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Broadcast Feedback Control of Cell Populations Using Stochastic Lyapunov Functions with Application to Angiogenesis Regulation

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Abstract—**This paper introduces a broadcast feedback approach to controlling the aggregate behavior of a population of cells. Control of the angiogenesis process, which is known to exhibit stochastic behavior, is the target application. A simple model is considered that assumes a cloud of independent cells that need to be controlled to a specific location or along a trajectory. Each cell makes a random decision to move to the right, to the left, or remain in its current location at each time step. Additionally, each cell has a unit time refractory period after a movement during which it cannot move again. Because the cells live in a "wet" environment, it is not feasible to control their behavior independently. Instead, the system output is the centroid of the cloud, and the controller uses the error between the output and the reference to broadcast a single probability of transitioning to the ensemble of cells. Conditions for stability in the output are obtained using a stochastic Lyapunov function. An analysis of the dispersion of the cloud of cells is given. Additional intercellular regulatory behavior is added to better represent a real system and leads to a method of variance control under some additional assumptions. Simulation verifies the theoretical results and affirms that aggregate output can be stably controlled to a reference or along a trajectory.**

I. Introduction

Angiogenesis is the process of creating a vascular network in a tissue matrix. Understanding and controlling angiogenesis is critically important for many pathological and physiologic research areas, ranging from cancer treatment and wound healing to morphogenesis, stem cells, and tissue engineering. It is known that angiogenesis is a stochastic process where vascular cells (endothelial cells) sprout, branch out, and reconnect to other cells. Occurrences of sprouting, branching, and extension are stochastic, having probabilities modulated by both local and global stimuli [1], [2]. Regulating and manipulating the angiogenesis process by means of active, real-time control is a truly challenging research issue, which will have a significant impact upon broad biological engineering and medical fields.

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Angiogenesis and other biological processes are fundamentally different from traditional engineering systems where control technology has been successfully applied. First, the system consists of a vast number of cells that have local controllers to perform a specific class of functions. Collective behavior of the cells exhibits meaningful functionality, such as constructing a vascular network. Second, cells are living in a "wet" environment, where signals propagate through diffusion. Stimuli to the process pervasively affect all the cells involved in the wet environment.

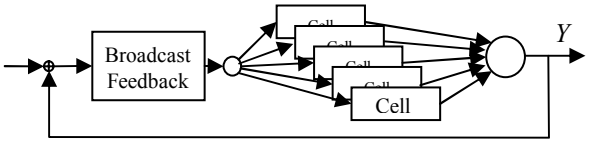


Figure 1: Broadcast feedback of cellular systems.

In constructing a control system, we have to note these features that are specific to biological systems. Figure 1 portrays the nature of biological control systems. The plant is a cell population comprising a vast number of individual cells. Their aggregate output Y is the controlled variable we wish to regulate or manipulate. The feedback controller evaluates the discrepancy between the aggregate output and its reference, and sends the error information to the cell population. It should be noted that the communication between the feedback controller and the individual cells is via the wet environment. Unlike traditional control systems, where control commands can be directed to individual units with discrete address bits, the communication in the wet environment is "broadcast" in nature. It is difficult or inefficient to generate and send each control command to each cell. Input stimuli will influence the entire cell population as it is unrealistic to think that we can manipulate individual cells selectively. Interventions in this case are limited to global, non-selective means, such as shear stress, pressure gradient, and biochemical factors concentration; called control factors. In turn, the process that we would like to control is not metered in terms of individual cell performance, but rather an aggregate output obtained from a vast number of cells. Each cell behaves stochastically, and therefore it does not reflect the global state of the process. Thus, "ensemble" behavior of a cell population is inevitably the variable to be controlled and describes the objective of the control system.

