OXYGEN DIFFUSION DYNAMICS WITHIN THE INTERVERTEBRAL DISC - A NANOSCALE AGENT-BASED MODEL

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Introduction

The intervertebral disc is the biggest avascular structure of the human body. In its central tissue, the Nucleus Pulposus (NP), a low amount of oxygen (O_2) molecules diffuses from the Cartilage Endplates, which separate the NP from the closest blood supply [1]. O_2 has a low solubility and travels through a tissue with only 4000 cells/mm^3. Hence, we hypothesize that O_2 molecules can travel through the extracellular matrix without being metabolized.

Methods

A 3D Agent-based (AB) model (Netlogo, v6.0.2) of a volume of ~1.1x10^{-3}mm^3 with 2x10^6 patches was equipped with a corresponding amount of 4 NP cells and a physio-logical volume fraction of 21% of extracellular matrix, mainly Aggrecan (Agg) and Collagen (Col) (Fig. 1). A representative amount of 300 O_2 agents was distributed within the model, allowing to diffuse at 3 µm/s [2]. O_2 travelled through Agg with a 50% reduced speed, while Col was considered as obstacle.

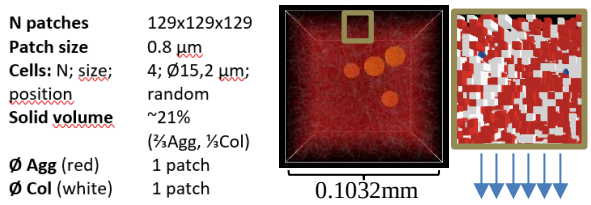

Figure 1: AB model and parameters; cells in semi-transparent ECM. Left: O_2 molecules (oversized, blue) within ECM. Directed diff of O_2. N: number

To define the molecule dynamics, we assumed: (i) an axial directed diffusion (d.diff, blue arrows, Fig. 1) caused by the metabolism of O_2 by the cells in the center of the NP; (ii) a reactivity layer (r.layer) around each cell due to its metabolism. r.layer was either the cell radius (~8 µm) or the cell diameter (~16 µm). Within r.layer, O_2 was attracted towards the cell. d.diff varied between maximal (100%), i.e. straight downwards movement, and minimal (0%), i.e. total random movement. According to the r.layer and d.diff variations, six O_2 reactive transport cases of 1h (3600 timesteps) were simulated (Tab. 1). Each case was run three times.

Case:	1	2	3	4	5	6
r.layer (µm)	8	8	8	16	16	16
d.diff (%)	20	50	80	20	50	80

Table 1: six conditions (con): r.layer; two sizes, d.diff; three intensities.

Results and Discussion

Compared to 50% d.diff, 80% d.diff did not lead to higher average or maximal travel distance. However, O_2 metabolism decreased at higher d.diff. High r.layer and low d.diff (Case 4) led to only ~12% free O_2 and less than 2 mm average travel distance (Tab. 2).

Case	1	2	3	4	5	6
Avg td (mm)	1.96	4.34	3.57	1.88	4.34	3.33
Max td (mm)	2.04	4.58	4.70	2.02	4.53	4.68
Met O_2 (%)	57.8	47.8	20.6	88.1	70.6	41.7

Table 2: Average (avg); maximal (max) travel distance (td) and metabolized (met) O_2 per condition

Less directionality is associated with reduced diffusion distances. Interestingly, case 5 (Tab. 2) coincides with results of an FE mechanotransport model, where at roughly 4 mm depth, the amount of metabolized O_2 was around 65%, according to Fick's diffusion law [3]. Residual O_2 seems in case 5, however, high, considering that O_2 tension can be as low as 1% in large discs [4]. Hence, a prudent interpretation of transport models using partial differential equations in homogenized continua might be reasonable, since Fick diffusion possibly overestimates the probability of O_2 to reach cells in the center of the NP.

Beta-testing was performed to approximate experimental measurements in canine NP [1] that have a ~3 fold higher cell density. Using Case 1 (Tab. 1), the model predicted 2.9±0.7% residual O_2 after 1.95 mm, while experimentally measured O_2 tension was found to be as low as ~4% of initial tension after 2 mm travel distance. To our knowledge, this is the first nanoscale AB model that tackles molecular dynamics within the NP. On the one hand, the AB model simulates the probability of an O_2 molecule to reach a cell and can approximate measurements. On the other hand, in the AB model, the fact that O_2 travels over increased distances with d.diff higher than 50%, does not mean that the molecule reaches a NP cell along the way, in contrast to what continuum diffusion models with axial concentration gradients would calculate [3]. Hence, we might expect that NP cells see less O_2 than continuum models have described previously.

References

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