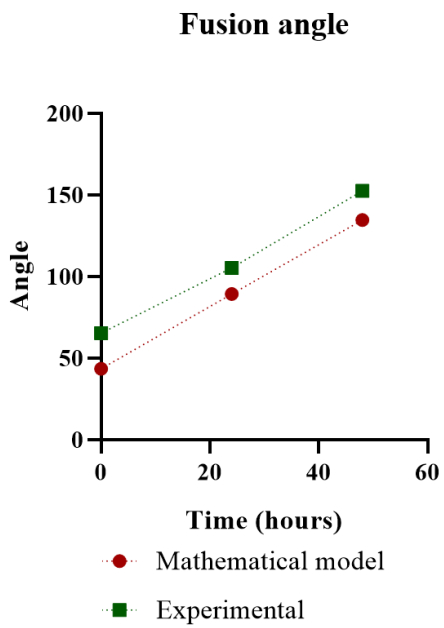
Model validation with other materials

Fusion angle



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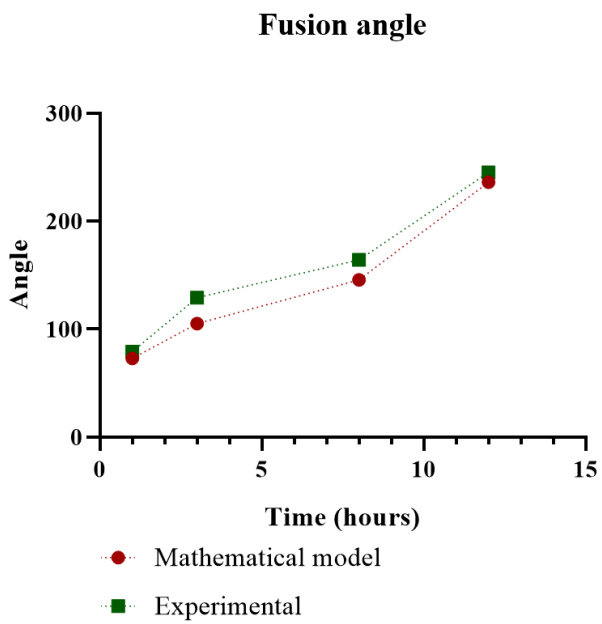

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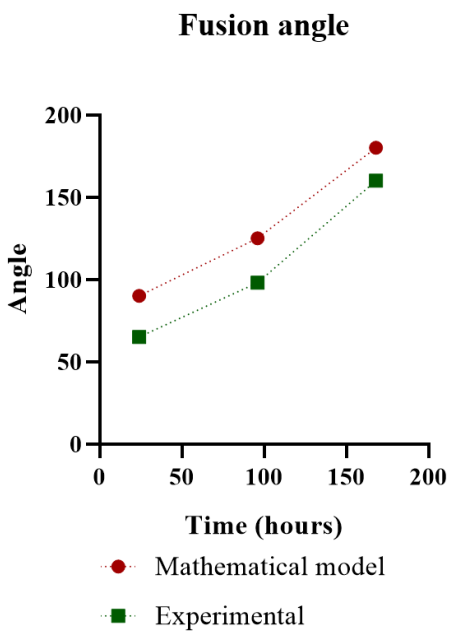

