A Hybrid Control Model of Fractone-Dependent Morphogenesis (part II)

Aaron Tamura-Sato

University of Hawaii at Manoa

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Model

- Positions of Cells, Meninges, and Fractones describe the Discrete state, q.
- Growth factor concentrations described by the continuous state X.
- Guard conditions, Domains, and Edges describe the discrete dynamics (cellular growth).
- Reset maps describes the movement of growth factor after growth.

Diffusion

Distribution of growth factors X given by a density function.
Thus $\dot{X}$ is some functional that describes the perturbed diffusion
But perturbed diffusion is difficult to describe in general:

- Boundary conditions on every cell that prevent diffusion through cells or meninges
- Boundary conditions on every fractone that describe the absorption

Model Simplifications

- Only 2 growth factors explicitly in system, and 1 implicitly present
- Growth factor only generated by meningial cells
- Fractone geometry is irrelevent and a fractone only attaches to one cell
- Only 2 types of fractones are present in the system
- Fractones contribute not just to accelerated mitosis but also to direction of growth
- Cells are of a prescribed shape.

Distance

Definition

For two sets of cell bodies $E_a = \{c_{ar}\}$ and $E_b = \{c_{bs}\}$, we define the *directed Hausdorff distance* between E_a and E_b by

$$d(E_a, E_b) = \max_{(i_a,j_a,k_a)\in E_a} \min_{(i_b,j_b,k_b)\in E_b} \|(i_a, j_a, k_a), (i_b, j_b, k_b)\|$$

where $\|\cdot\|$ is the standard Euclidean distance:
$\sqrt{(i_a - i_b)^2 + (j_a - j_b)^2 + (k_a - k_b)^2}$.

Distance

Definition

For two sets of cell bodies $E_a = \{c_{ar}\}$ and $E_b = \{c_{bs}\}$, we define the *directed Hausdorff distance* between E_a and E_b by

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where $\|\cdot\|$ is the standard Euclidean distance: $\sqrt{(i_a - i_b)^2 + (j_a - j_b)^2 + (k_a - k_b)^2}$.

Definition

We define the *Hausdorff distance*, D_H, by:

$$D_H(E_a, E_b) = \max(d(E_a, E_b), d(E_b, E_a))$$

Distance

Definition

We define the *directed age distance*, d_a of two biological structures with sets of cells C_a and C_b. For a given set of cells C_i, let the center of cell $c_{ir} \in C_i$ be denoted (x_{ir}, y_{ir}, z_{ir}).

$$d_a(C_a, C_b) = \max_{C_a} \min_{C_b} [\|(x_{ar}, y_{ar}, z_{ar}), (x_{bs}, y_{bs}, z_{bs})\| + \kappa(|t_{ar} - t_{bs}|)]$$

for $\kappa \in \mathbb{R}$.

We further define the *age distance*, D_a of two biological structures,

$$D_a(C_a, C_b) = \max\left(d_A(C_a, C_b), d_A(C_b, C_a)\right)$$

Distance

Definition

We define the *directed Hausdorff fractone distance*, d_F, of two sets of fractones, F_a, F_b,

$$d_F(F_a, F_b) = \max_{(i_a,j_a,k_a)\in F_a} \min_{(i_b,j_b,k_b)\in F_b} \|(i_a, j_a, k_a), (i_b, j_b, k_b)\|$$

We further define the *Hausdorff fractone distance*, D_F, of two sets of fractones, F_a, F_b,

$$D_F(F_a, F_b) = \min\left(d_F(F_a, F_b), dF(F_b, F_a)\right)$$

Distance

Definition

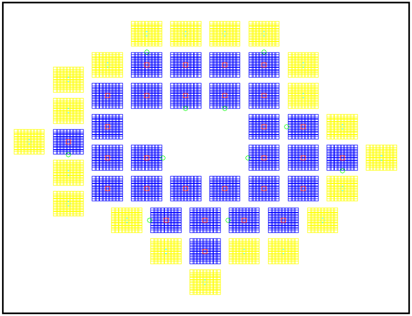
For $q_a, q_b \in Q$, using the previous notation, we define $B_a = \{C_a, F_a^+, F_a^-\}$ and $B_b = \{C_b, F_b^+, F_b^-\}$. Thus B_a and B_b represents all of the information in q_a and q_b except for the meninges. We define the biological structure distance, D_B, between B_a, B_b, as:

$$D_B(B_a, B_b) = D_H(E_a, E_b) + D_A(C_a, C_b) + D_F(F_a^+, F_b^+) + D_F(F_a^-, F_b^-)$$

