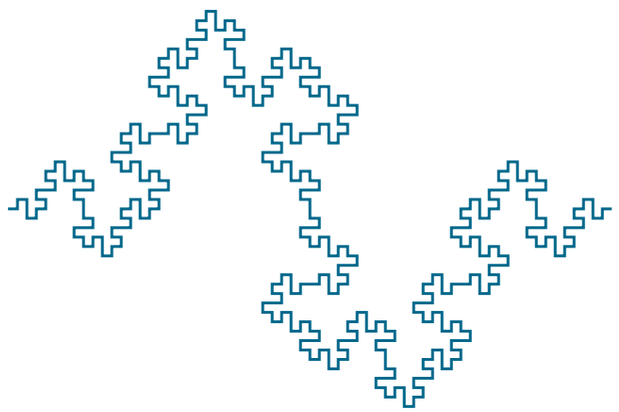
# Oxygen gradients in oxygen delivery system

Presenters: Huaifa Zhang, Jake Barralet (McGill)
by: Sean Bohun, Joe Fehribach,
Nilima Nigam, Oluwole Olobatuyi
thanks also to: Chris Budd, Huaxiong Huang and Jim Keener.



August 14, 2014

# Reminder of Monday's presentation

We need oxygen.

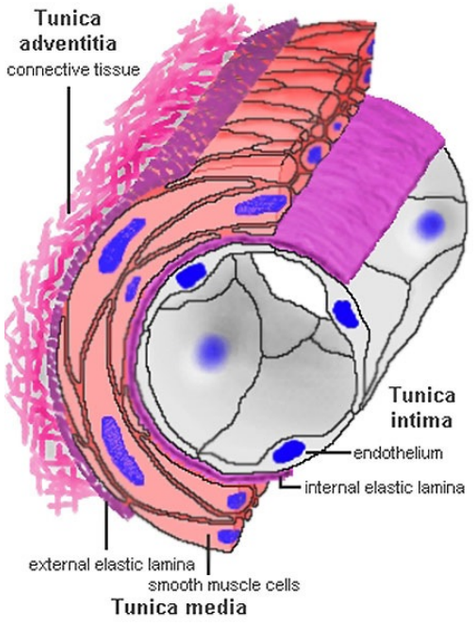
- Oxygen is critical for metabolic activity of cells
- An *Oxygen delivery system (ODS)* is constructed to deliver oxygen to an artery in a culture medium
- Goals for the workshop:
  - Quantify total oxygen at artery as a function of time
  - Compute oxygen gradient across the walls of the artery

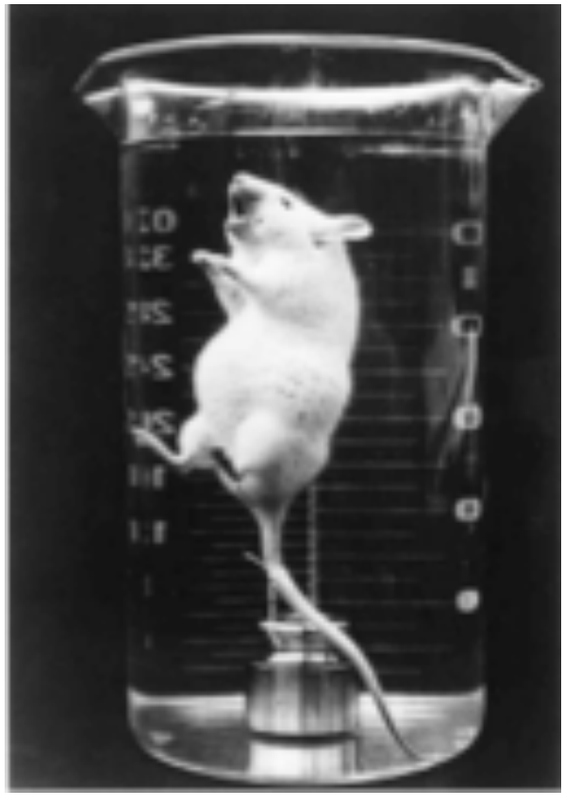
# Experiment

**Blood vessel**

**Rat aorta size**

| | |
|---|---|
| ***Diameter (mm)*** | ***2.24±0.07*** |
| ***Wall thickness (mm)*** | ***0.102±0.007*** |

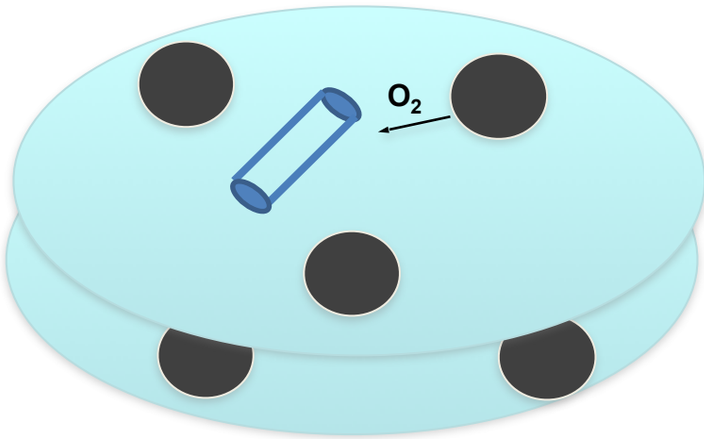


http://embryology.med.unsw.edu.au/embryology/index.php?title=HM_Practical_-_Blood_Vessel_Histology
H. WOLINSKY, *Circulation Research*, 1971, 28, 622-637.

# Background and modelling goals

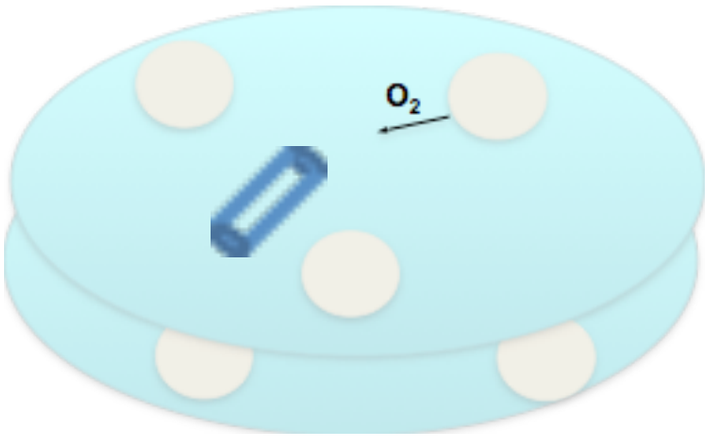
## Self-oxygenating scaffold

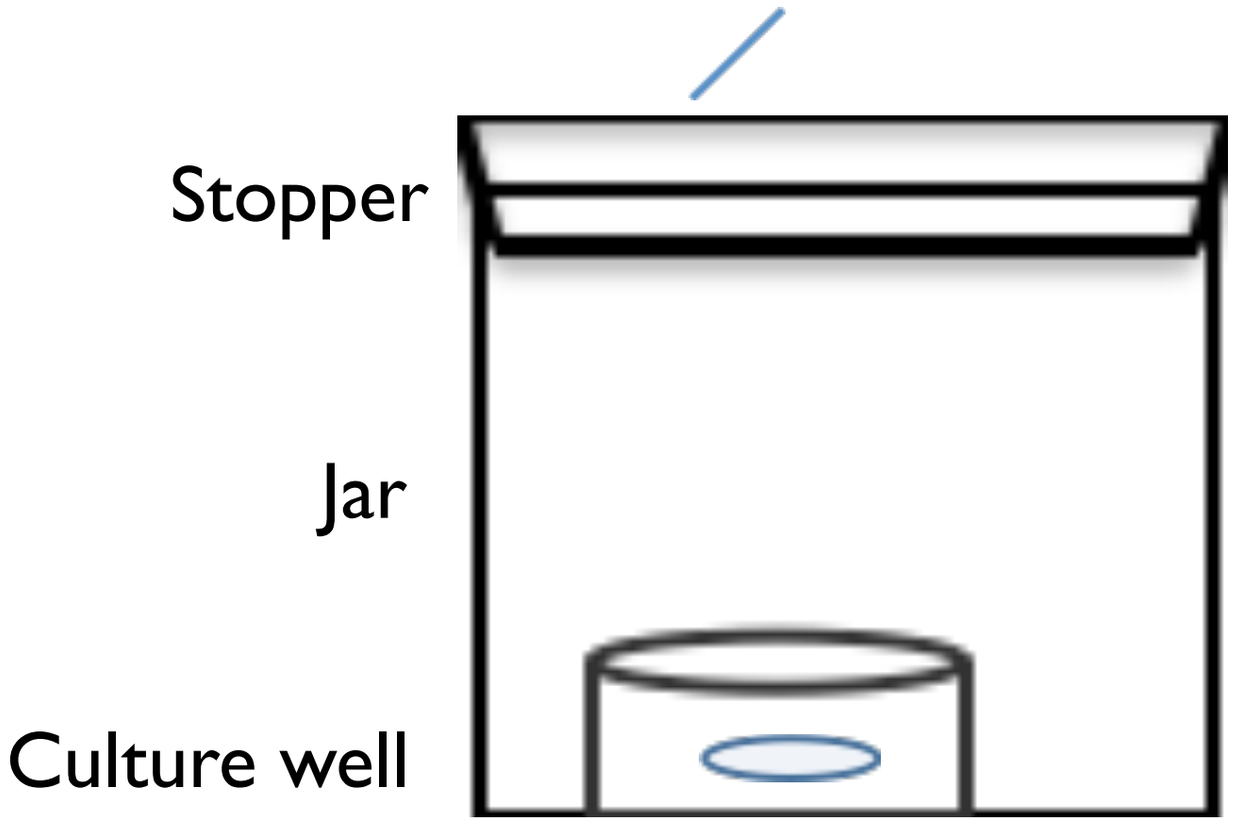



- $O_2$-generating agent
- Alginate hydrogel
- Artery

**$O_2$-generating agent: $CaO_2$-polycaprolactone (PCL)**

# Experiment



## Experimental set-up

Step 1. Mix calcium peroxide $CaO_2$ (solid) with polycaprolactone $PCL$ (liquid hydrophobic polymer).

Step 2. Solidify mixture into balls, size $\approx 50 - 100\mu m$.

Step 3. Pour solid particles into alginate solution. Solid particles tend to sediment. At this stage, some $Ca(OH)_2$ is released. Size of particles does not appreciably change.

Step 4. Stir alginate+particles, and add artery.

Step 5. Add $Ca$ ions ($CaCl_2 + H_2O$ in a 0.1 molar solution), creating gel through cross-linkages. $H_20$ is in the gel. $Cl$ reacts with the $Na$ in the gel and gets dissolved in $H_2O$.

Step 6. Immerse gel into container with culture medium.

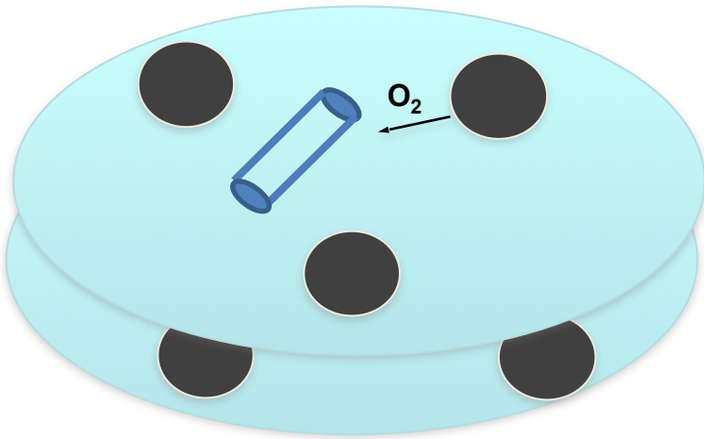
Step 7. $H_20$ diffuses into particles, reacts with $CaO_2$ to produce $O_2$.

Step 8. $O_2$ diffuses from particle into gel, from gel into medium.

Step 9. $H_2O$ from gel goes into particle, also from medium into gel.