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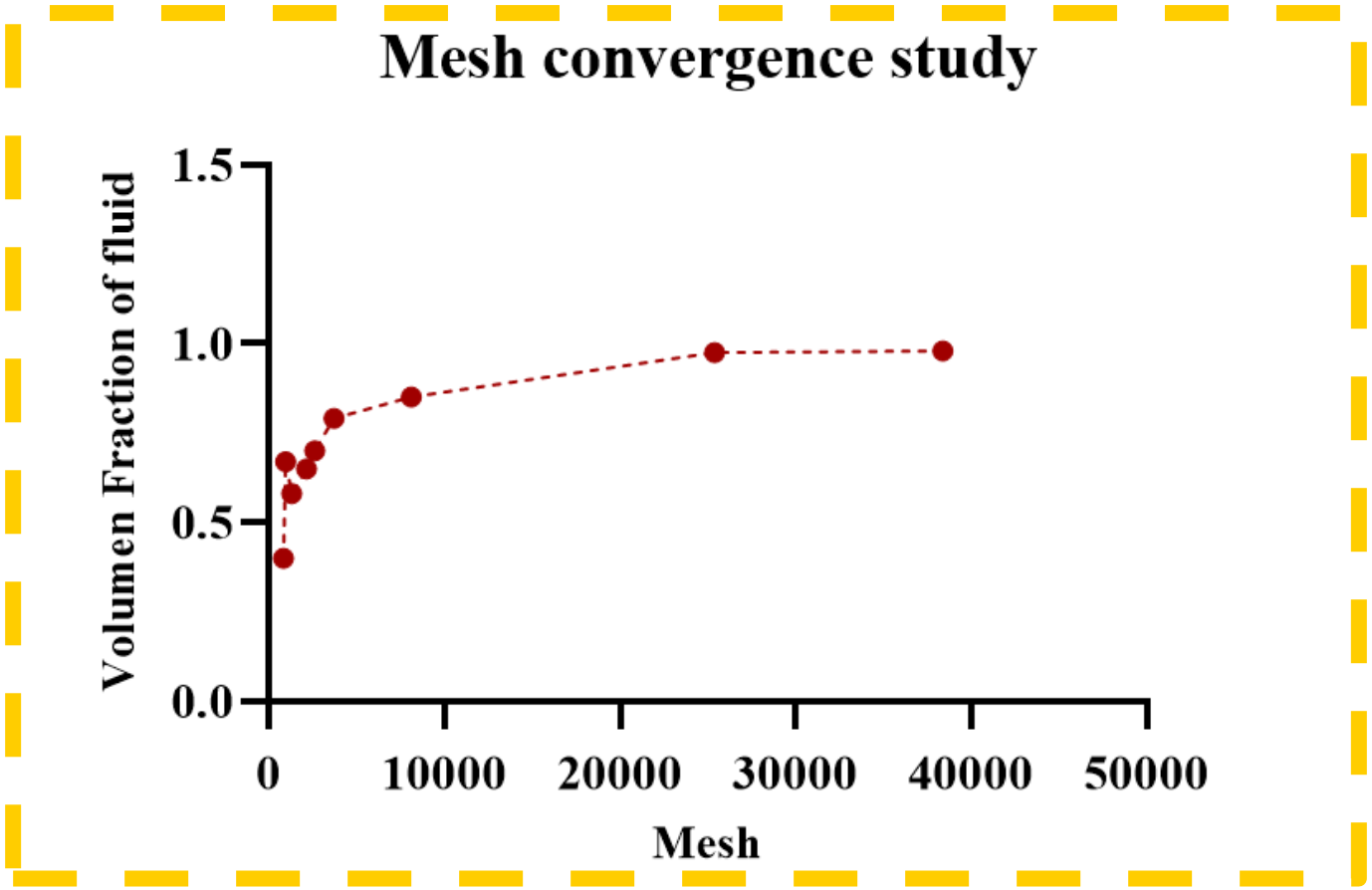
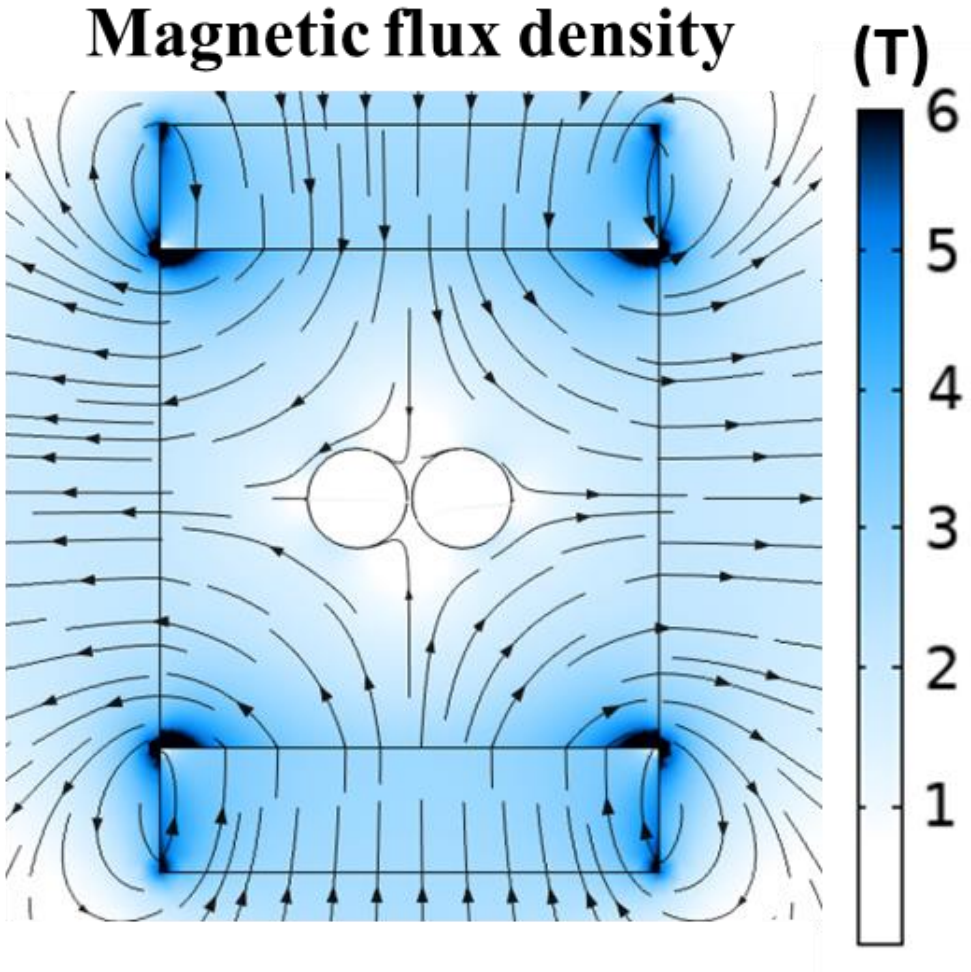