The authors' group has presented the framework of this "Broadcast Feedback" control and has developed a methodology for designing a stable stochastic regulator [3],

[4],[5]. The theoretical foundation of the stable stochastic regulator stems from the seminal work on stochastic dynamic systems by Doob [6] and stochastic Lyapunov functions by Kushner [7],[8]. The method has been applied to cellular muscle actuators comprising a number of ON-OFF actuator units. It has been demonstrated that broadcast feedback based on stochastic recruitment can stably control the ensemble of the vast number of ON-OFF actuators, i.e. the aggregate output successfully tracked an arbitrary trajectory [4],[5].

The objective of this paper is to apply this broadcast feedback to a simple angiogenesis process. A simple model describing individual cell behavior as well as aggregate behavior will be presented, and stability conditions based on stochastic Lyapunov functions will be developed. Simulation experiments will verify the theoretical results.

II. Modeling and Control of a Stochastic Cell Population

A. Control Overview

Angiogenesis is a highly complex process. It is beyond the scope of this paper to include many facets of the process. Rather, this paper focuses only on the migration process of Endothelial Cells (EC) in response to control factors globally affecting a cloud of ECs. Figure 2a illustrates the migration process of ECs induced by a tumor that emits tumor angiogenesis factor (TAF). ECs sprout out from a blood vessel and migrate toward the tumor in response to TAF propagating through the tissue matrix. Based on the literature of angiogenesis, the following properties of angiogenesis are known (some of which we will take into account in our simple model):

- Individual ECs make discrete state transitions labeled as: Migrating, Dividing, Staying, and Dying. When Migrating, the EC moves to an adjacent spot in the tissue matrix; when dividing, it goes through a cytokinesis process to create another EC; when staying, it does not do anything; and when dying, it dilutes and disappears.
- Once each EC has made a state transition, it cannot make another transition for a certain time period, i.e. a *refraction* period.
- When each EC is not in a refraction period, it makes a discrete state transition stochastically, which is affected by the control factors received by the EC.

One of the missing links in the literature is the lack of explanation for how control factors influence the state transition. Although many control factors have been identified, it is not known how these factors affect the state transition process. Some qualitative mechanism descriptions have been supplied, but their quantitative understanding remains a challenging issue. Based on published data as well as the in vitro experiments conducted by the collaborators of the authors, we hypothesize in this paper that these control factors influence the stochastic state transition by modulating the transition probabilities. In other words, the cellular state transition probabilities, p_{ij}, are functions of control factors. This modeling assumption has not yet been fully supported by experiments, but it is natural to assume this property, which allows us to build a quantitative model and analyze the process dynamics. This thought experiment will elucidate important aspects of the angiogenesis process.

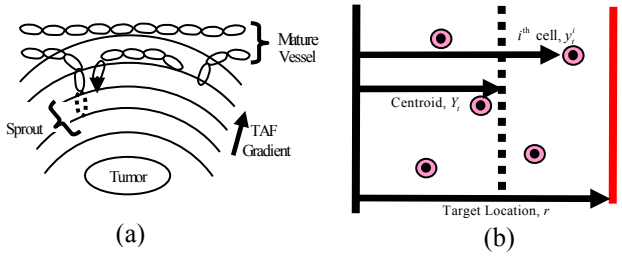


Figure 2: Endothelial cell migration (a); and cloud of N independent cells at locations y_t^i with centroid Y_t at time t broadcast controlled in 1 dimension to a reference location, r (b).

B. Simple Cell Model

Consider a cloud of N independent cells that we wish to migrate toward a target position in one dimensional space. See Fig. 2b. Each cell makes a stochastic decision to migrate one unit to the right (+1), one unit to the left (-1), or stay at the current position. After a cell moves, it enters a refractory period during which it is unable to move again for one time step.

We have a means of controlling the *global* probabilities p and q that a non-refractory cell will move the right and left, respectively during the next time step. As described in the previous section, a variety of external stimuli may be used for global control.