# Background and modelling goals

## Self-oxygenating scaffold




- $O_2$-generating agent
- Alginate hydrogel
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**$O_2$-generating agent: $CaO_2$-polycaprolactone (PCL)**

# Reactions

Reaction 1. $CaO_2 + 2H_2O \underset{k_2}{\overset{k_1}{\rightleftharpoons}} Ca(OH)_2 + H_2O_2$ (in particle)

Reaction 2. $2H_2O_2 \underset{k_4}{\overset{k_3}{\rightleftharpoons}} 2H_20 + O_2$ (in particle)

Reaction 3. $Ca(OH)_2 + CO_2 \underset{\epsilon}{\overset{k_5}{\rightleftharpoons}} CaCO_3 \downarrow + H_2O$ (in particle)

Reaction 4. $Ca(OH)_2 + HCO_3^- \underset{\epsilon}{\overset{k_6}{\rightleftharpoons}} CaCO_3 \downarrow + H_2O + OH^-$

Reaction 5. $Ca(OH)_2 + CO_3^{2-} \underset{\epsilon}{\overset{k_7}{\rightleftharpoons}} CaCO_3 \downarrow + 2(OH^-)$

$$2CaO_2 + 2CO_2 \rightleftharpoons 2CaCO_3 \downarrow + O_2 \uparrow$$

# Reaction (3-5) in detail

Reaction 6. $CO_2 + H_2O \underset{k_9}{\overset{k8}{\rightleftharpoons}} H_2CO_3$ (in medium)

Reaction 7. $H_2CO_3 \underset{k_{11}}{\overset{k_{10}}{\rightleftharpoons}} H^+ + HCO_3^-$ (in medium)

Reaction 8. $HCO_3^- \underset{k_{13}}{\overset{k_{12}}{\rightleftharpoons}} CO_3^{2-} + H^+$ (in medium)

Reaction 9. $H_2O \underset{k_{15}}{\overset{k_{14}}{\rightleftharpoons}} H^+ + OH^-$ (in medium)

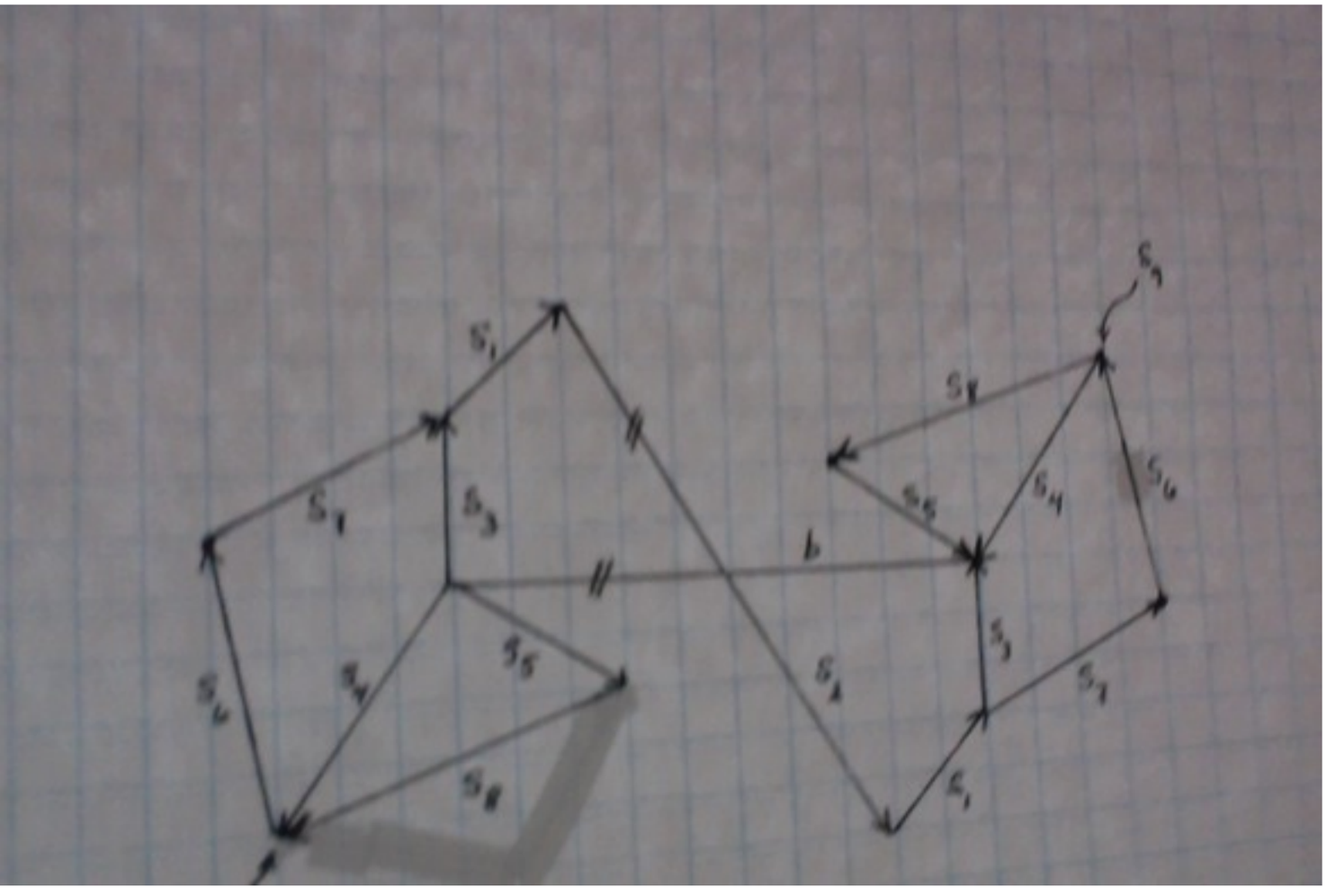
Reaction 10. $HCO_3^- + OH^- \underset{k_{17}}{\overset{k_{16}}{\rightleftharpoons}} CO_3^{2-} + H_2O$ (in medium)

Reaction 11. $Ca(OH)_2 \underset{k_{19}}{\overset{k_{18}}{\rightleftharpoons}} Ca^{2+} + 2(OH)^-$ (in particle)

Reaction 12. $Ca^{2+} + CO_3^{2-} \underset{k_{21}}{\overset{k_{20}}{\rightleftharpoons}} CaCO_3$ (on surface of particle AND close to $CaO_2$ particle)

Reaction 13. $CO_2(gas) \underset{k_{23}}{\overset{k_{22}}{\rightleftharpoons}} CO_2$ (aqueous) (in medium)

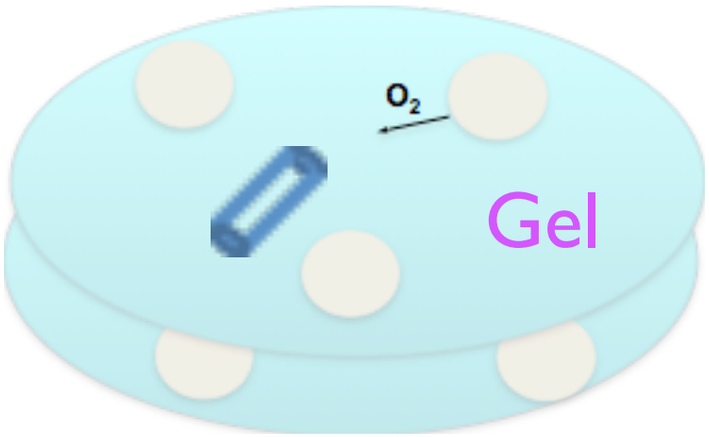
# Kirchoff diagram

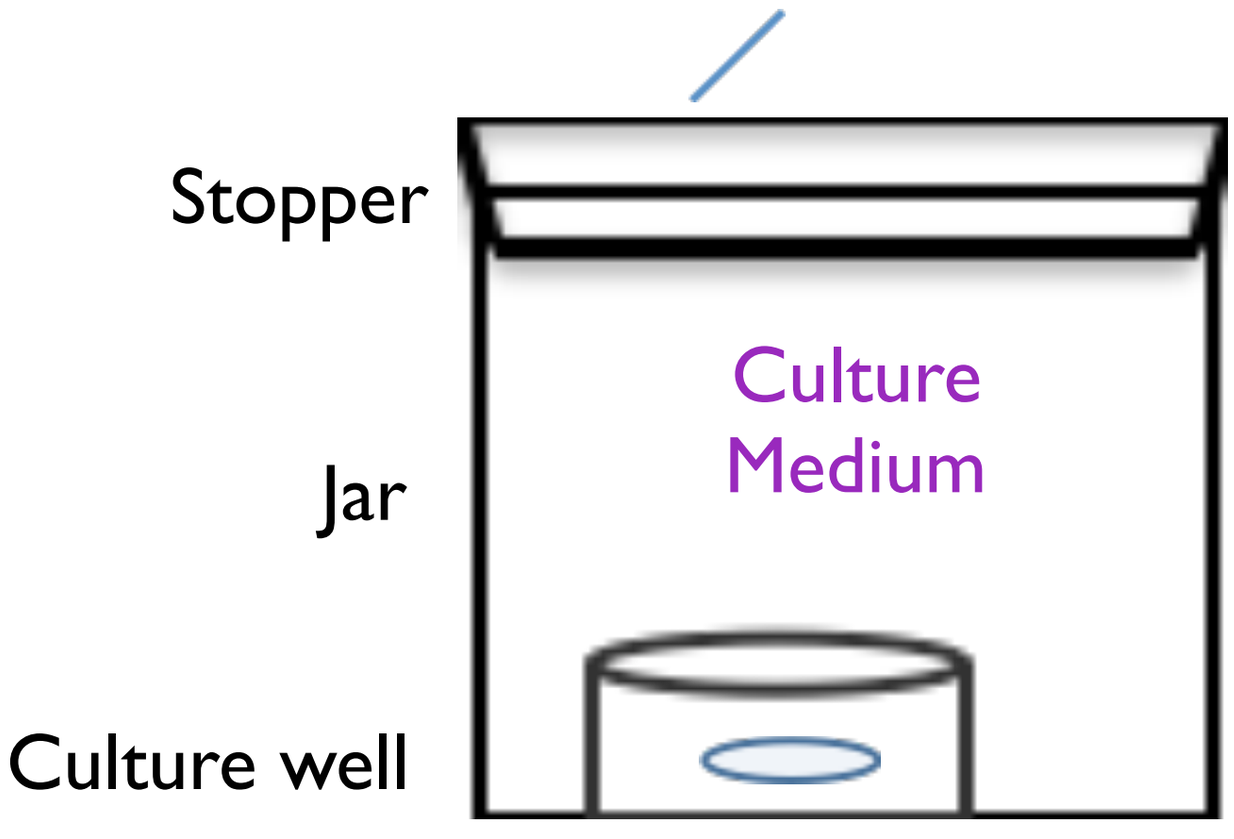


Kirchhoff Graph (Circuit Diagram) for the first nine steps of the reaction network.

The graph is a two dimensional view of a twelve dimensional structure sitting in the stoichiometrical space for
the reaction steps.

# Experiment



# Macroscopic model

$c(x, y, z, t)$ denotes the (molar) concentration of $O_2$ at time $t$.

Eqn.1. Diffusion in medium:

$$\frac{\partial c}{\partial t} = \nabla \cdot (\kappa_{medium} \nabla c)$$

Eqn.2. In gel:

$$\frac{\partial c}{\partial t} = \nabla \cdot (\kappa_{gel} \nabla c) + \underbrace{\sum_i f_i(r, t)}_{production} - \underbrace{S(r, t)}_{consumption}$$

Eqn.3. In artery

$$\frac{\partial c}{\partial t} = \nabla \cdot (\kappa_{artery} \nabla c)$$

Eqn.4. $O_2$ is consumed by artery tissue at $5.71 \times 10^{-5} mol/(100cc)/min$.

# Macroscopic model contd.

Across interfaces

Eqn.5. Across medium-gel interface: $[\kappa \frac{\partial c}{\partial n}] = 0$ (no jump in flux)

Eqn.6. Across gel-artery interface: $[\kappa \frac{\partial c}{\partial n}] = 0$ (no jump in flux)

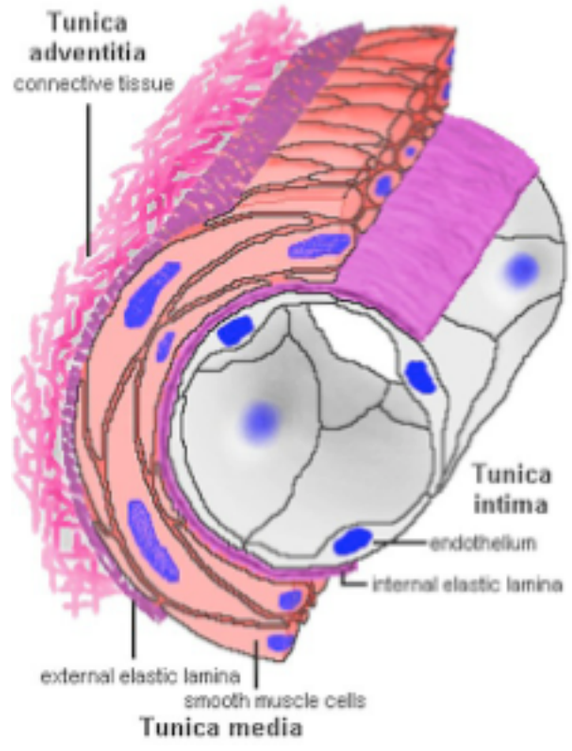
Boundary conditions

Eqn.7. Gel rests on container bottom, $y = 0$

Eqn.8. $\frac{\partial c}{\partial y} = 0$ at the air-medium interface, container walls and on $y = 0$.