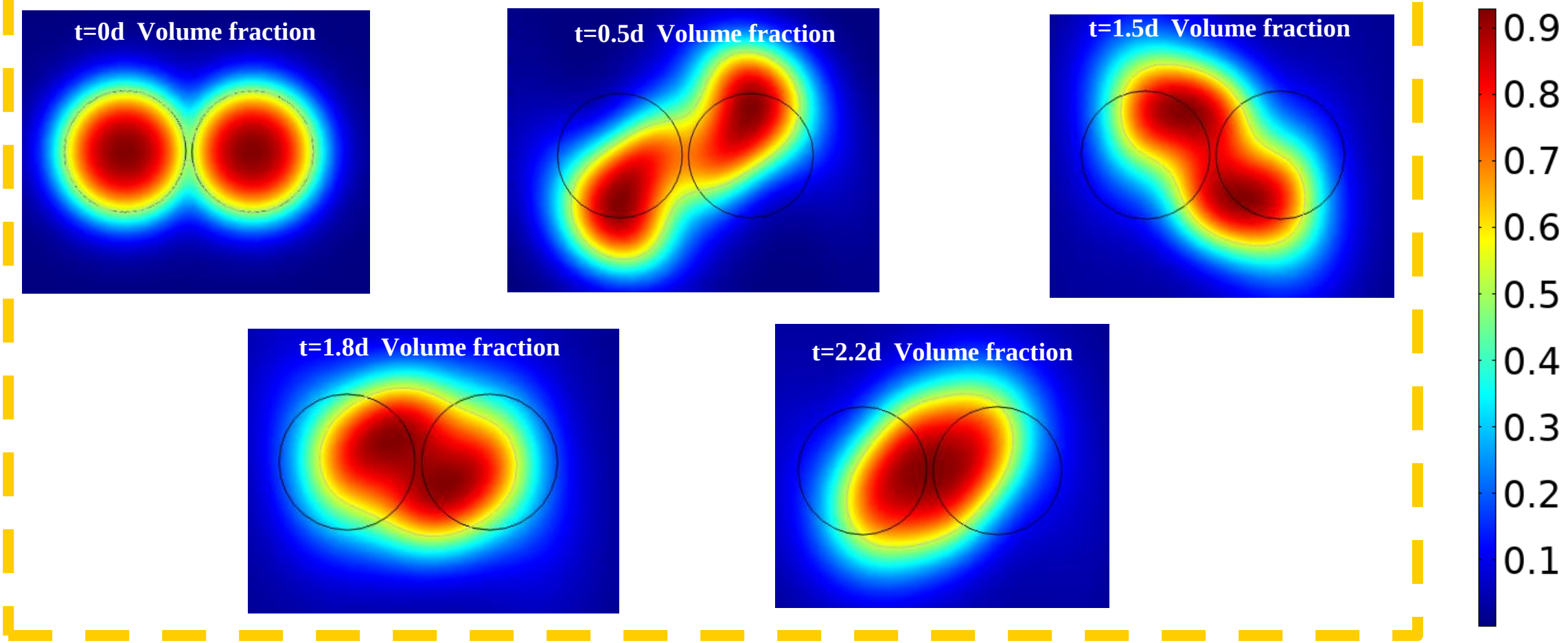
Mesh convergence with 17664 domain elements