As shown in Fig. 2b, at time t, the cells are located at positions y_t^i, where i is the cell index. The cloud centroid is given by

$$Y_t = \frac{1}{N}\sum_i y_t^i \tag{1}$$

and the error between the centroid and its desired location is

$$e_t = r - Y_t \tag{2}$$

The behavior of each cell is modeled as shown in Fig. 3. Based on the current global control and the time histories of each cell, the probabilities will be $v^i = v^i\left(p, q, y_t^i, y_{t-1}^i\right)$ and $w^i = w^i\left(p, q, y_t^i, y_{t-1}^i\right)$ of moving forward and backward, respectively.

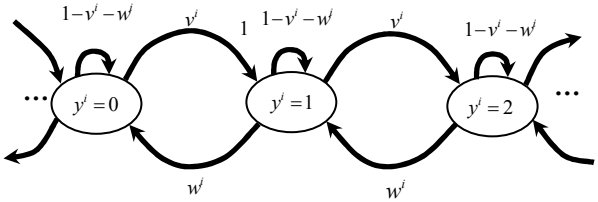


Figure 3: Output transition state model of i^{th} cell.

The probabilities v^i and w^i incorporate the refractory behavior by being conditioned on the cell's state during the current and previous time steps:

$$v^i\left(p,q,y_t^i,y_{t-1}^i\right)=\begin{cases}0, & y_t^i\neq y_{t-1}^i\\ p, & y_t^i=y_{t-1}^i\end{cases}$$
$$w^i\left(p,q,y_t^i,y_{t-1}^i\right)=\begin{cases}0, & y_t^i\neq y_{t-1}^i\\ q, & y_t^i=y_{t-1}^i\end{cases} \quad (3)$$

Thus, a cell refuses to move during the time step after its previous move. The full state of each cell is defined not only by its location y_t^i, but also by whether it was at that location in the previous time step.

Based on the position transition probabilities in Eq. (3), the expected position of each of the cells during the next time step can be written as

$$E\left[y_{t+1}^i \mid y_t^i=y_{t-1}^1\right]=y_t^i+p-q$$
$$E\left[y_{t+1}^i \mid y_t^i\neq y_{t-1}^1\right]=y_t^i \quad (4)$$

and the variance can be written as

$$Var\left[y_{t+1}^i \mid y_t^i=y_{t-1}^1\right]=p+q-\left(p-q\right)^2$$
$$Var\left[y_{t+1}^i \mid y_t^i\neq y_{t-1}^1\right]=0 \quad (5)$$

From Eqs. (4) and (5), the expectation of the centroid is

$$\begin{aligned}&E\left[Y_{t+1} \mid y_t^1,\ldots,y_t^N,y_{t-1}^1,\ldots,y_{t-1}^N\right]\\ &=\frac{1}{N}\left[\sum_{\forall i\ :y_t^i=y_{t-1}^i}\left(y_t^i+p-q\right)+\sum_{\forall i\ :y_t^i\neq y_{t-1}^i}\left(y_t^i\right)\right]\\ &=Y_t+\frac{N_t^R}{N}\left(p-q\right)\end{aligned} \quad (6)$$

where N_t^R is the number of cells that are outside of the refractory period, or *ready*, for their next transition. The variance of the centroid is given by

$$Var\left[Y_{t+1} \mid y_t^1,\ldots,y_t^N,y_{t-1}^1,\ldots,y_{t-1}^N\right]=\frac{N_t^R}{N^2}\left[p+q-\left(p-q\right)^2\right] \quad (7)$$

These statistics will be used in the next section for determining the statistics of the system state, which will later be used for developing a stable control law.

C. Controllable State

We are interested in controlling the aggregate behavior of the cell population, understanding that only global control is available. This means that if we consider the full system state to be the locations of all cells at the previous two time steps, we cannot expect state convergence. In fact, as will be discussed in Chapter III, the individual cell locations tend to diverge in time.

In order to consider stability (and develop a stable control law), we must define a system state that we have control authority over: the aggregate output. However, in general, it is not possible to write the state transition equations in terms of the aggregate output alone.