# Zooming in....

- What is really of interest is the amount of oxygen available to the cells in the tissue.



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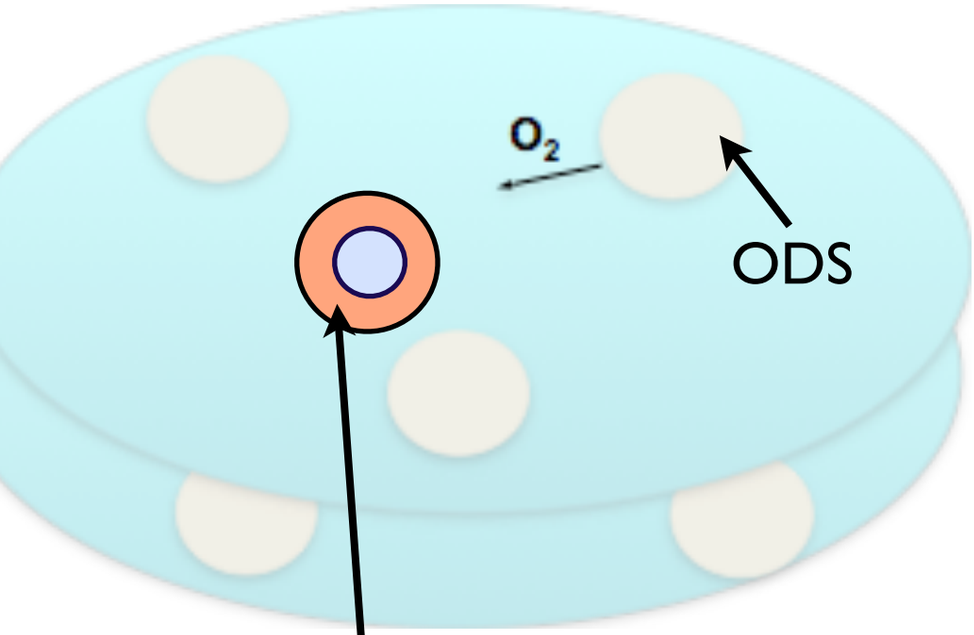
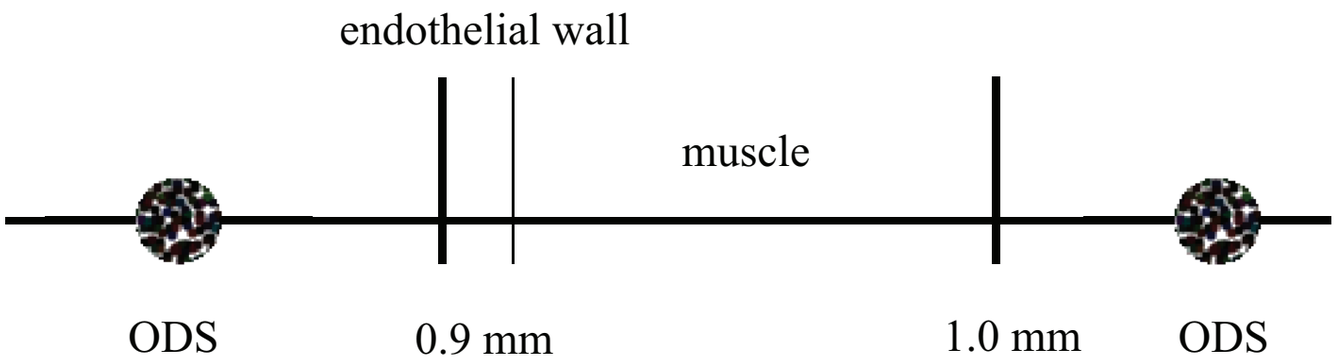
- If the particles are within $r_{kill}$ of the cells, the cells will initially get too much $O_2$.
- The critical distance $r_{kill}$ depends on the $c_{max}$.

# In the arterial wall



## At tissue...

$$\kappa_a\left(\frac{\partial^2 c}{\partial r^2}+\frac{1}{r}\frac{\partial c}{\partial r}\right) = \frac{\partial c}{\partial t}+\underbrace{S(r)}_{consumption}, \qquad r_1 < r < r_2$$

$$\kappa_a\frac{\partial c^-}{\partial r} = \kappa_{gel}\underbrace{\frac{\partial c^+}{\partial r}}_{\text{O2 in exterior gel}}, \qquad r = r_2$$

$$-\kappa_a\frac{\partial c}{\partial r} = h_E\left(c(r_1,t)-\underbrace{c_{inner}(r_1,t)}_{\text{O2 in interior gel}}\right)$$

$$c(r,0) = c_0$$

# Important scales in the problem

- Length of artery= 5mm, radius = 1mm, thickness is 0.1mm.
- Diffusion rate of $O_2$ in tissue = $\kappa_a = 2 \times 10^{-4} mm^2/s$
- Consumption of $O_2$ by epithelial cells = $s_e = 1.510^{-17} mol/cell/s$, by muscle = $(2.6)s_e$
- Thickness of epithelial cells= $10^{-3} mm$,

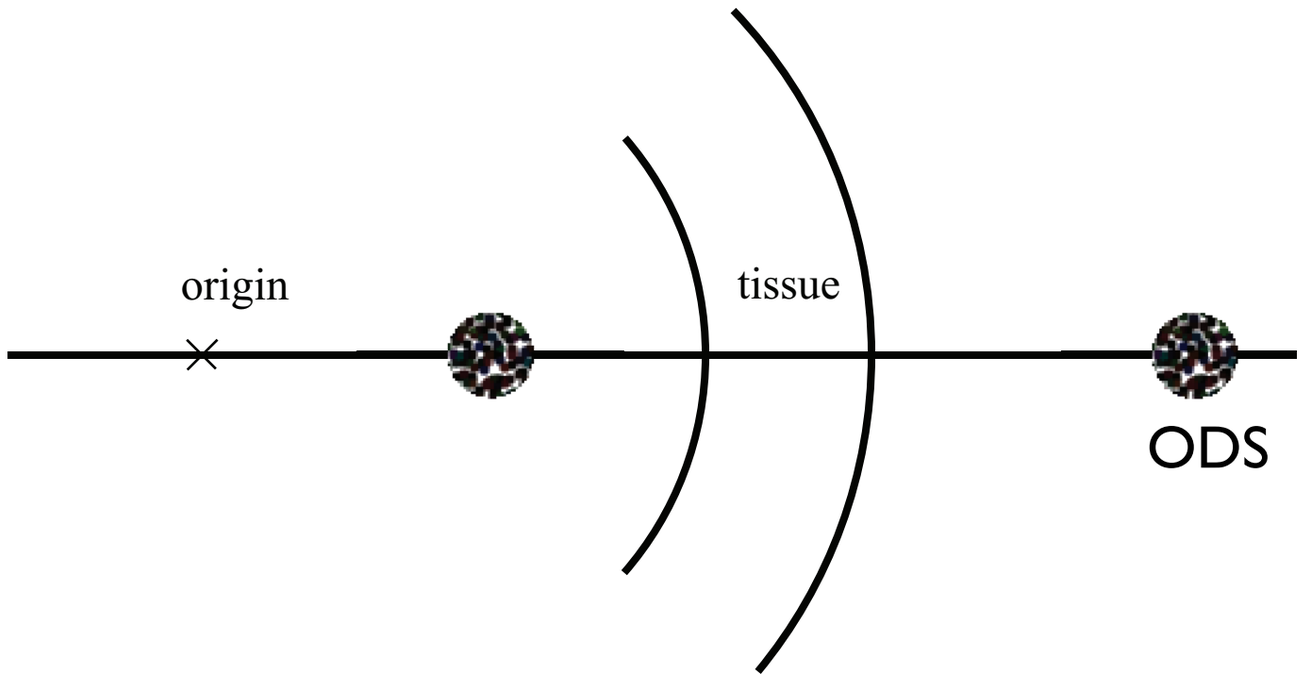
# Nondimensionalization

- $r = [r]x$, with $[r] =$ thickness of artery wall
- $t = [t]\tau$, with $[t] := \frac{[r]^2}{\kappa_a}$
- $c = [c]w$, with $[c] \approx 10^{-11} mol$ for muscle

# Modeling assumptions

- Reduce to axially symmetric geometry
- ODS particles are further than $r_{kill}$ from the tissue
- Endothelial cells (only 1 layer!!) effectively act as a 'wall', thickness $\epsilon$
- Neglect detailed modelling of cell damage
- Neglect details of ODS chemistry for now (very fast reactions)

# In the arterial wall



# Scaled system

$$\bar{S}(x,\tau) \approx 0.5\exp(-A_0(u-1)^2)$$

where $A_0 = \frac{c_0^2}{\epsilon^2}$

$$\begin{aligned}
u_{xx} + \frac{1}{x}u_x - \bar{S}(x,\tau) &= u_\tau, \qquad x_1 < x < x_2, \tau > 0 \\
u(x,0) &= 1, \qquad x_1 < x < x_2 \\
-\frac{\partial u}{\partial x}|_{x=x_1} &= \frac{1}{\epsilon}\frac{h_o}{\kappa_a}\left(u(x_1,\tau) - u_{gel}(x_1,\tau)\right) \\
\frac{\partial u^-}{\partial x} &= \frac{\kappa_{gel}}{\kappa_a}\frac{\partial u_{gel}}{\partial x}(x_2,t), \qquad x = x_2
\end{aligned}$$