Magnetic flux density norm

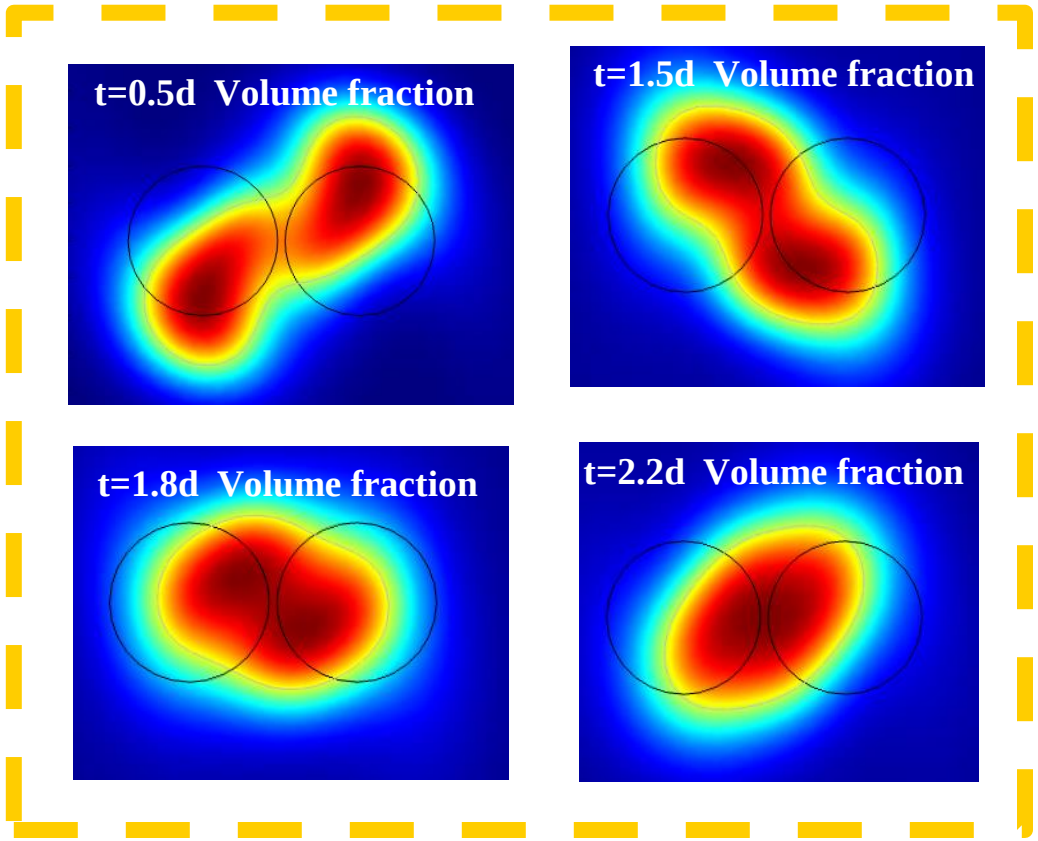


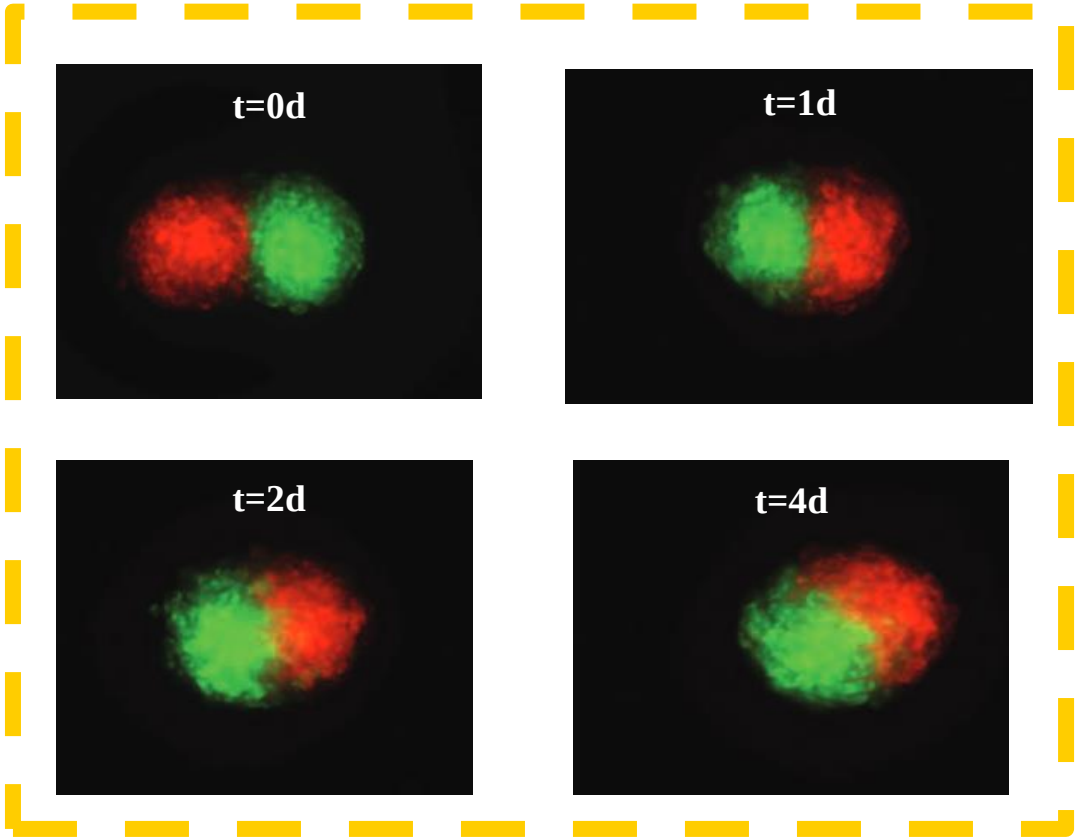
The Magnetic Flux Density Norm is lower in the center, so the spheroids will be pushed to the center by an inverse force generated by the magnetic medium.

