**Tissue damage**

**09-17-20**

**Article:** Jin-Combining experimental and mathematical modeling to reveal mechanisms of macrophage-dependent left ventricular remodeling-BMC systems biology

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Based on the size of damage site TGF-β activated (by an input signal uT). TGF-β recruit macrophage and fibroblast. Fibroblast deposit collagen.

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**Figure:** Macrophage migration rate M(Tβ), fibroblast growth rate Fg(Tβ), and fibroblast secretion rate Fc(Tβ) plotted as functions of TGFβconcentration.

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Assuming baseline = 0, followings are the function for macrophage migration, fibroblast recruitment and secretion.

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and follows the dynamics. But don’t match experimental observation even with baseline value.

**is the input signal from damaged site**

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The activation function peaked at 15, 30, and 60 pg/μL/day, according to active expression levels observed in small, median, and very large infarcts, respectively peaked at day 2, and returned to normal levels after day 7 in mice post-myocardial infarction

**Simplified ODEs**

The above model is written skipping the effect of MMP9 in collagen degradation and cell crowding from article 1 model.

**Table: List of parameters**

|  |  |  |
| --- | --- | --- |
| **Symbol** | **Biological meaning** | **Value** |
|  | Macrophage removal rate | 0.6 day-1 |
|  | Fibroblast growth rate | 0.924 day-1 |
|  | Fibroblast apoptosis rate | 0.12 day-1 |
|  | Macrophage TGF-β production rate | 0.07 pg/cell/day |
|  | Fibroblast TGF-β production rate | 0.004 pg/cell/day |
|  | TGF-β degradation rate | 15 day-1 |
|  | Fibroblast collagen production rate | 20 μg/cell/day |

**Simulated result for constant supply of μL/day**

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**Agent based model**

* Start from an immune model where tissue is not completely destroyed (faster T recruitment and faster T kill)
* When CD8+ T cell kills an infected cell that will become the source point for secretion of anti-inflammatory cytokine (source term uT)
* Anti-inflammatory cytokine will diffuse
* Recruitment of fibroblast depends on the concentration of anti-inflammatory cytokine ()
* Fibroblast chemotaxis towards the source of maximum secretion source of anti-inflammatory cytokines
* Fibroblast deposit collagen in the damages site

**Faster T recruitment:** We also increased the recruitment rate of CD8+ T cells to the tissue in response to inflammatory cytokines by reducing 𝜌min from 0.4 to 0.1, and by reducing 𝜌sat from 0.7 to 0.4

**Faster T kills:** the rate of CD8+ T cell killing was doubled by reducing the threshold contact time for cell death from 50 min to 25 min

* Anti-inflammatory cytokine
* Diffusion coefficient
* Fibroblast
* Cell migration rate along damaged tissue life in voxel: ?