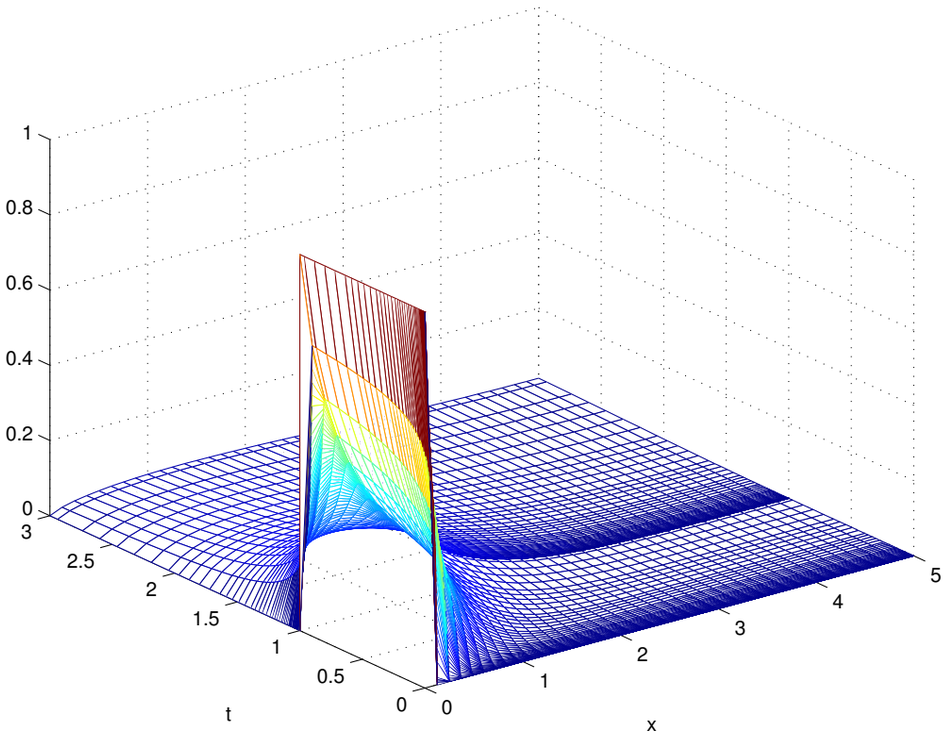
# $O_2$ in the gel

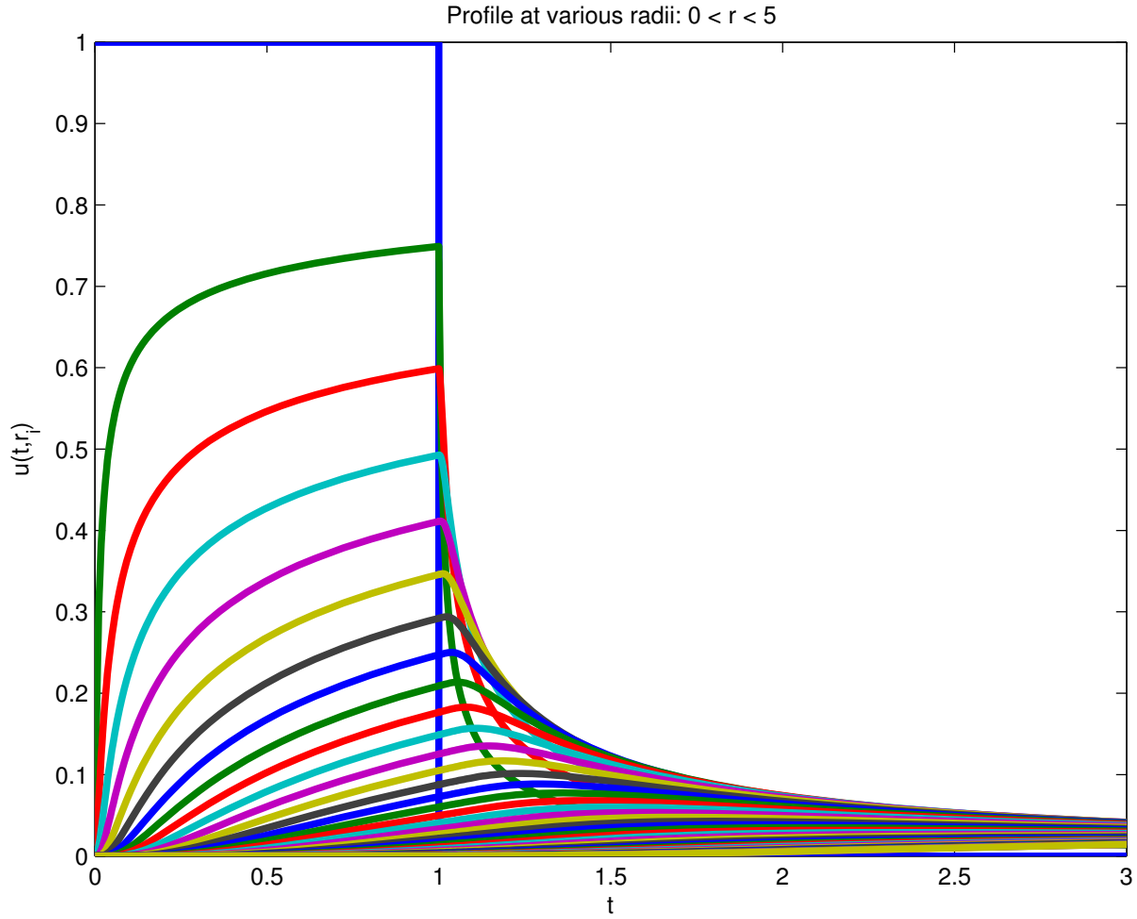
ODS produces $O_2$ for a maximum of $t_0$ s.
$O_2$ concentration in the hydrogel due to ODS at the origin, is (roughly) given by

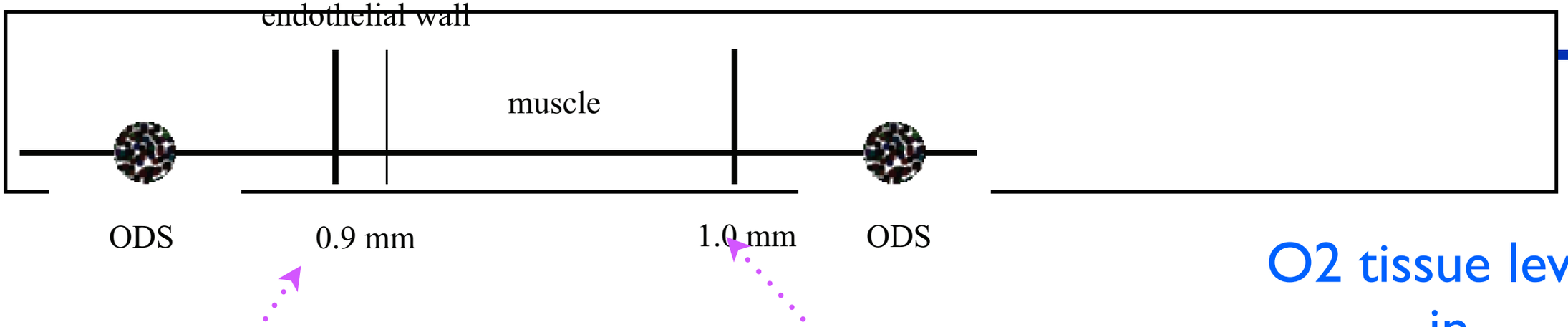
$$u_{gel}(R,\tau) = \int_0^{[t]\tau} \int_{y<x_0} \int_0^{2\pi} (4\pi\kappa_{gel}[t](\tau - s))^{-1} \exp\left(\frac{y^2 + R^2 - 2yR\cos(\phi)}{4\pi\kappa_{gel}[t](s-\tau)}\right)$$

Clearly there are two regimes of interest: $[t]\tau < t_0$ and $[t]\tau > t_0$.

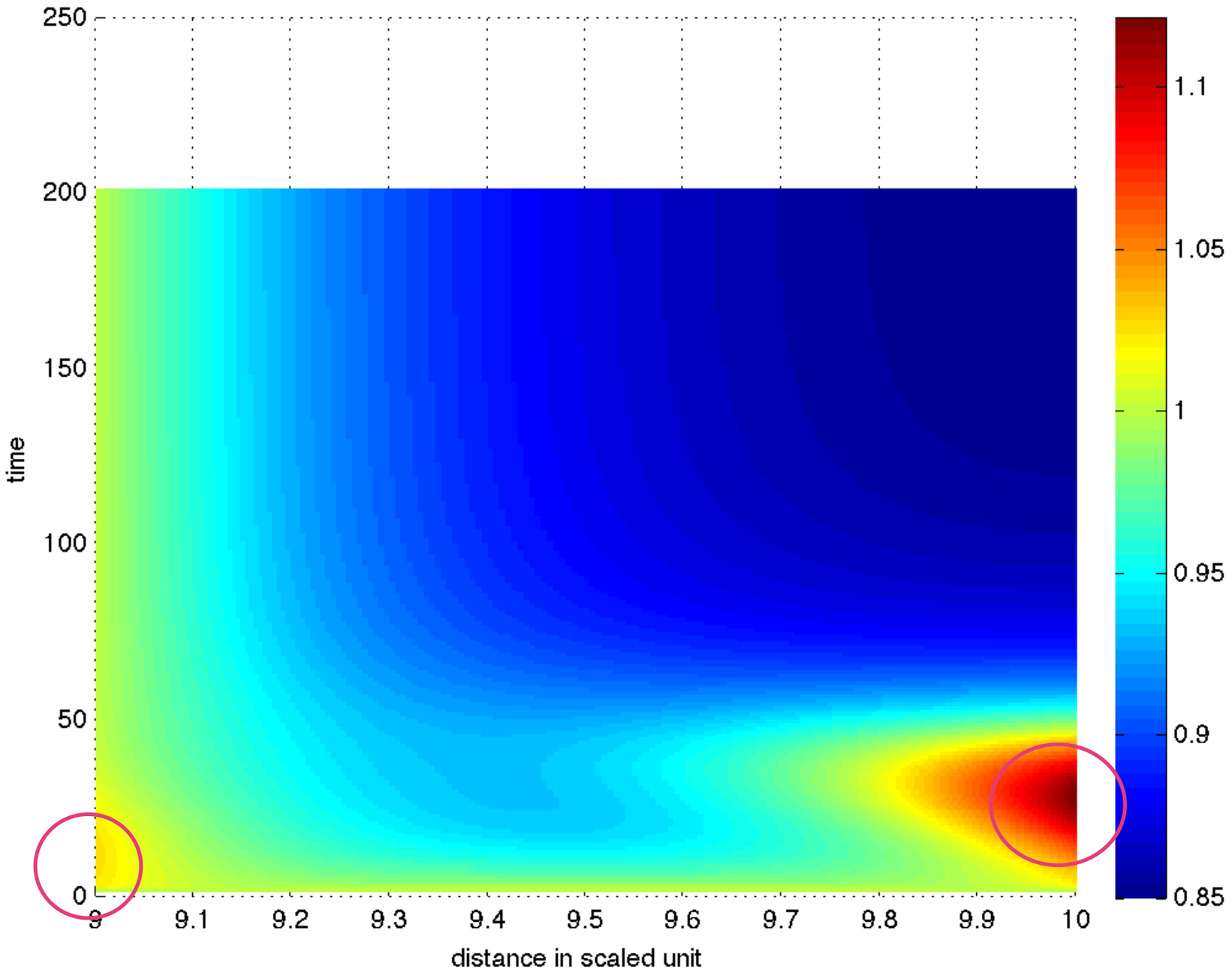
# In the gel


1
0.8
0.6
0.4
0.2
0
3
2.5
2
1.5
1
0.5
0
t
0
1
2
3
4
5
x


Profile at various radii: 0 < r < 5
u(t,r_i)
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.5
1
1.5
2
2.5
3
t



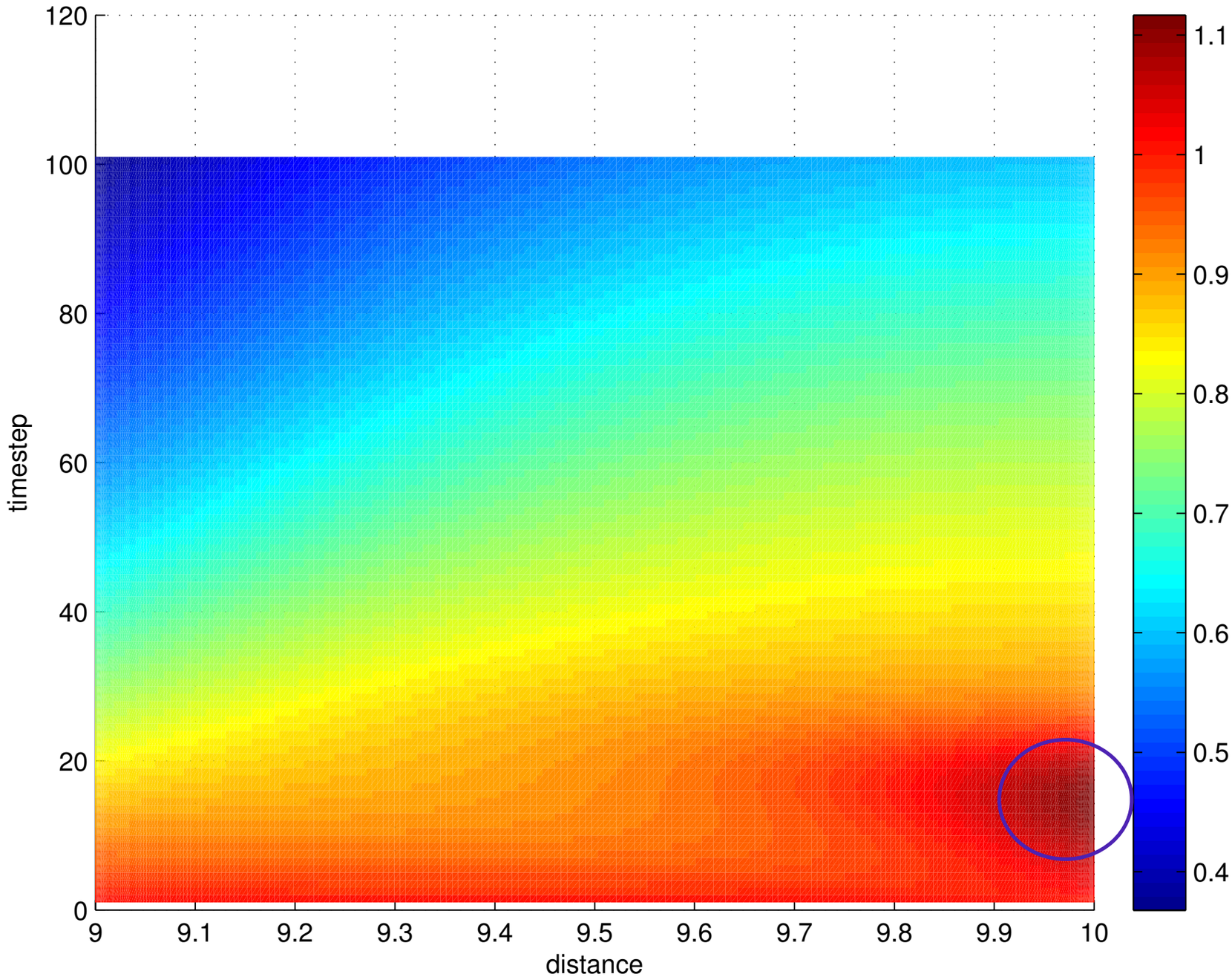

O2 tissue levels
in
SCALED units




Inner ODS
turns on at
10 ts.