Magnetic flux density norm



2D Model with magnetic field





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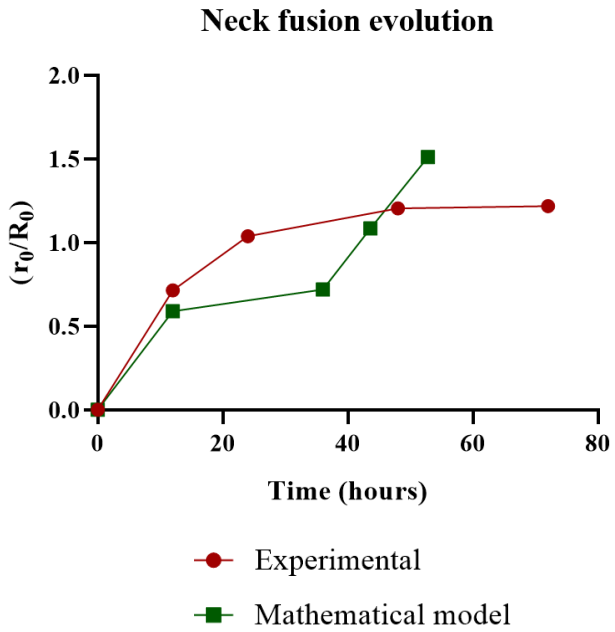
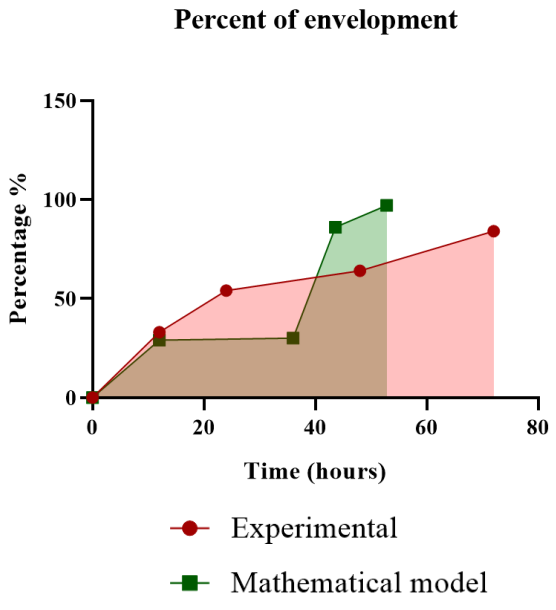
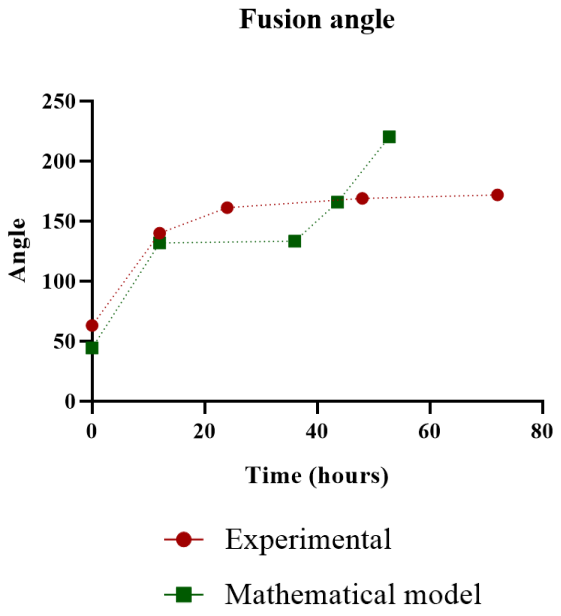
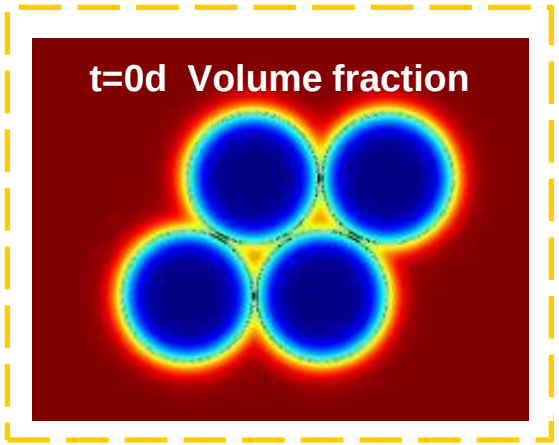