Decay rate can be estimated from the ODEs

**PhysiCell Implementation**

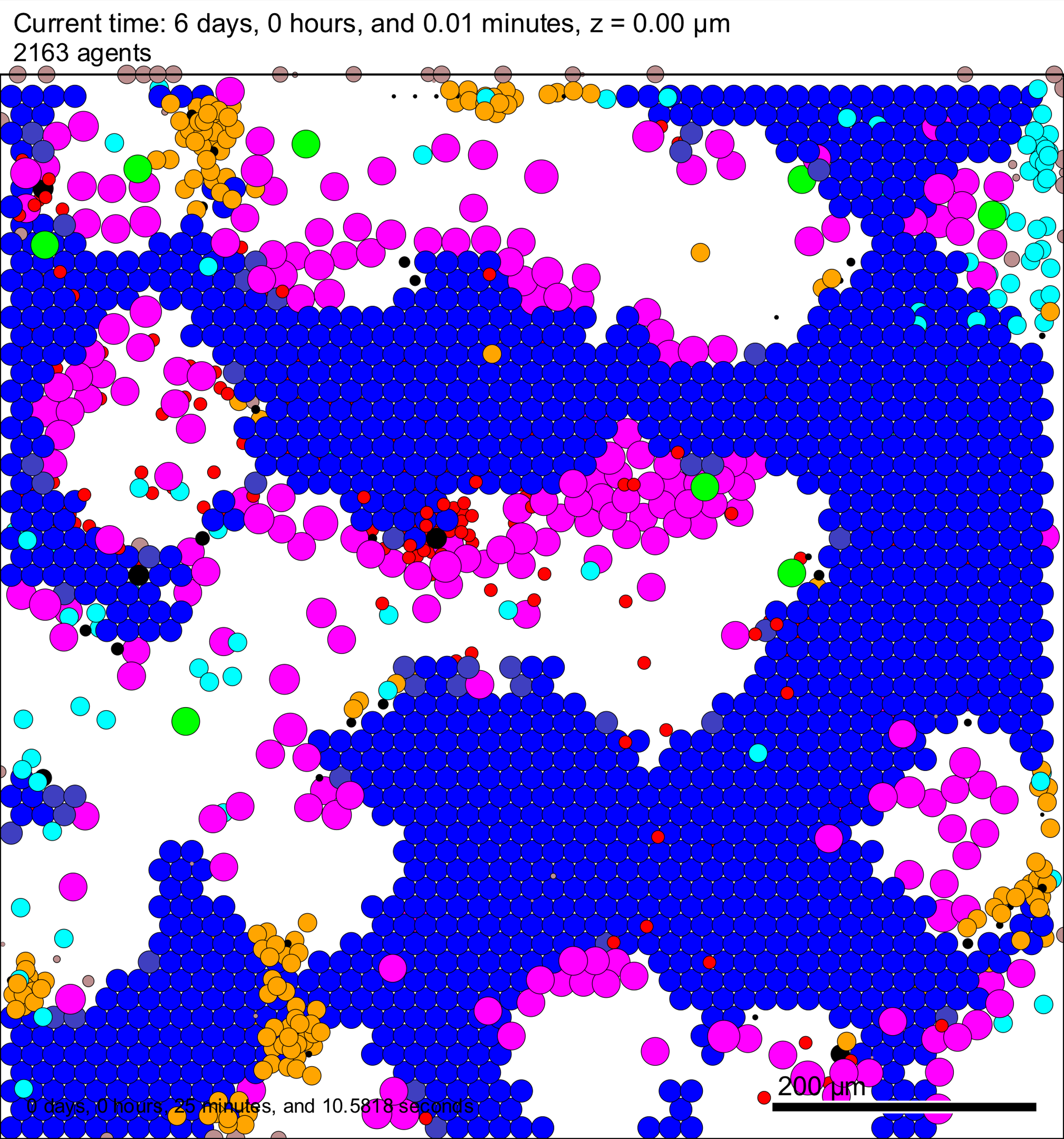
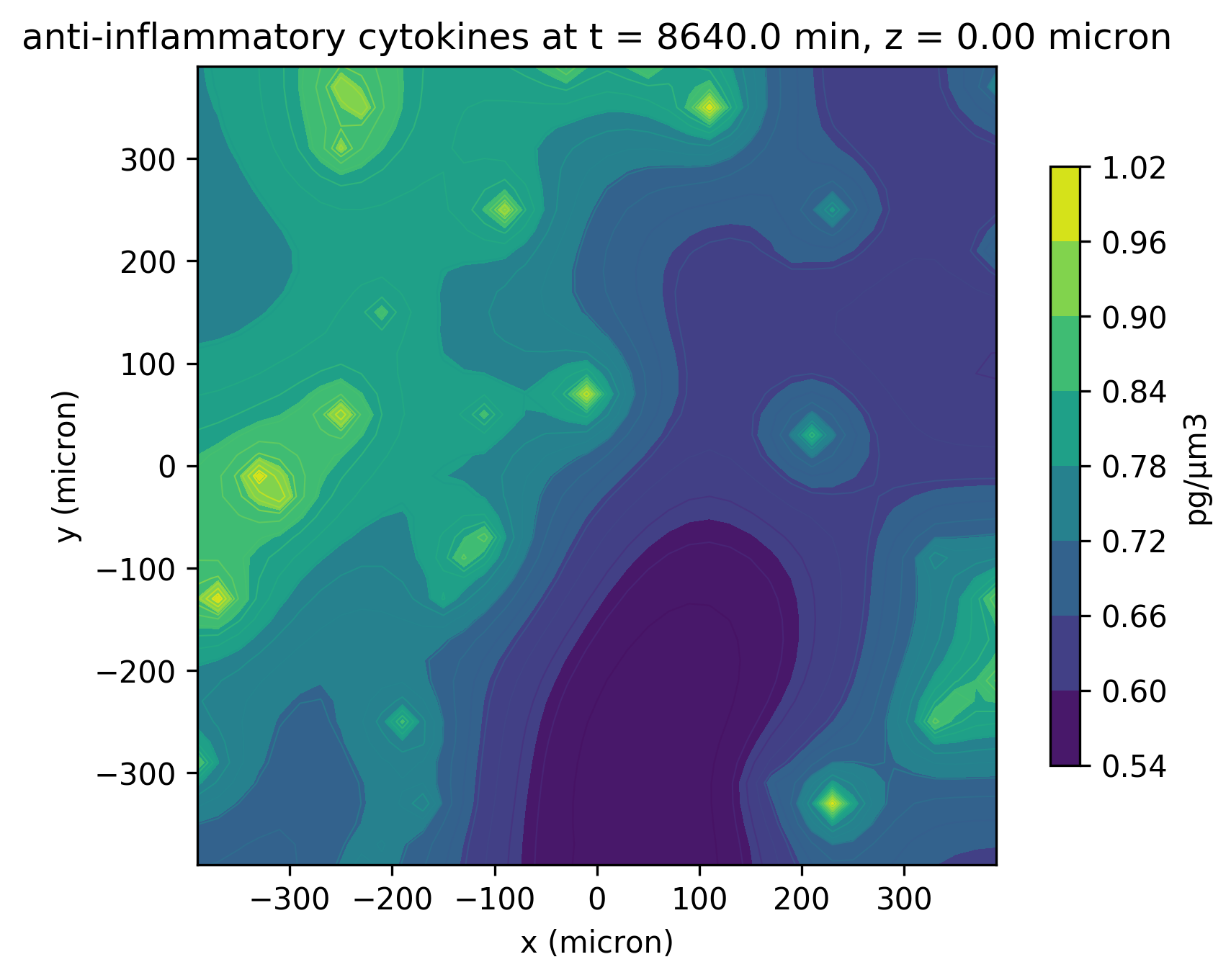
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**In epithelium\_submodel.cpp line 183**, I have added condition for secretion of anti-inflammatory cytokines while killed by CD8+ T cells. But probably this is applied only at one time point instead of constant supply