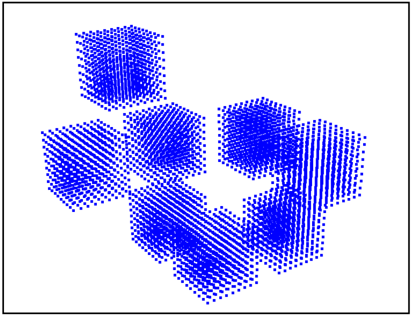
Proposition

D_B is a metric on the set of all B_i

Numerical Implementation

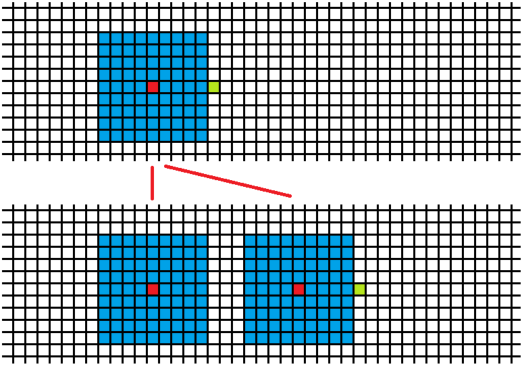


(a)

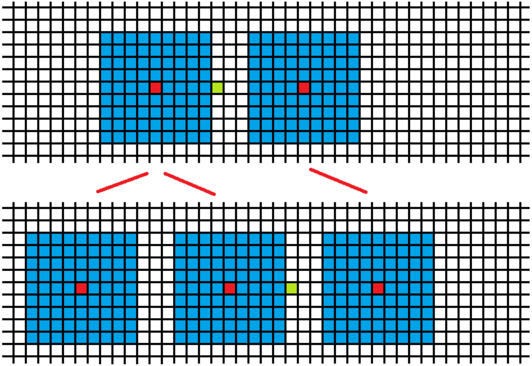


(b)

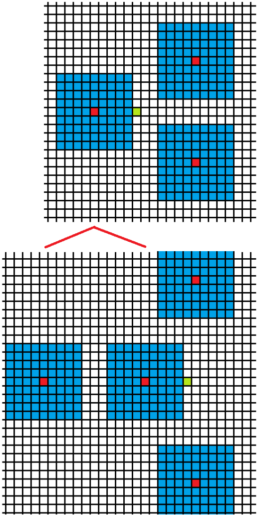
Pushing Algorithm



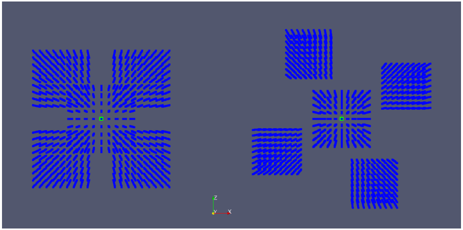
Pushing Algorithm

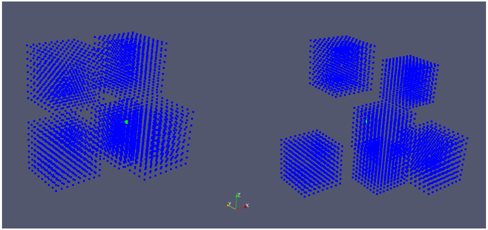


Pushing Algorithm



Pushing Algorithm





Diffusion

When far from a fractone, diffusion occurs freely, according to:

$$\dot{x}^{+}_{i,j,k}(t) = \nu^{+} \sum_{\substack{(\delta,\beta,\gamma)\in\Delta \\ (i+\delta,j+\beta,k+\gamma)\in Diff(t)}} \left(x^{+}_{i+\delta,j+\beta,k+\gamma}(t) - x^{+}_{i,j,k}(t) \right) \tag{1}$$

where
$\Delta = \{(1,0,0),(-1,0,0),(0,1,0),(0,-1,0),(0,0,1),(0,0,-1)\}$.