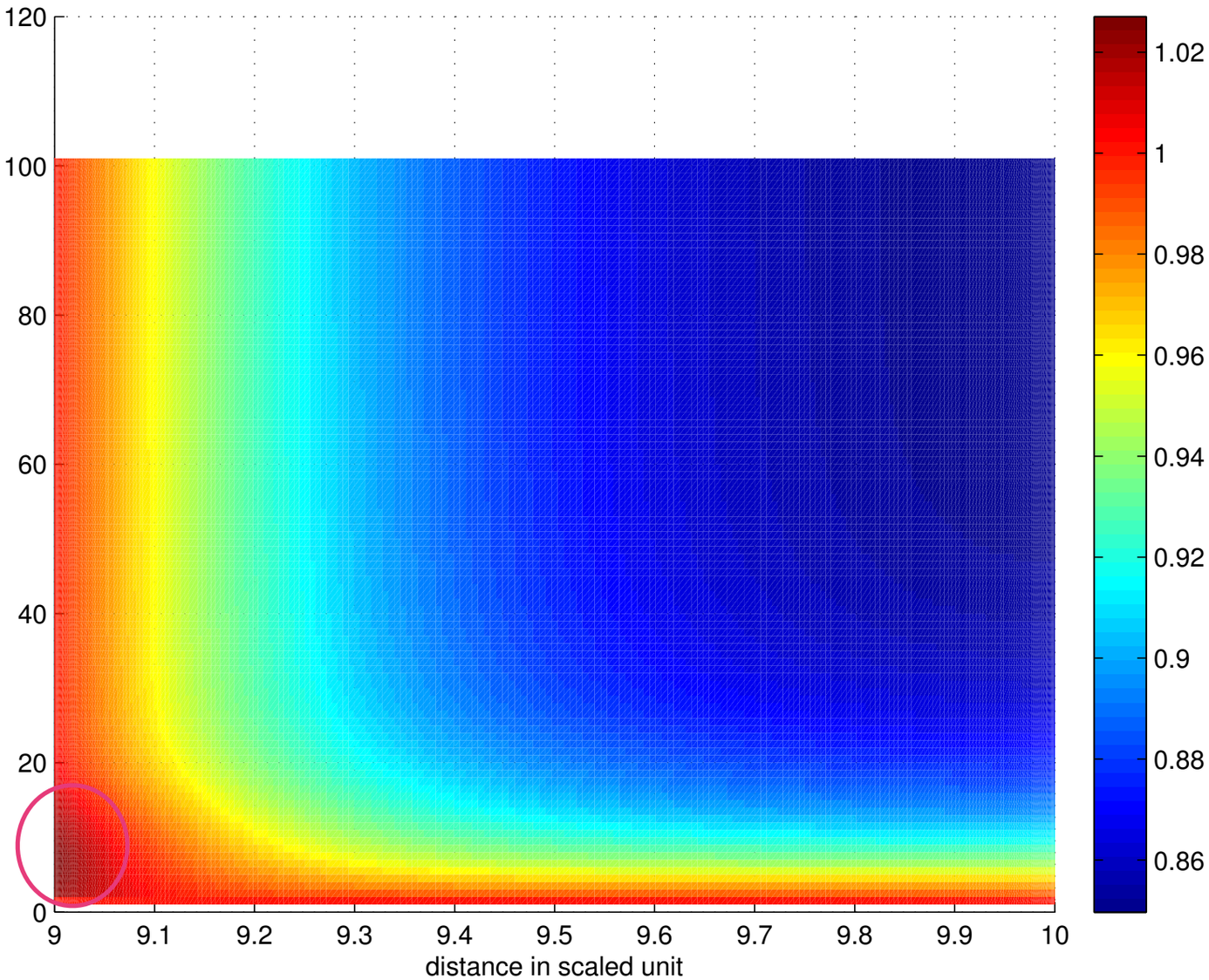
Outer ODS
turns on at
20 ts.

# No ODS inside artery



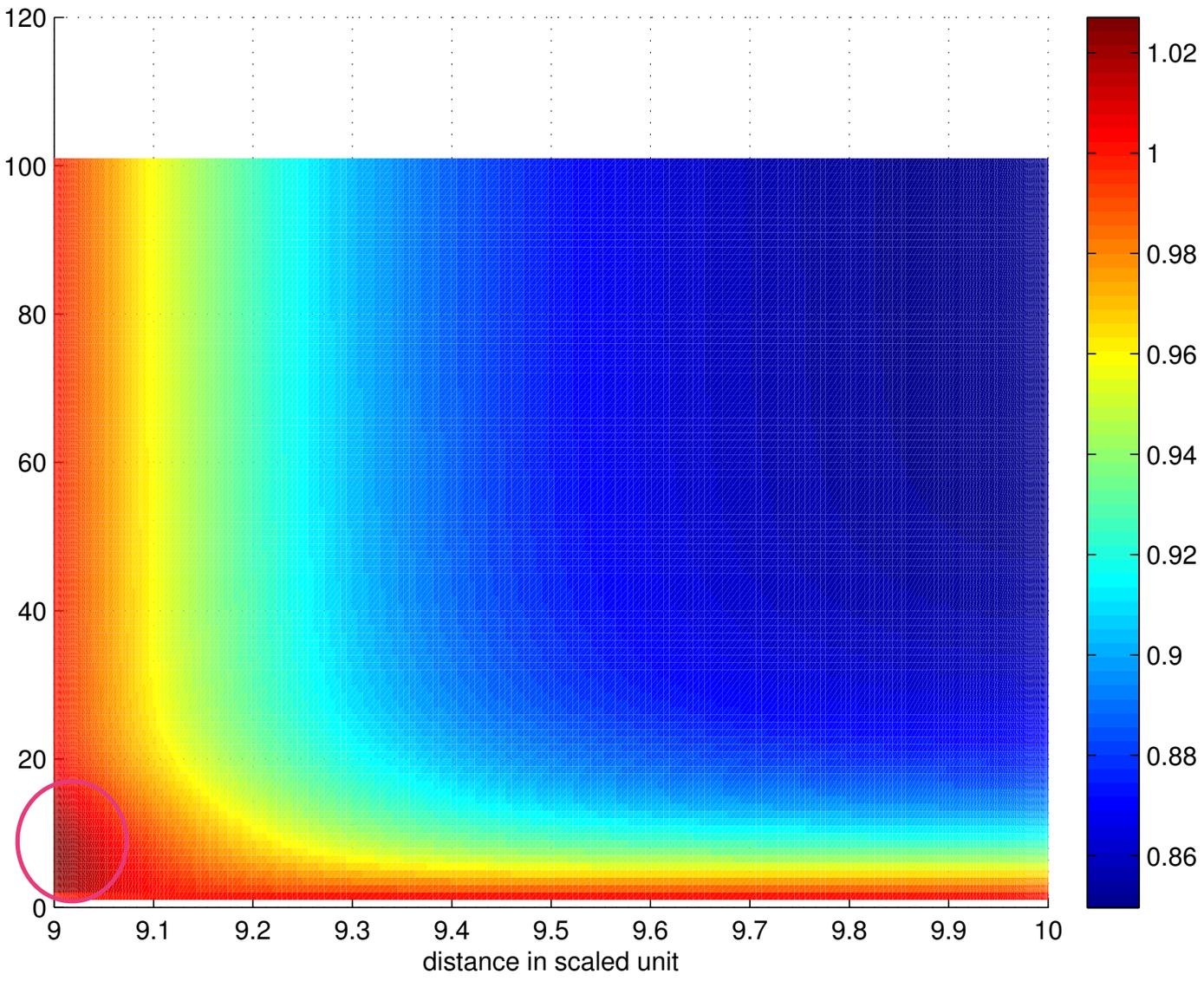

Red: 1.1, Blue: 0.4
scaled conc.

# No ODS outside artery

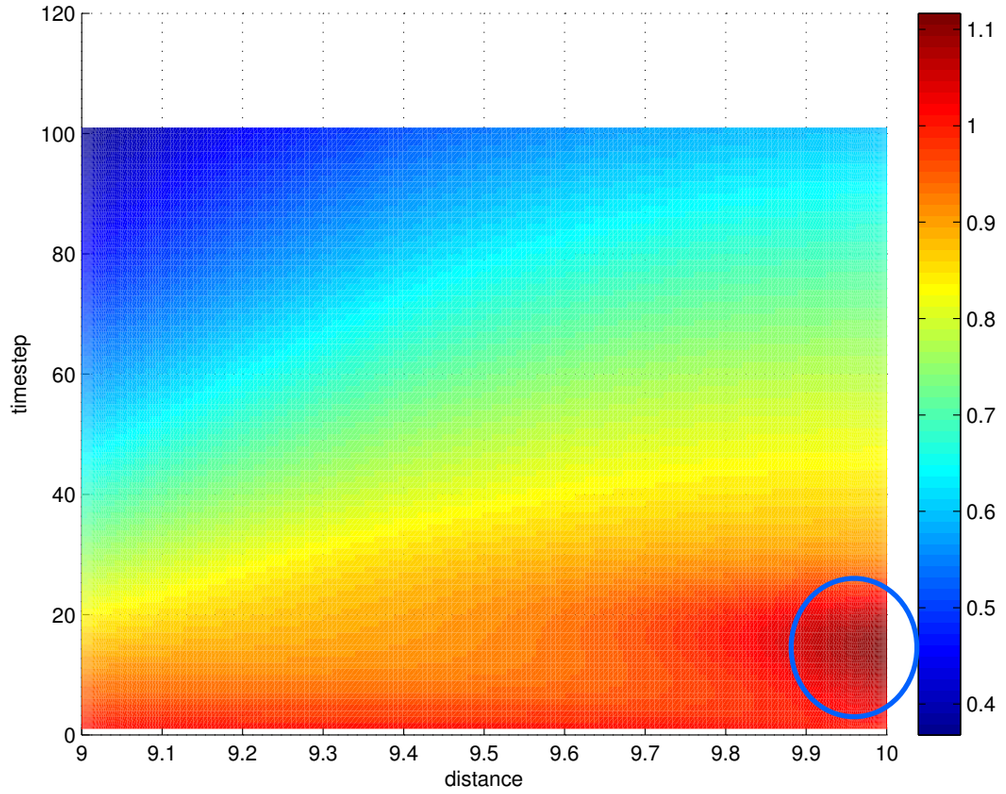



Red: 1.02, Blue: 0.86
scaled conc.

# No ODS outside artery

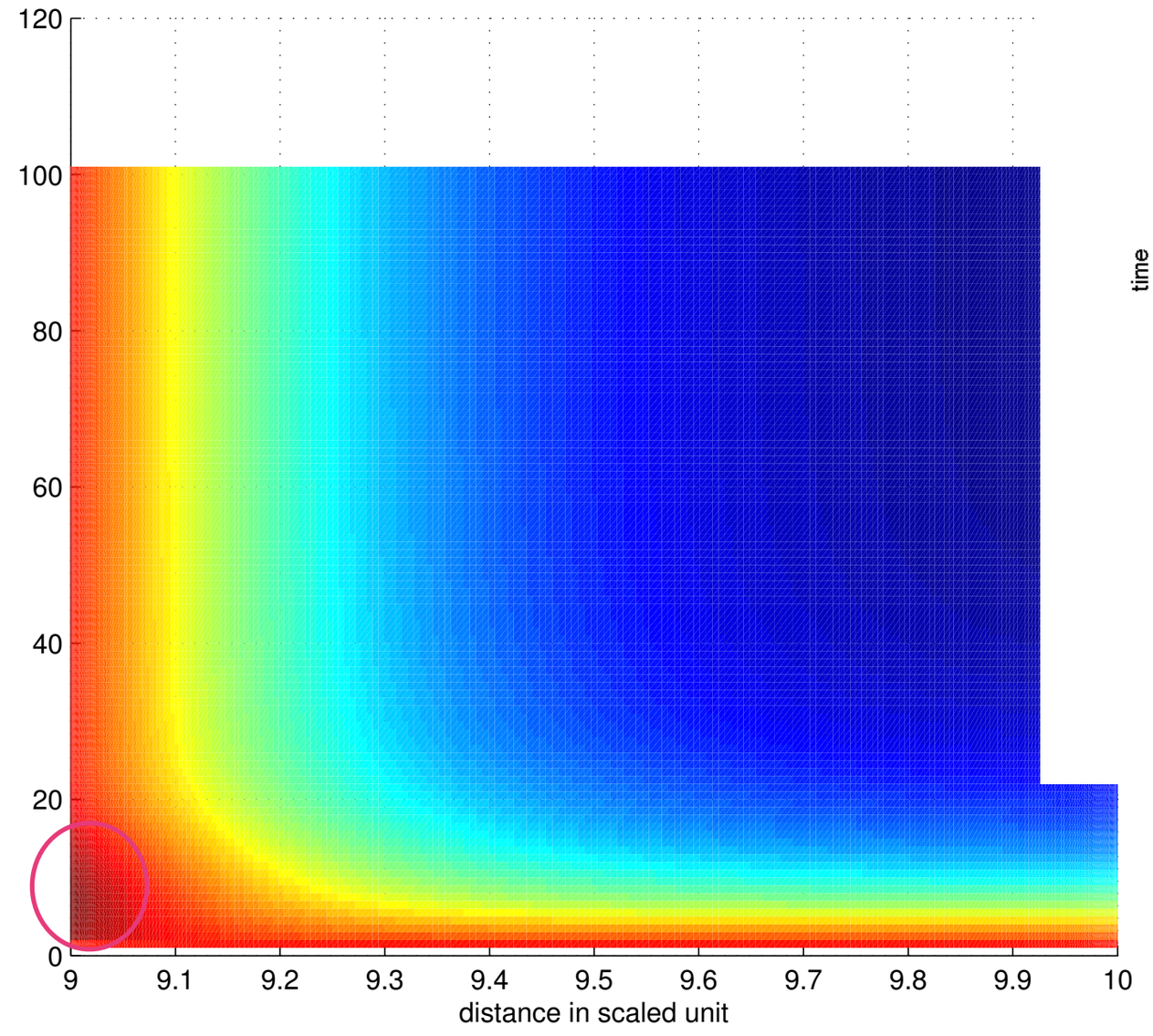



Red: 1.02, Blue: 0.86
scaled conc.