We can reduce the problem to state transition equations in terms of output alone by considering unilateral control so that there is zero probability that a cell will move to the left when $e_t>0$ and zero probability that a cell will move to the right when $e_t<0$:

$$p=\begin{cases}0, & e_t<0\\ p\left(e_t\right), & e_t>0\end{cases}$$
$$q=\begin{cases}q\left(e_t\right), & e_t<0\\ 0, & e_t>0\end{cases} \quad (8)$$

Under assumption (8),

$$N_t^R=\begin{cases}N-\left(\sum_{i=1}^N y_t^i-\sum_{i=1}^N y_{t-1}^i\right), & e_{t-1}>0\\ N+\left(\sum_{i=1}^N y_t^i-\sum_{i=1}^N y_{t-1}^i\right), & e_{t-1}<0\end{cases} \quad (9)$$

which is valid because there is no ambiguity due to some cells moving backward which would be present if bilateral transitions were allowed. It follows, then, that

$$N_t^R=\begin{cases}N\left(1-Y_t+Y_{t-1}\right), & e_{t-1}>0\\ N\left(1+Y_t-Y_{t-1}\right), & e_{t-1}<0\end{cases} \quad (10)$$

Now, assuming $e_t,e_{t-1}>0$, Eqs. (6) and (7) can be recast in terms of the aggregate output alone as

$$\begin{aligned}E\left[Y_{t+1} \mid y_t^1,\ldots,y_t^N,y_{t-1}^1,\ldots,y_{t-1}^N\right]&=\left(1-p\right)Y_t+pY_{t-1}+p\\ &=E\left[Y_{t+1} \mid Y_t,Y_{t-1}\right]\end{aligned} \quad (11)$$

$$\begin{aligned}Var\left[Y_{t+1} \mid y_t^1,\ldots,y_t^N,y_{t-1}^1,\ldots,y_{t-1}^N\right]&=\frac{p-p^2}{N}\left[1-Y_t+Y_{t-1}\right]\\ &=Var\left[Y_{t+1} \mid Y_t,Y_{t-1}\right]\end{aligned} \quad (12)$$

Equations (11) and (12) follow naturally for other conditions on the global error (i.e. $e_t,e_{t-1}<0$, $e_t>0,e_{t-1}<0$, $e_t<0,e_{t-1}>0$).

The previous equations mean that all information required to determine the system behavior during the next time step can be written in terms of the aggregate output during the previous two time steps. Thus, the full system state is

$$\mathbf{X}_t=\begin{bmatrix}Y_t & Y_{t-1}\end{bmatrix}^T \quad (13)$$

and the probability distribution of $\mathbf{X}_{t+1}$ is dependent on $\mathbf{X}_t$ alone, so the process is Markovian:

$$\Pr\left(\mathbf{X}_{t+1} \mid \mathbf{X}_t,\mathbf{X}_{t-1},\ldots\right)=\Pr\left(\mathbf{X}_{t+1} \mid \mathbf{X}_t\right) \quad (14)$$

The control problem can now be fit into a standard stochastic control analysis as described in the next section.

Before moving on, we should note that assumption (8) may seem artificial. However, it reduces the control architecture to a form that can be analyzed using standard stochastic control techniques. Also, it may not be unreasonable to assume that a cell, when needed at a certain location will have very low likelihood of traveling away from the location where it is required.

D. Stability Analysis

Since we are using a stochastic model to describe the cellular behavior, we cannot use traditional deterministic analysis to ascertain stability and a stable control law. Therefore we resort to a stochastic Lyapunov-like stability theory considered by Kushner [7],[8] and used by the authors' group for controlling stochastically behaving

cellular actuators in [5]. Conditions for asymptotic stability adapted from [7] and [8] are given in Theorem 1.