Diffusion

Affine Control System

$$\dot{x}^{+}(t) = F_0(x(t)) + \sum_{(i,j,k)\in \mathrm{Diff(t)}} F^{(i,j,k)}(x(t))u^{+}_{i,j,k}(t)$$

Diffusion

Affine Control System

$$\dot{x}^+(t) = F_0(x(t)) + \sum_{(i,j,k)\in \mathrm{Diff(t)}} F^{(i,j,k)}(x(t))u^+_{i,j,k}(t)$$

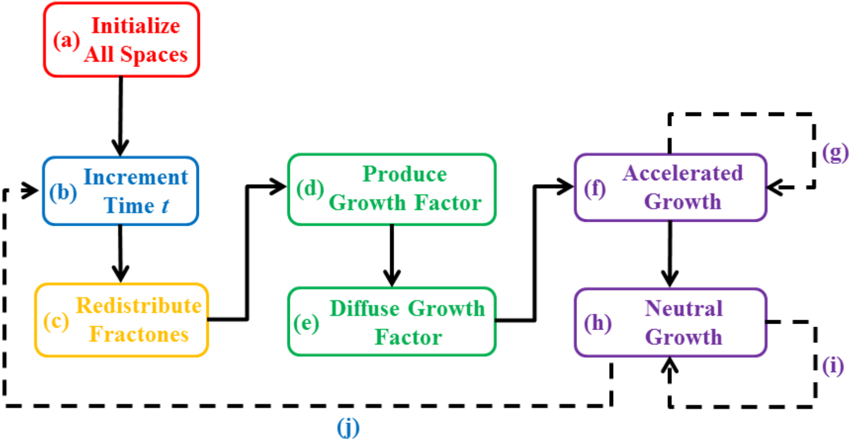
The (i, j, k)th component of vector field $F^{(i,j,k)}$ is given by:

$$\nu^+ \sum_{\substack{(\delta,\beta,\gamma)\in\Delta \\ (i+\delta,j+\beta,k+\gamma)\in Free(t)}} \left(x^+_{i,j,k}(t) - x^+_{i+\delta,j+\beta,k+\gamma}(t) + \alpha^+_1 x^+_{i+\delta,j+\beta,k+\gamma}(t) \right)$$

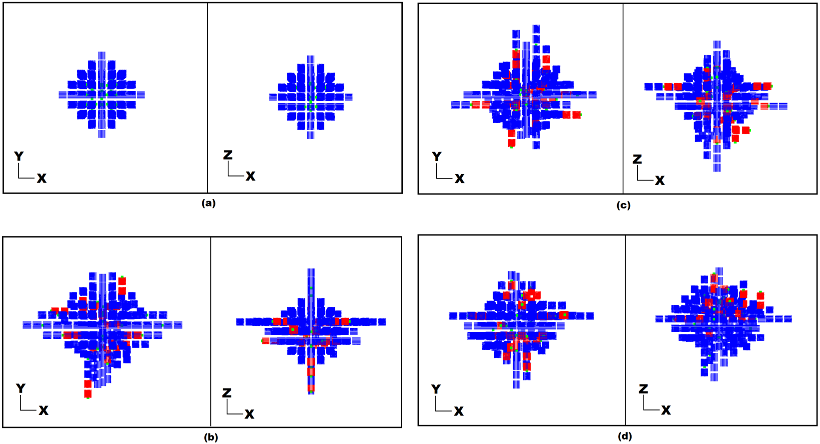
and component $(i + \delta, j + \beta, k + \gamma)$, $(\delta, \beta, \gamma) \in \Delta$, is given by :

$$\nu^+ \left(x^+_{i,j,k}(t) - x^+_{i+\delta,j+\beta,k+\gamma}(t) - \alpha^+_1 x^+_{i+\delta,j+\beta,k+\gamma}(t) \right)$$