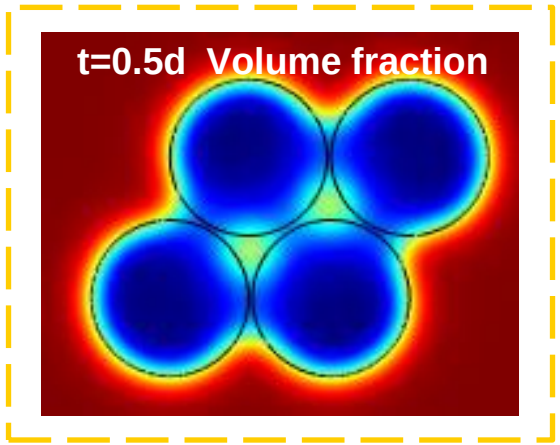


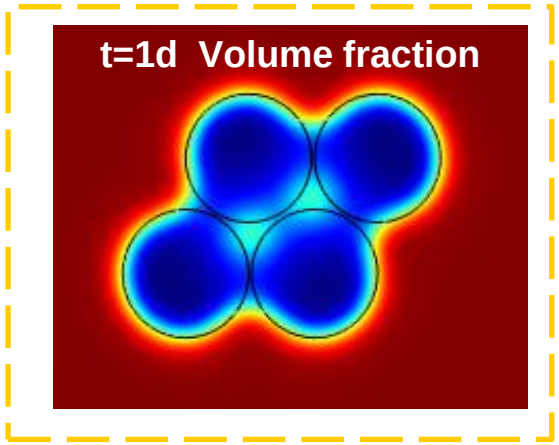


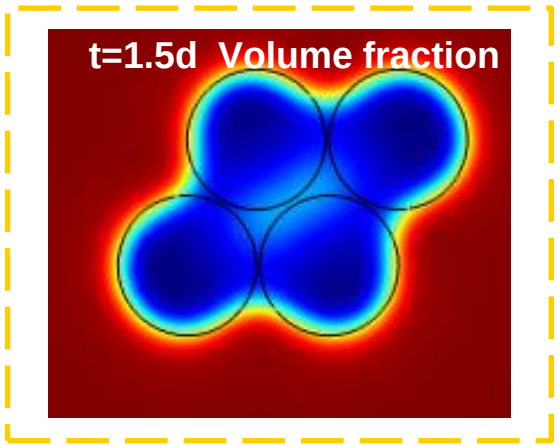
The Fusion accelerates in the second half of the process