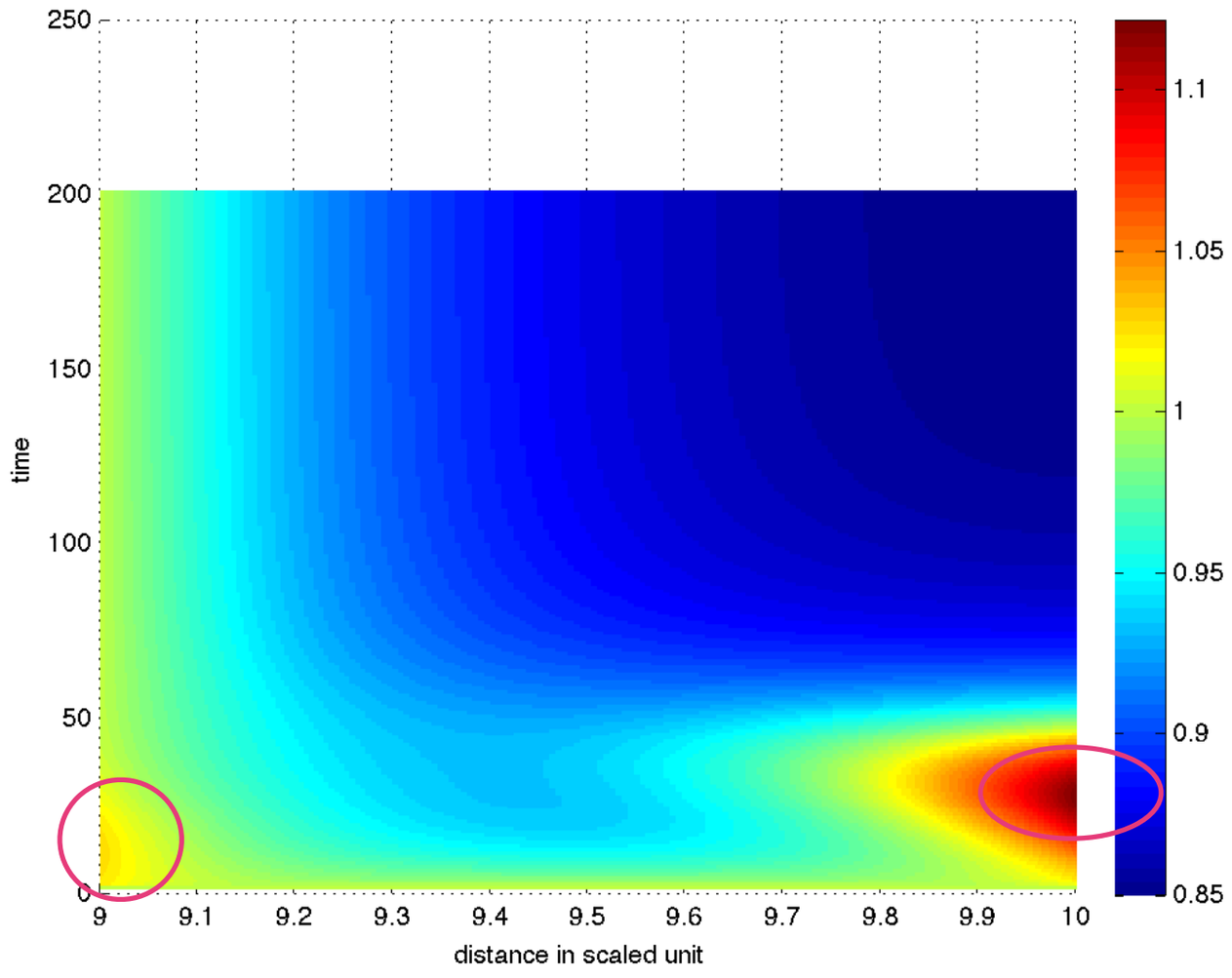

Red: 1.1, Blue: 0.4
scaled conc.

# No ODS outside artery



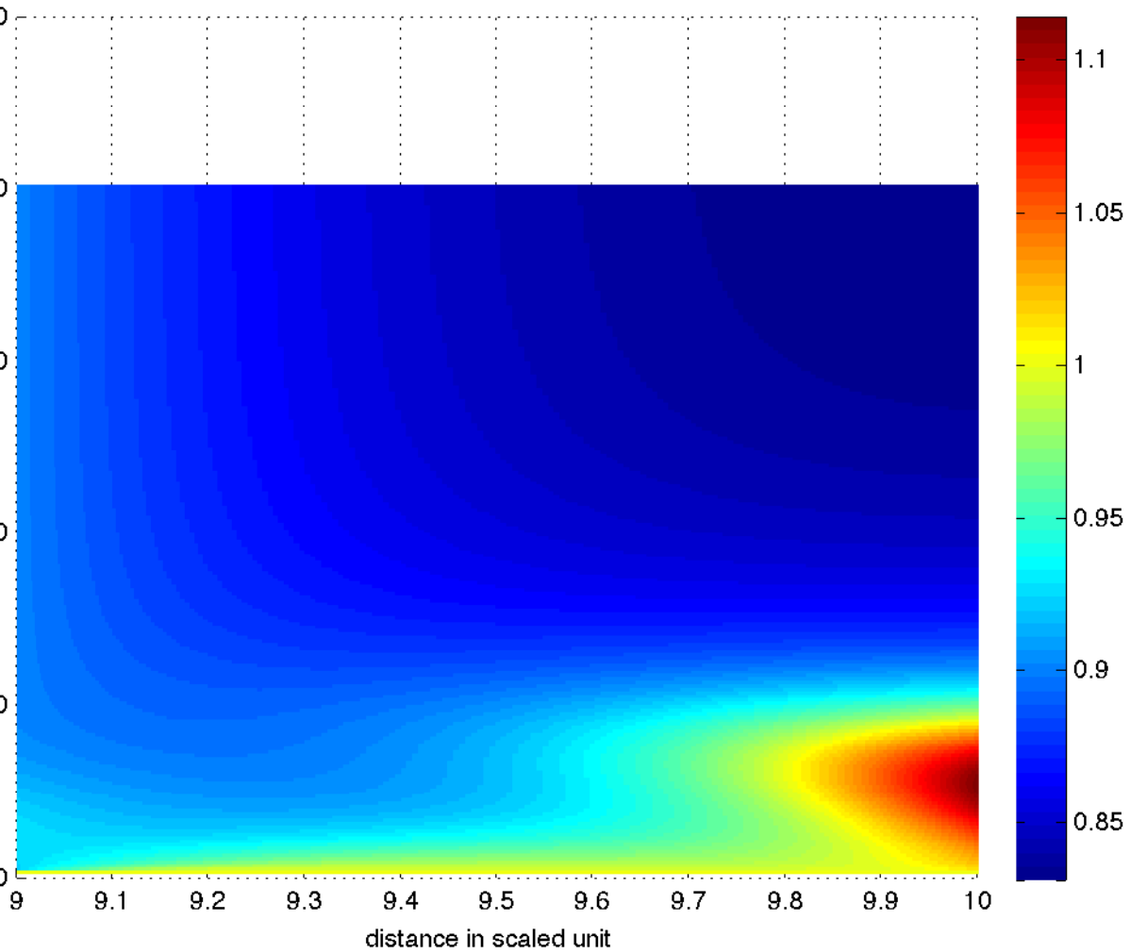

Red: 1.02, Blue: 0.86 scaled conc.