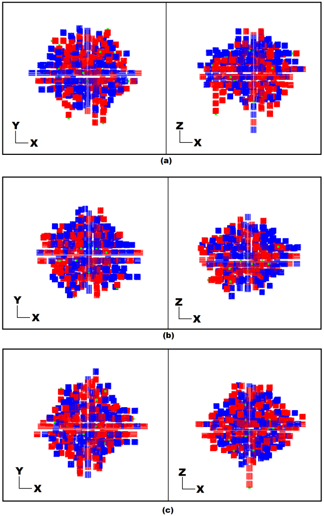
Numerical Implementation



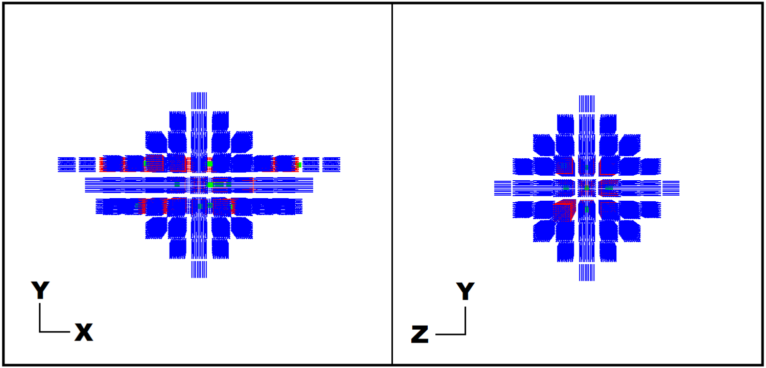
Uniform Growth



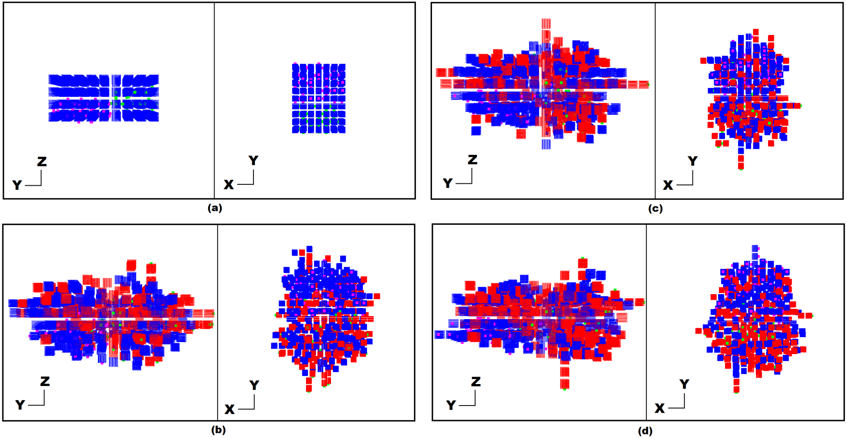
Uniform Growth



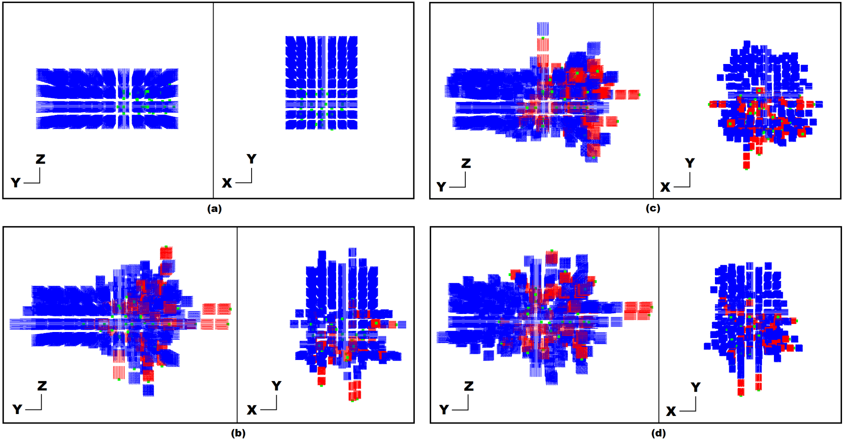
Directed Growth



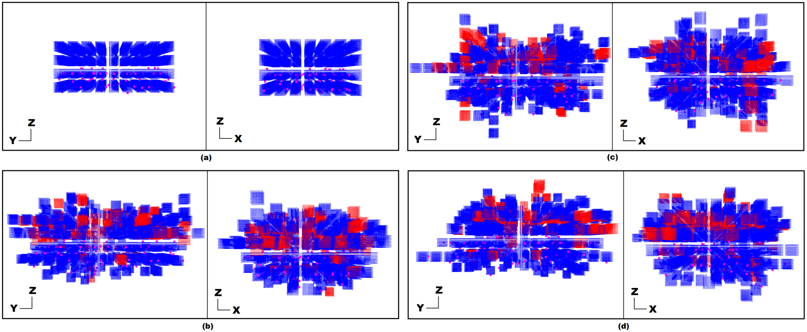
Directed Growth



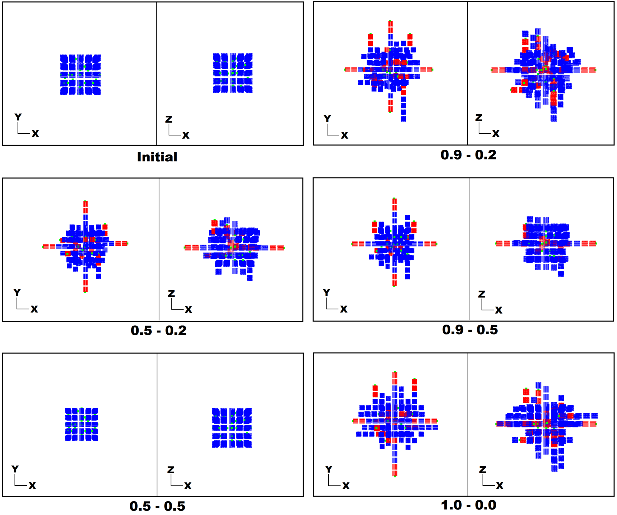
Directed Growth



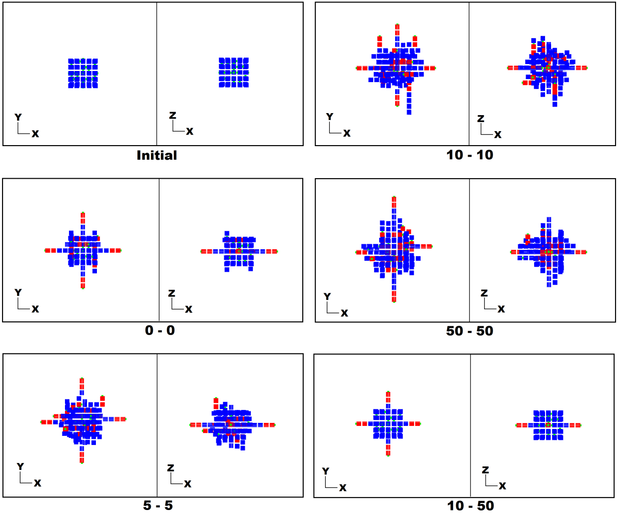
Directed Growth



Absorption Constant



Initial GF Distribution



Evolutions of a system

We denote the evolution of a discrete state by $\hat{q}(\cdot) : \mathbb{R} \to \mathbf{Q}$ and we denote the evolution of a continuous state by $\hat{X}(\cdot) : \mathbb{R} \to \mathbf{X}_0 \times \mathbf{X}_0$.

Definition

For any $T \in \mathbb{R}_{\geq 0}$, a control, u, defined on $[0, T]$ is *admissible* for the evolution of the discrete state $\hat{q}$ defined on $[0, T]$ if $u(x, t) = 1$ if and only if x lies in a fractone in biological structure $q = \hat{q}(t)$ for all $x \in A$ and $t \in [0, T]$.

Definition

For a given admissible control, u, defined on $[0, T]$ and initial conditions $(q_0, X_0) \in \mathbf{Q} \times \mathbf{X}$, we define an *end-point* on $[0, T]$ as a specific evolution of the system, $(\hat{q}(t), \hat{X}(t))$, with $\hat{q}$ and $\hat{X}$ defined on $[0, T]$ and $\hat{q}(0) = q_0$, $\hat{X}(0) = X_0$.

Evolutions of a system

Definition

For any $T \in \mathbb{R}_{\geq 0}$, and a given hybrid control system H with admissible control $u(x, t)$ defined on $[0, T]$, and initial conditions $(q_0, X_0) \in Init$, we define the *end-point set*, $\Lambda_H(q_0, X_0, u, T)$, as the set of all possible end-points on $[0, T]$.