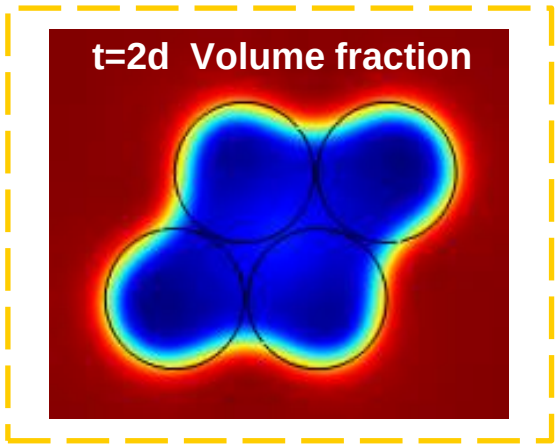
Complex 2D structures





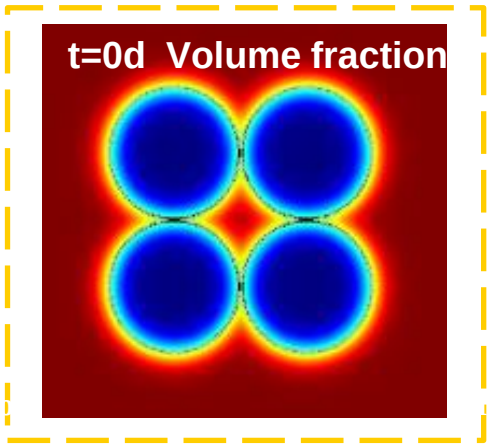


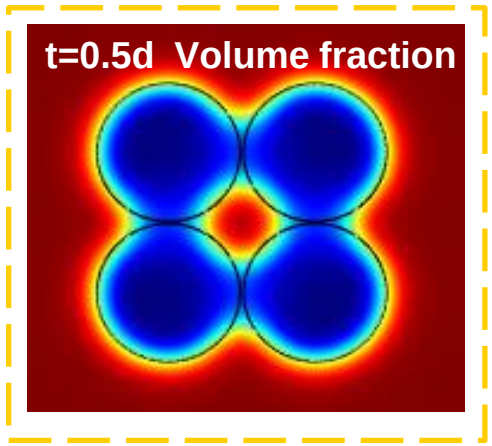


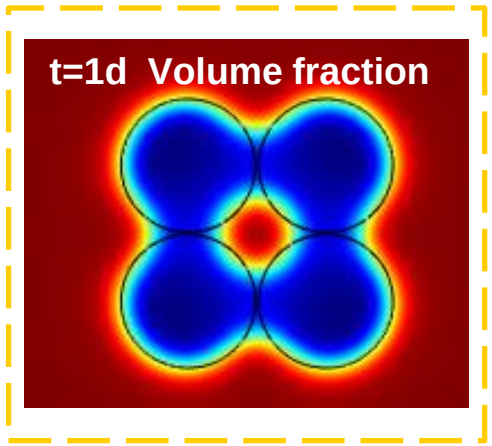


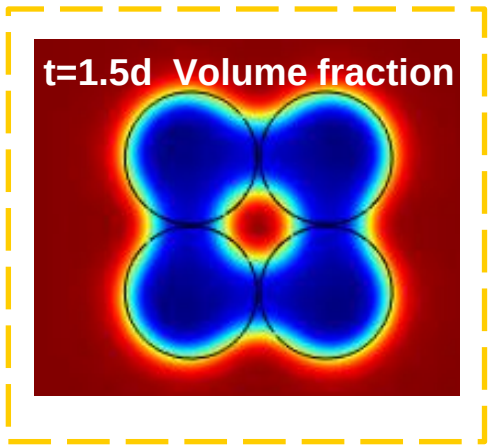
Controlling Cell Position in Complex Heterotypic 3DMicrotissues by Tissue Fusion DOI: 10.1002/bit.22162

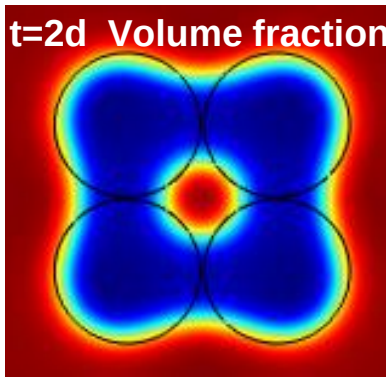
Complex 2D structures











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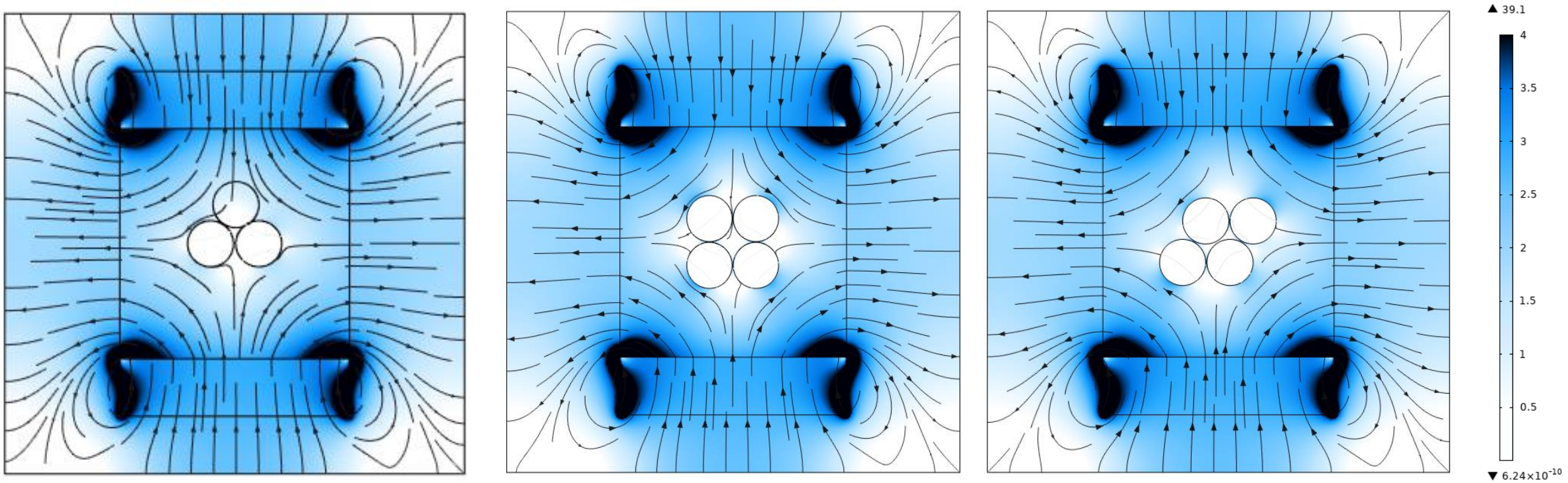
Complex 2D structures



The Magnetic Flux Density Norm is lower in the center, so the spheroids will be pushed to the center by an inverse force generated by the magnetic medium.