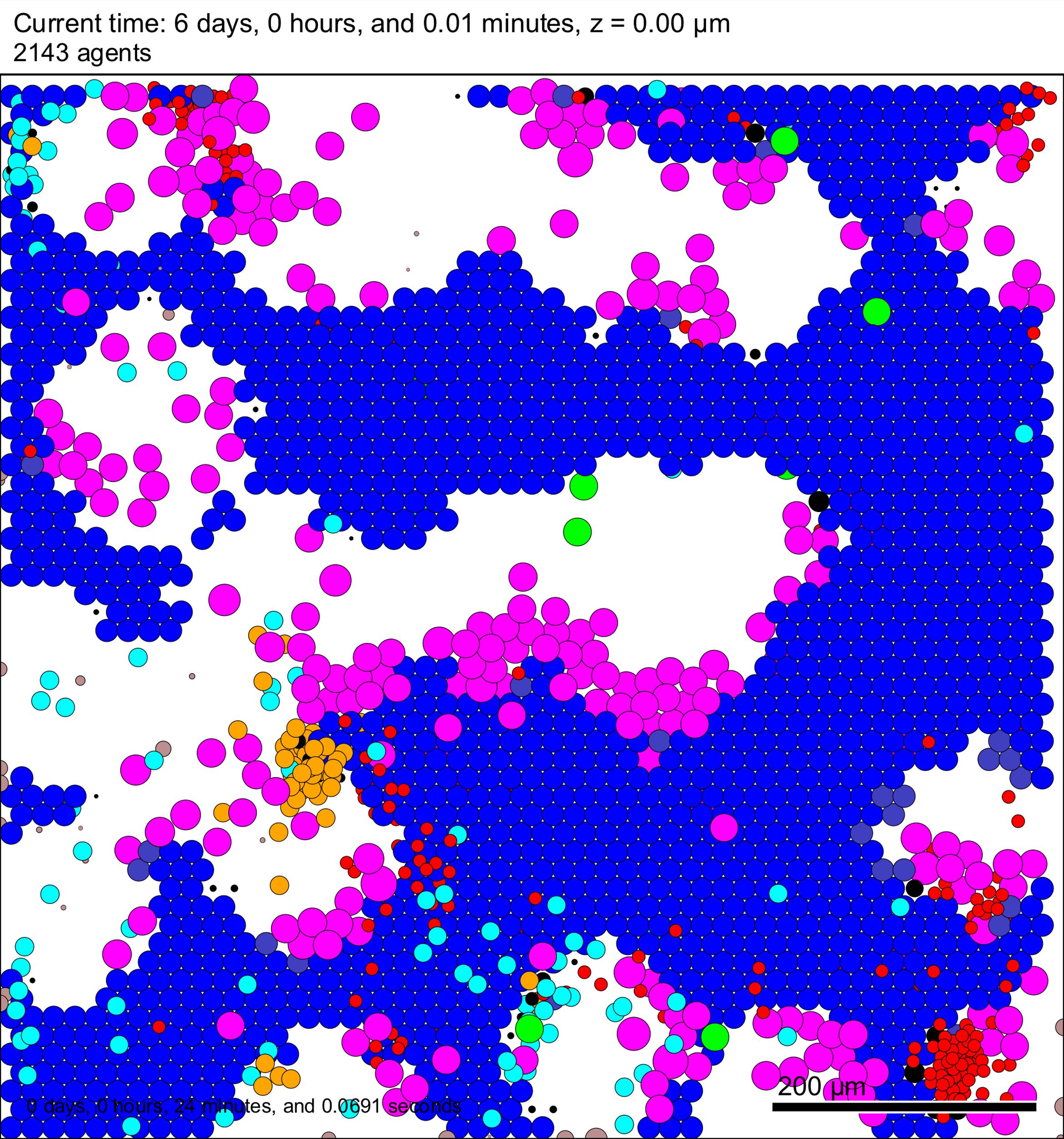
**Setting anti-inflammatory secretion rate = 100**

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**Setting anti-inflammatory secretion rate = 10**

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**In immune\_submodels.cpp line 412,** I set phenotype.motility.is\_motile = true. Added other function for fibroblast and anti-inflammatory cytokines. The parameter values are added in PhysiCell\_settings.xml file. But not sure whether this command will automatically add the anti-inflammatory cytokine gradient for fibroblast motility (find no direct connection in code file).