If random growth is ignored, then Λ becomes a singleton set, and we call this end-point the *end-point map*, denoted $\chi_H(t, q_0, X_0, u(\cdot), T) = \left(\hat{q}(t), \hat{X}(t)\right)$

Evolutions of a system

Definition

Define the *evolution set of H at T* by
$Evol_H(T) = \bigcup_{U,Init}\{\chi_H(t, q_0, X_0, u(\cdot), T)\}$, where U is the set of all admissible controls defined on $[0, T]$.

Definition

Define the *evolution set of H* by $Evol_H = \bigcup_{T\geq 0} Evol_H(T)$.

Evolutions of a system

Definition

Define the set of all *reachable* states of H at T by

$$Reach_H(T) = \Big\{(q, X) \in \mathbf{Q} \times \mathbf{X} | q = \hat{q}(T), X = \hat{X}(T)$$

$$\text{for some } (\hat{q}, \hat{X}) = \chi_H \in Evol_H(T)\Big\}$$

Definition

Define the set of all *reachable* states of H by

$$Reach_H = \bigcup_{T \geq 0} Reach_H(T)$$

Statement Of Problem

Definition

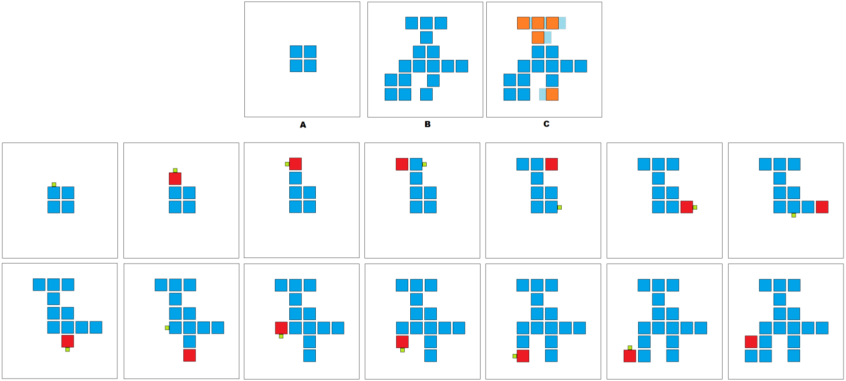
Define the set of *end structures* of hybrid system H by $End_H = Reach_H(1440)$

Controllability

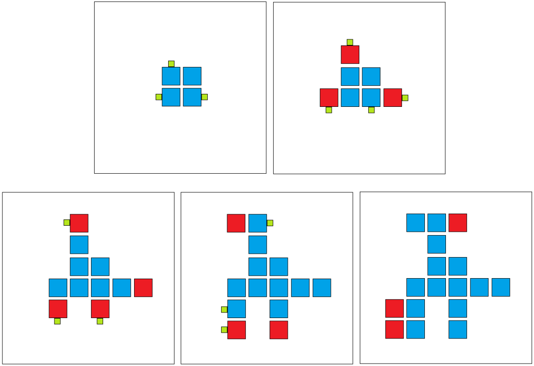
Given an admissible initial set of cell bodies, E_0; a target admissible set of cell bodies, E_f, with $E_0 \subset E_f$; an initial growth factor distribution, $X_0 \in \mathbf{X}$; and ignoring random neutral growth, can we find a control $u(x,t)$ and initial $q_0 \in \mathbf{Q}$, where q_0 has the set of cell bodies E_0, such that for the resulting hybrid control system H, $\exists (q_f, X_f) \in End_H$, where q_f has the set of cell bodies, E, and $D_H(E, E_f) \leq 12$?

$D_H(E, E_f) = 12$ is the distance between one cell and an immediate neighbor.