## Inside ODS at 1.9, outside

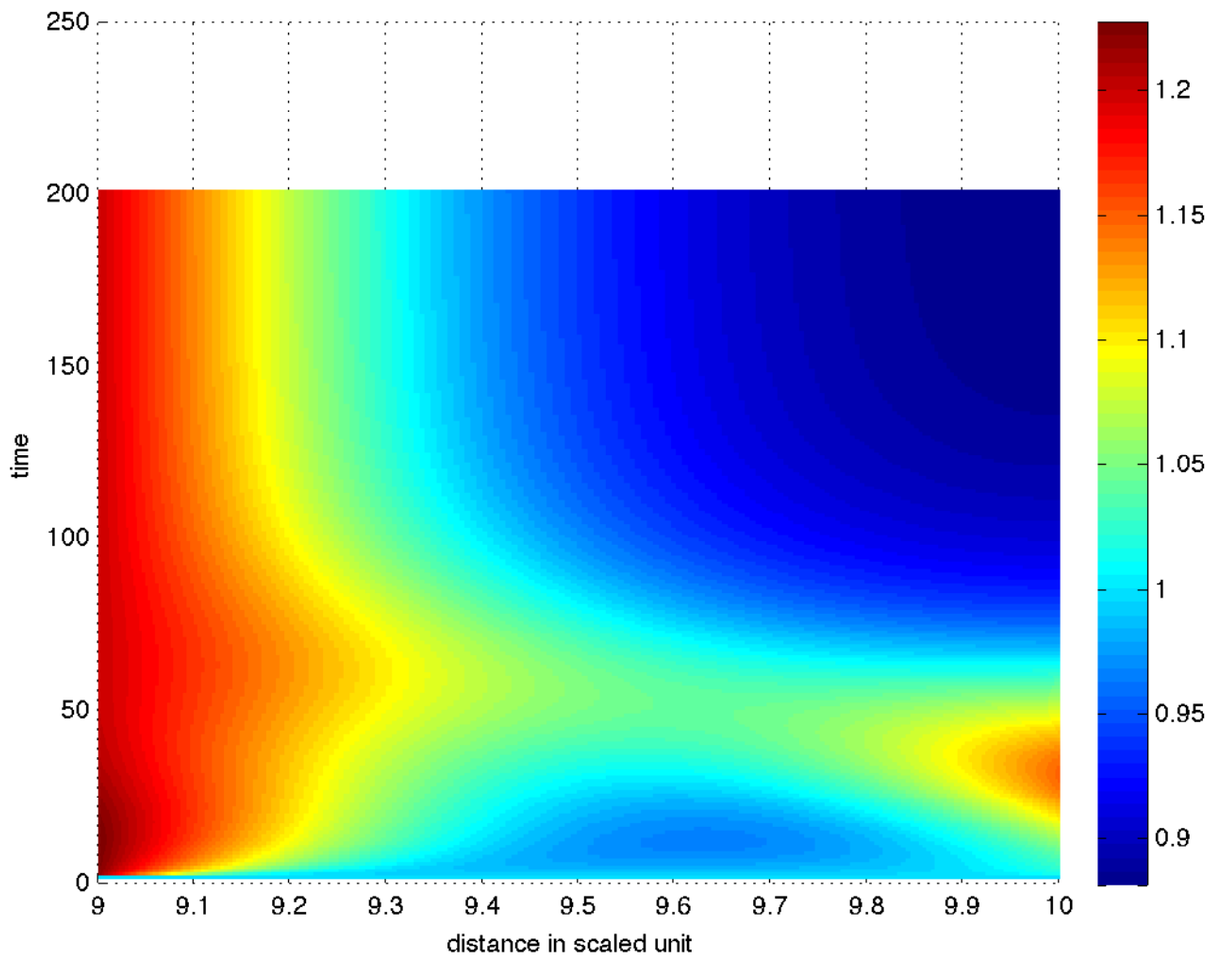


# Effect of saturation $O_2$ in hydrogel

90%



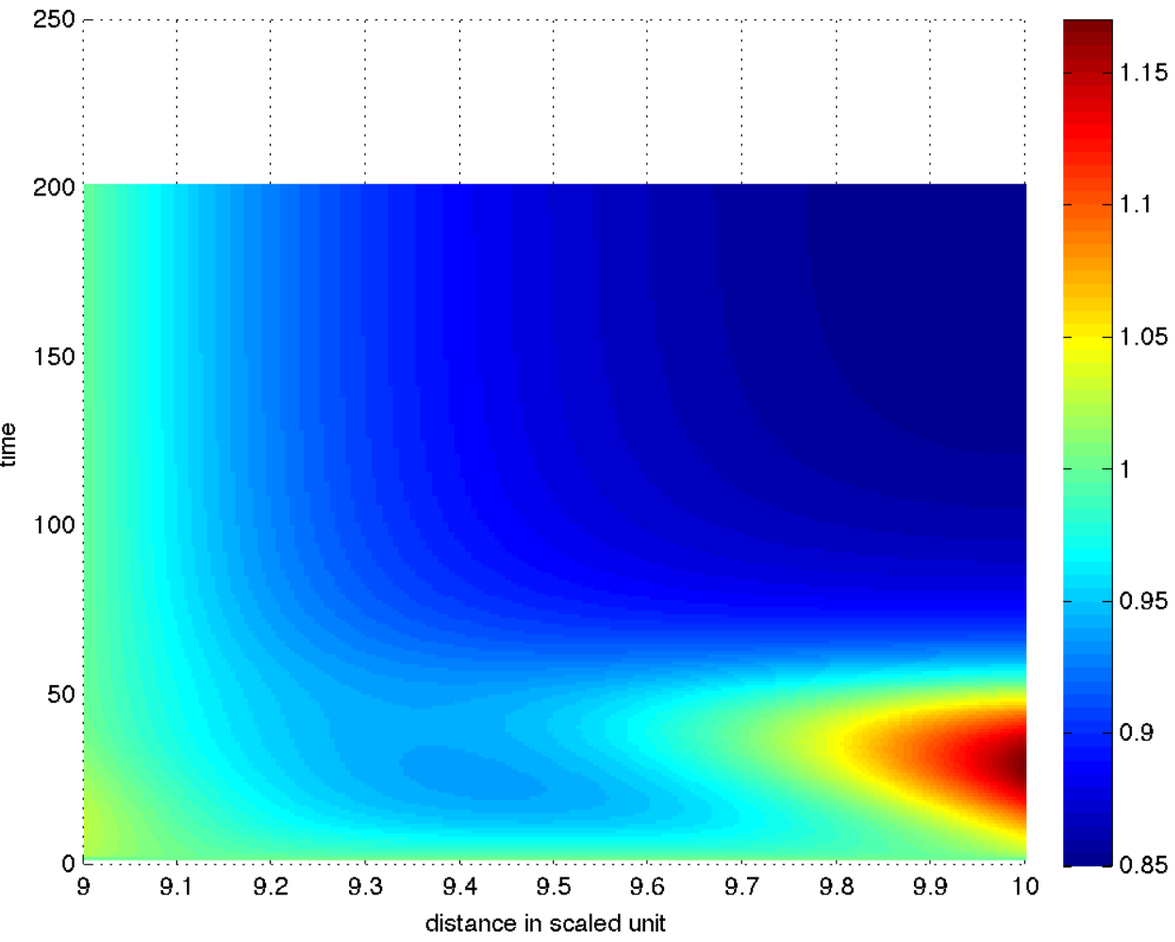

120%




Blue=0.8, red=1.1

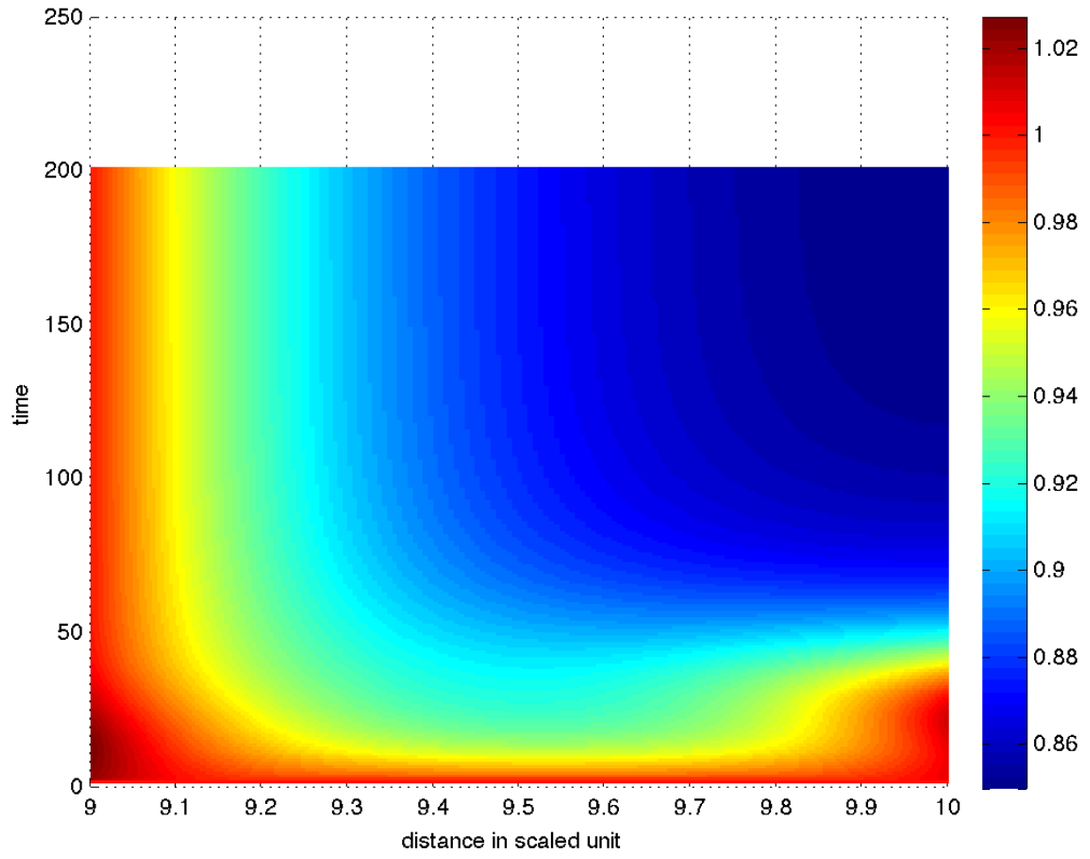
Blue=0.9, red=1.2

# Effect of ODS distance




ODS at .25 from tissue

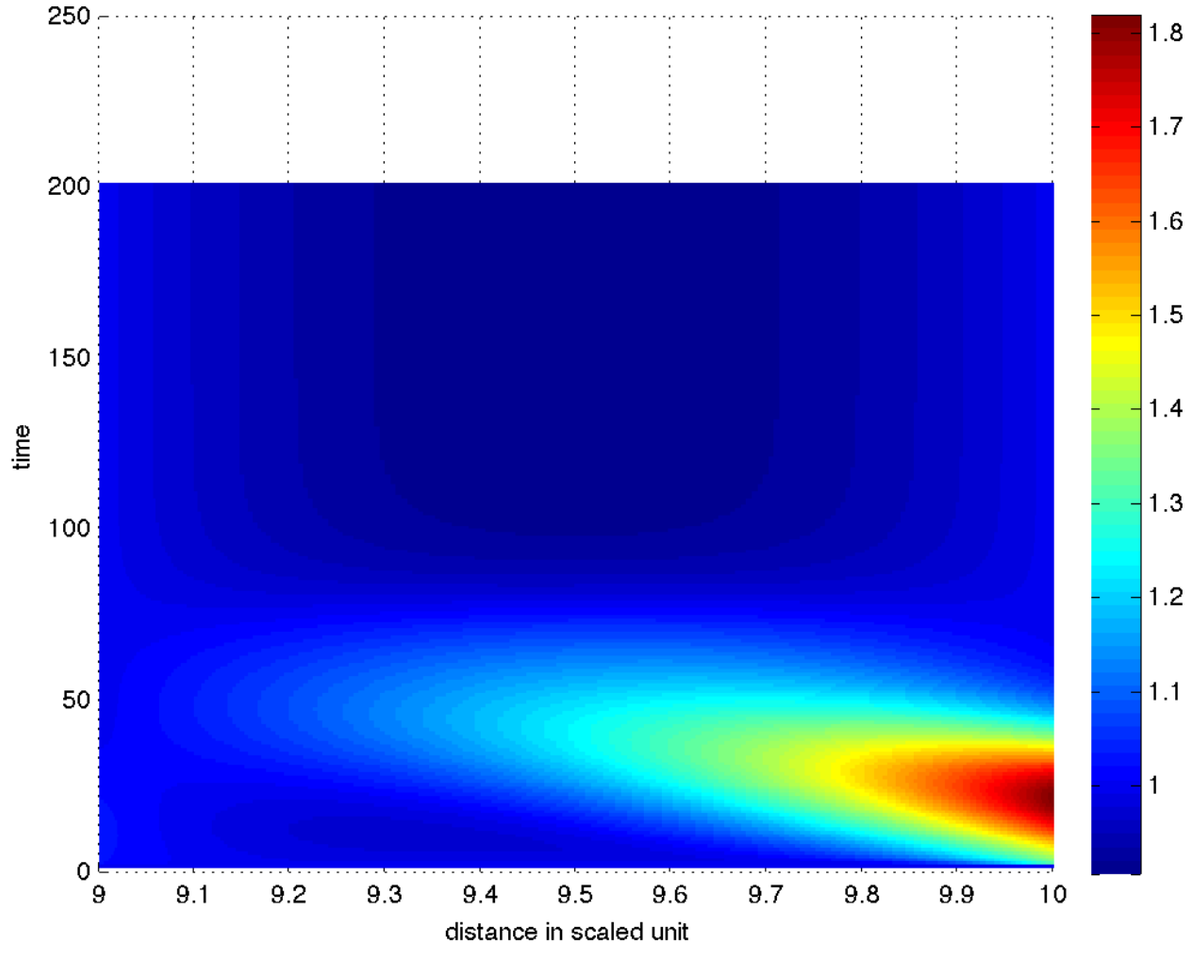
Blue: .85, red=1.1




ODS at .85 from tissue

Blue: .85, red=1.02

# Endothelial cells



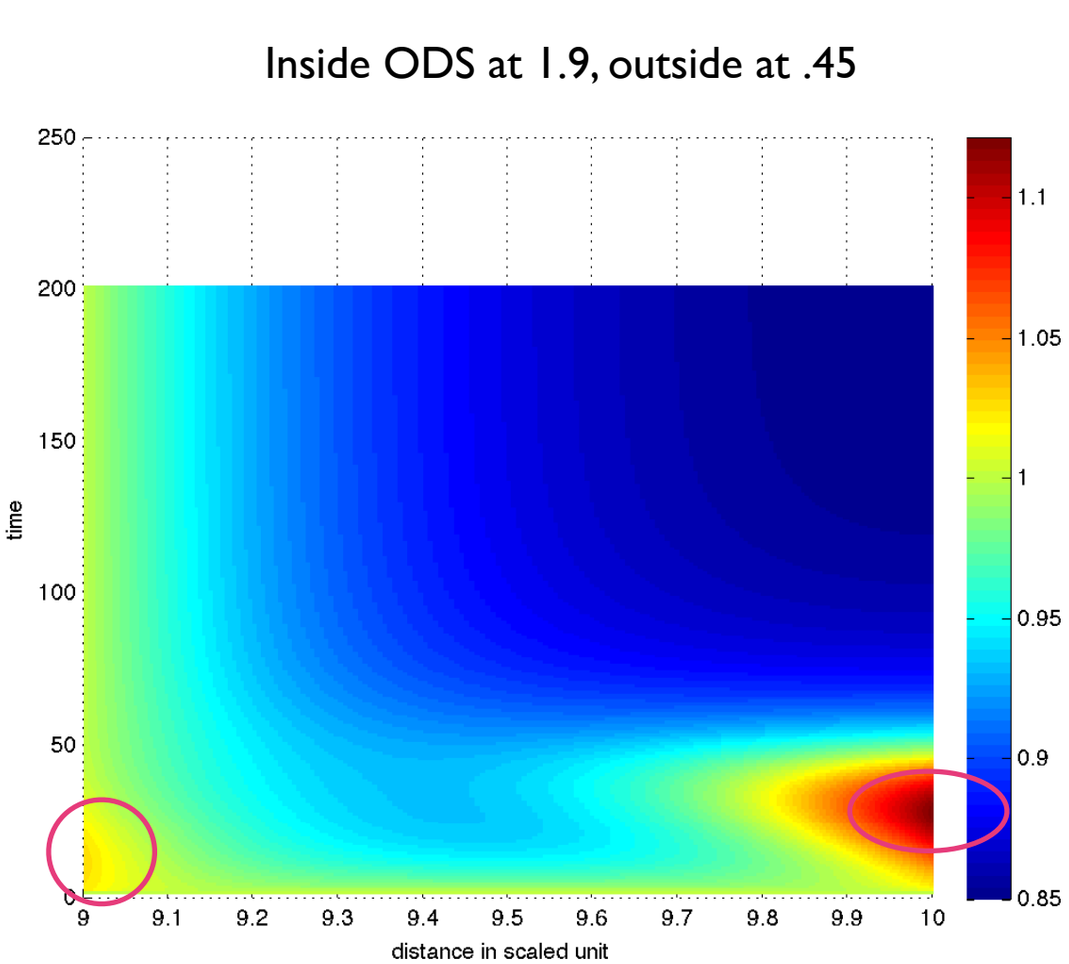

Endothelial on inner artery wall

blue: .85, red:1.1

Endothelial on both walls

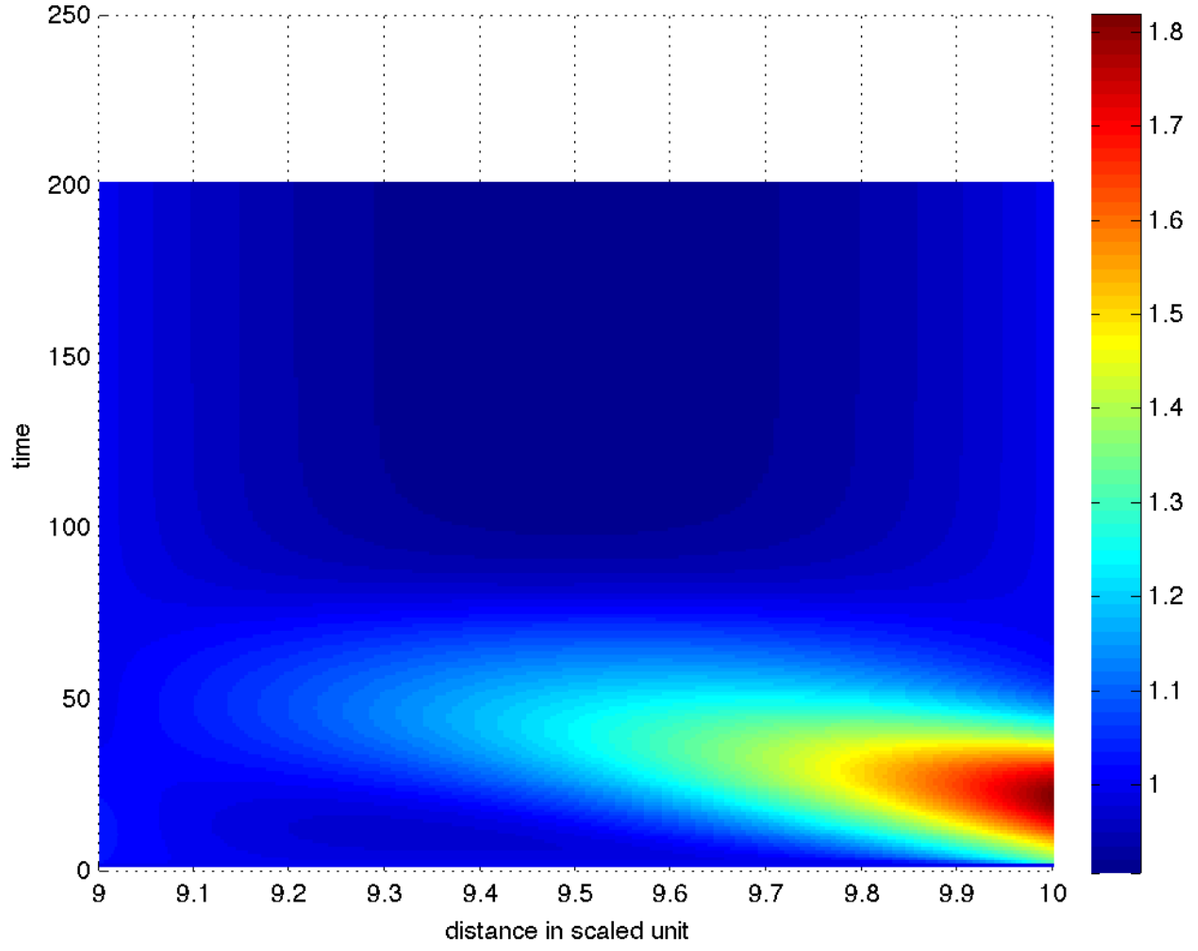