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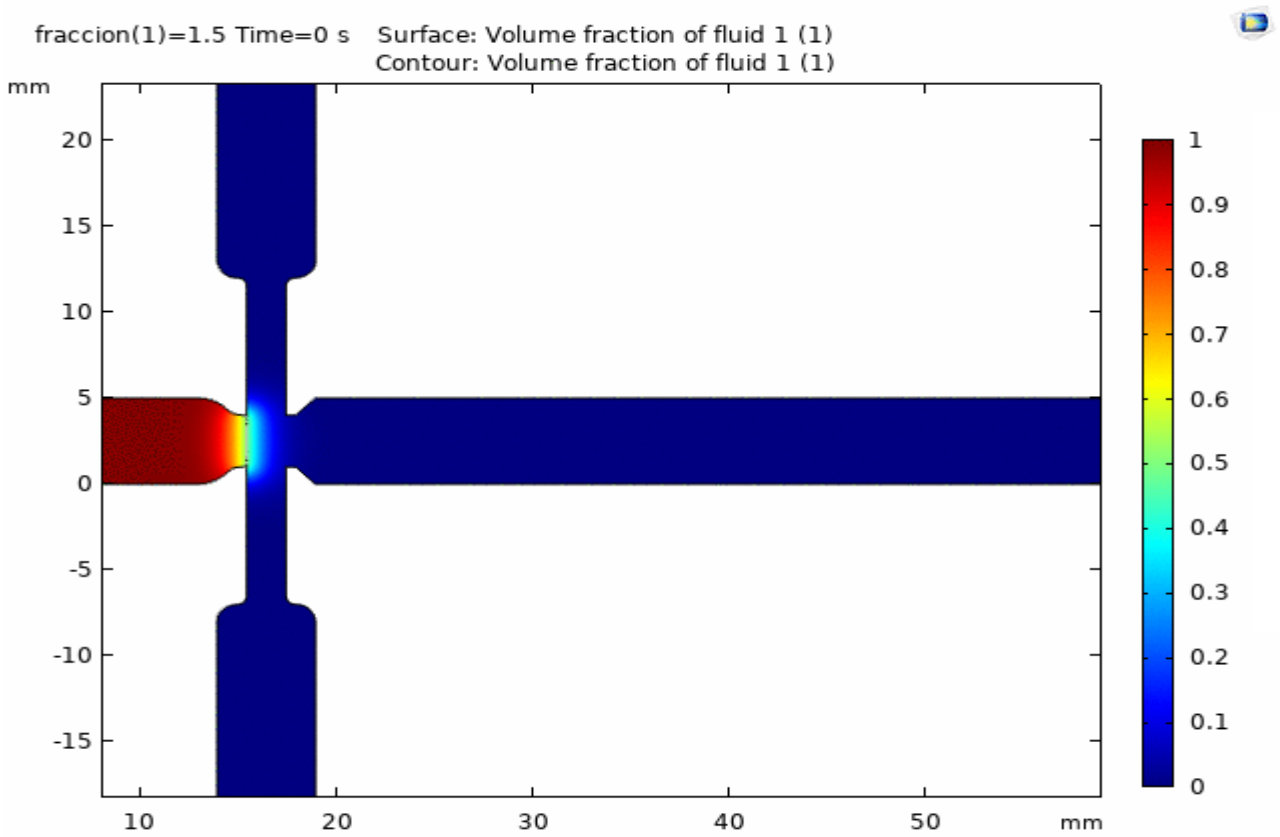
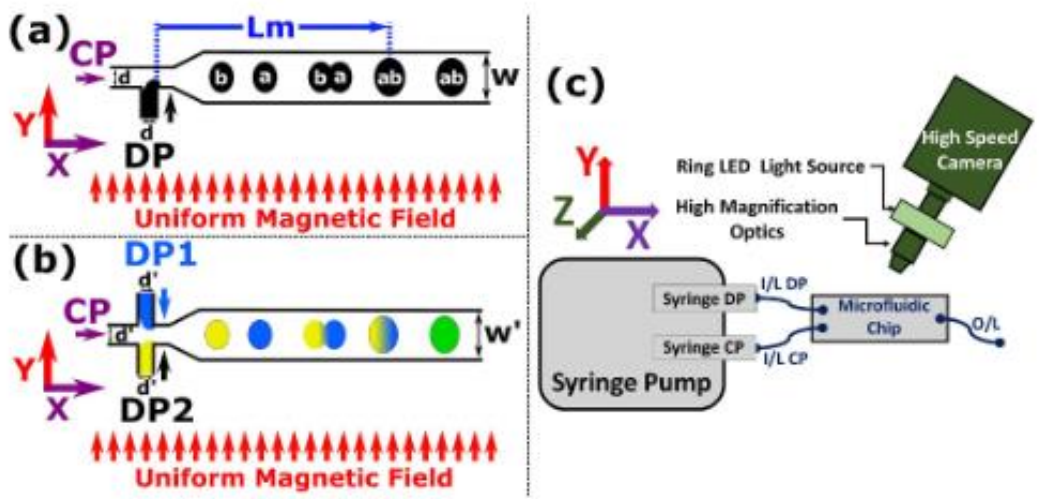
Conclusions

- **Magnetized spheroid fusion** reached a max. force of 6T for the magnetic field, which induced cell-cell interactions.
- **Fusion process was improved approximately 45-50%** due to the magnetic field gradient.
- The fusion process described:
  - a **similar increase in spheroid size**
  - presence of a bonding bridge after the first contact
  - a slow and constant fusion
  - The formation of a single oval spheroid.

Future work





Droplet merging on a lab-on-a-chip platform by uniform magnetic fields. DOI: 10.1038/srep37671

Research group

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