Controllability



Controllability

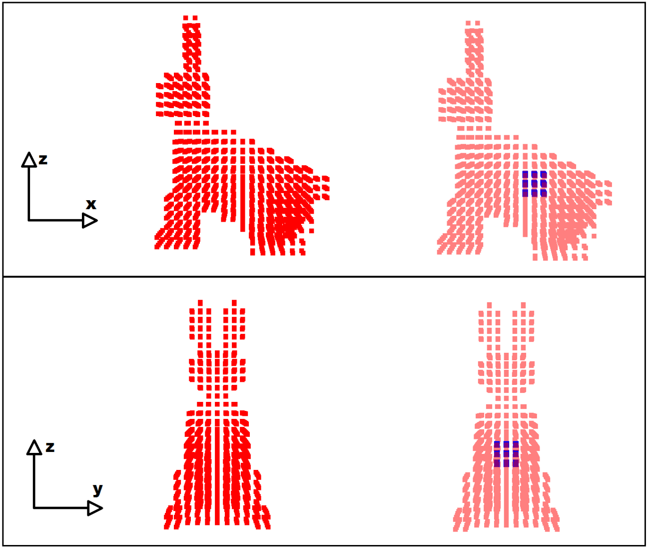


Controllability

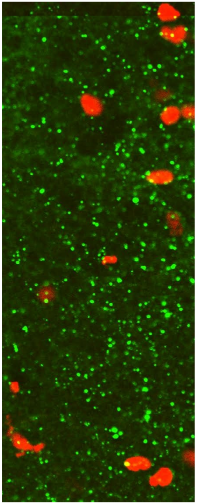
Proposition

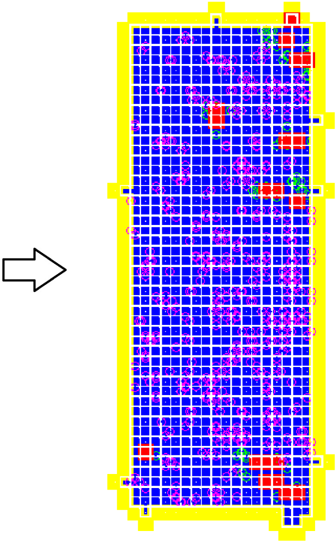
Given an admissible initial set of cell bodies, E_0; a target admissible set of cell bodies, E_f, with $E_0 \subset E_f$; an initial growth factor distribution, $X_0 \in \mathbf{X}$; and ignoring random neutral growth, $\exists$ admissible $u(x,t)$ and $q_0 \in \mathbf{Q}$, where q_0 has the set of cell bodies E_0, such that for the resulting hybrid control system H, $\exists (q_f, X_f) \in Reach_H$, where q_f has the set of cell bodies, E, and $D_H(E, E_f) \leq 12$.

Controlled Growth

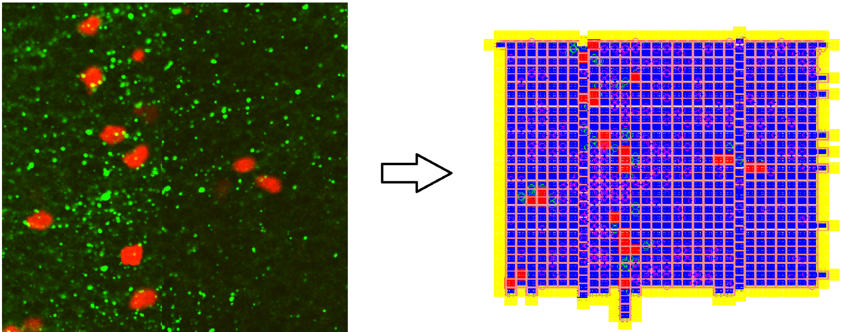


Biological Maps

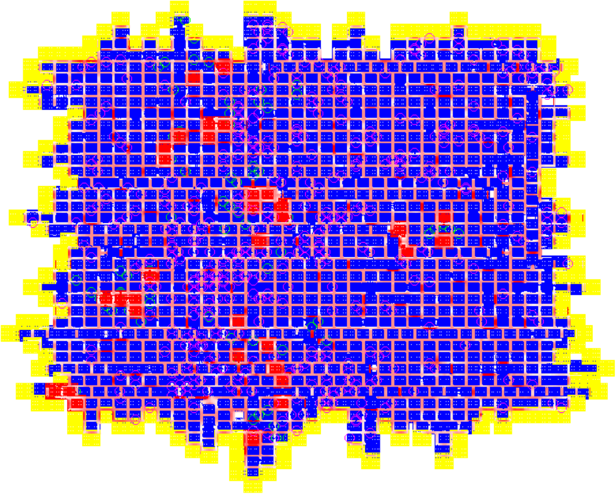




Biological Maps



Biological Maps



Future Work

- 3D Biological maps
- Tuning of parameters
- Controllability with random neutral growth
- Optimization problem