blue: .1, red:1.8

# Endothelial cells




Endothelial on inner artery wall

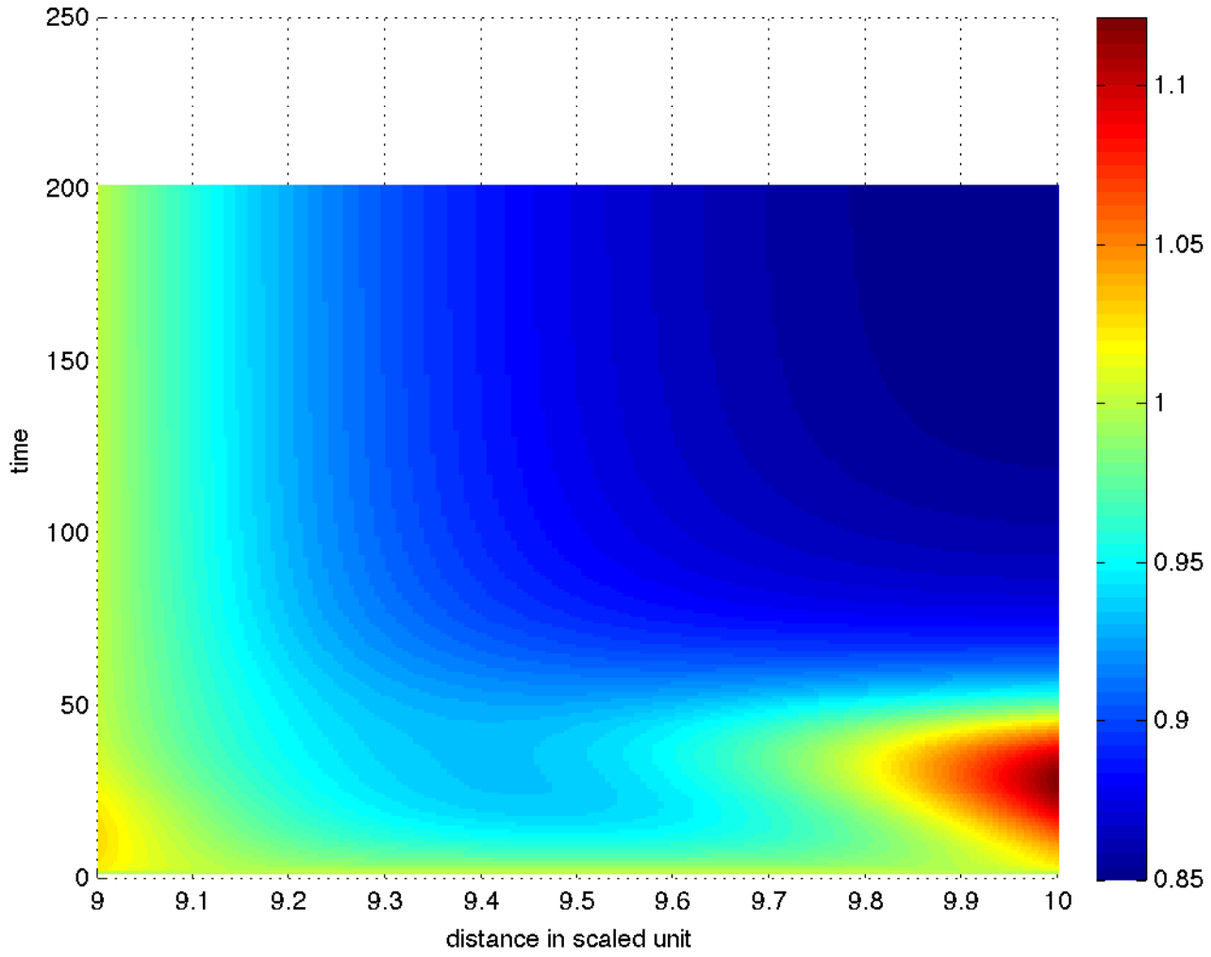
blue: .85, red:1.1



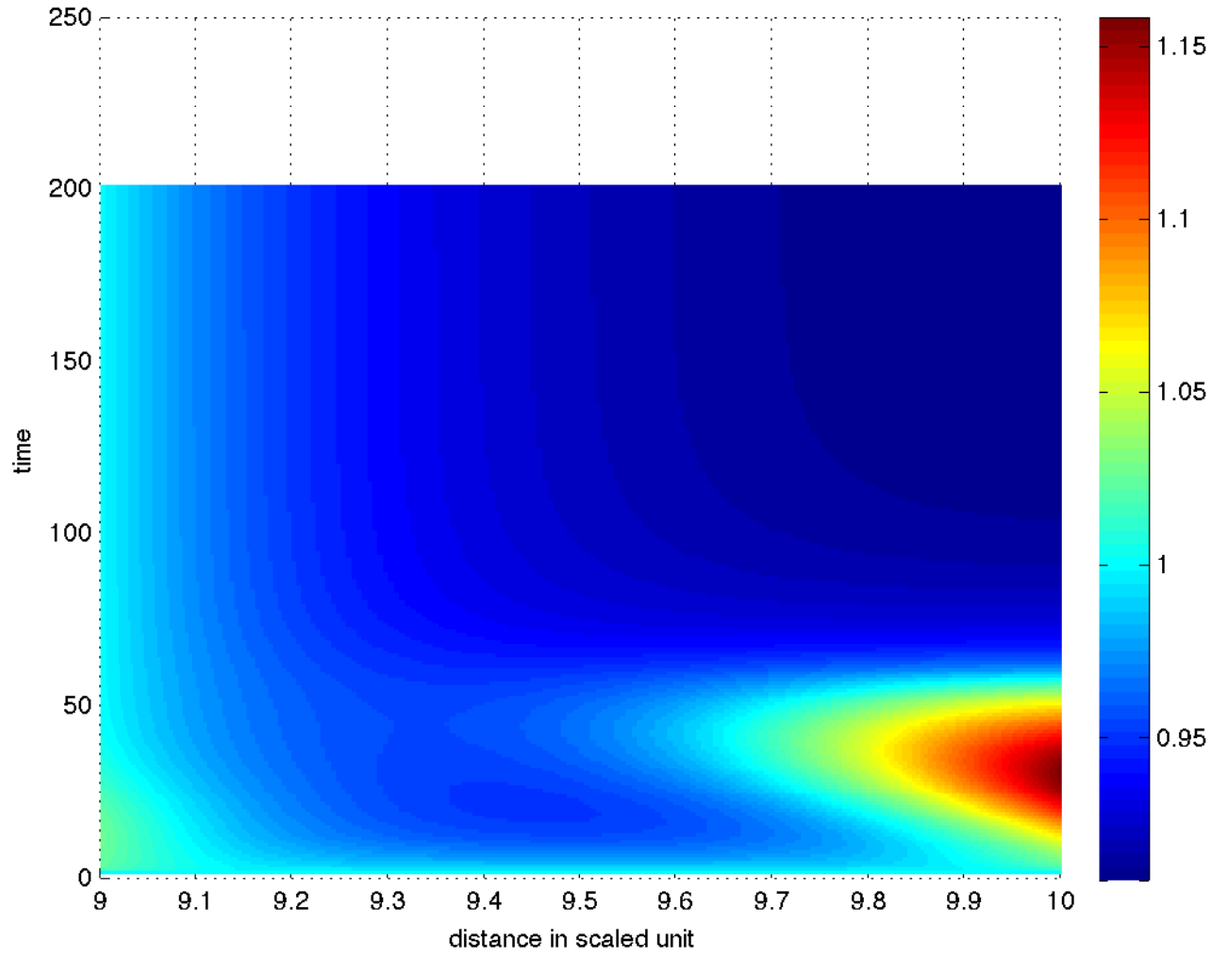

Endothelial on both walls

blue: .1, red:1.8

# 'Tolerance' of cells to $O_2$ change




blue=.85, red=1.1




blue=.85, red=1.15

cell tolerance is halved.

# Conclusion

- Built conceptually simple models for ODS+tissue interaction
- Endothelial tissues play a major role
- System is sensitive to 'tolerance' of cells for oxygen
- Distance of ODS from tissue is important factor