Theorem 1: Asymptotic Stability of Discrete Parameter System [7]

Let $V^S(\boldsymbol{\varepsilon})$ be a scalar-valued, non-negative function satisfying $V^S(\boldsymbol{\varepsilon}=\mathbf{0})=0$ and $V^S(\boldsymbol{\varepsilon})>0, \boldsymbol{\varepsilon}\neq 0$. Define $Q_m=\left[\boldsymbol{\varepsilon}: V^s(\boldsymbol{\varepsilon})<m\right]$, $m<\infty$. Let $\boldsymbol{\varepsilon}_0, \boldsymbol{\varepsilon}_1, \ldots$ be a vector valued discrete parameter Markov process, where $\boldsymbol{\varepsilon}_0$ is the initial condition in Q_m. If a non-negative, real, scalar function $k(\boldsymbol{\varepsilon}_t)$ exists such that the difference between $V^S(\boldsymbol{\varepsilon}_t)$ and the conditional mean $E\left[V^S(\boldsymbol{\varepsilon}_{t+1})\,|\,\boldsymbol{\varepsilon}_t\right]$ at time $t+1$ is bounded as

$$E\left[V^S(\boldsymbol{\varepsilon}_{t+1})\,|\,\boldsymbol{\varepsilon}_t\right]-V^S(\boldsymbol{\varepsilon}_t)\triangleq -k(\boldsymbol{\varepsilon}_t)\leq 0 \tag{15}$$

in Q_m, then $\boldsymbol{\varepsilon}_t$ converges to

$$\boldsymbol{\varepsilon}_t \to P_m = Q_m \cap \left\{\boldsymbol{\varepsilon}: k(\boldsymbol{\varepsilon})=0\right\} \tag{16}$$

with a probability no less than $1-V^S(\boldsymbol{\varepsilon}_0)/m$. If $V^S(\boldsymbol{\varepsilon})$ can be chosen such that *m* is arbitrarily large, then the probability of convergence is 1.

$V^S(\boldsymbol{\varepsilon}_t)$ is referred to as a stochastic Lyapunov function. Let us assume that we wish the centroidal position to converge to the reference, *r*, which is a constant. The origin of the state $\mathbf{X}_t$ can be shifted to satisfy the theorem by defining the new state

$$\boldsymbol{\varepsilon}_t=\begin{bmatrix} r & r\end{bmatrix}^T-\mathbf{X}_t=\begin{bmatrix} e_t & e_{t-1}\end{bmatrix}^T \tag{17}$$

Consider, then, the candidate Lyapunov function

$$V_t^S=\boldsymbol{\varepsilon}_t^T\mathbf{U}\boldsymbol{\varepsilon}_t; \qquad \mathbf{U}=\begin{bmatrix} 1 & -1/2\\ -1/2 & 1\end{bmatrix} \tag{18}$$
$$=e_t^2-e_te_{t-1}+e_{t-1}^2$$

which satisfies $V^S(\boldsymbol{\varepsilon}_t=\mathbf{0})=0$ and $V^S(\boldsymbol{\varepsilon}_t)>0,\ \boldsymbol{\varepsilon}_t\neq 0$.

For asymptotic stability, and to find a control law that provides stability, require $\Delta V_t^S\leq 0$, where ΔV_t^S is given by

$$\begin{aligned}\Delta V_t^S &\equiv E\left[V_{t+1}^S\,|\,x_t\right]-V_t^S\\ &=E\left[e_{t+1}^2-e_{t+1}e_t+e_t^2\,|\,\boldsymbol{\varepsilon}_t\right]-\left[e_t^2-e_te_{t-1}+e_{t-1}^2\right]\\ &=E\left[e_{t+1}^2-e_{t+1}e_t\,|\,\boldsymbol{\varepsilon}_t\right]+e_te_{t-1}-e_{t-1}^2\\ &=Var\left[e_{t+1}\,|\,\boldsymbol{\varepsilon}_t\right]+E\left[e_{t+1}\,|\,\boldsymbol{\varepsilon}_t\right]^2-e_tE\left[e_{t+1}\,|\,\boldsymbol{\varepsilon}_t\right]+e_te_{t-1}-e_{t-1}^2\end{aligned} \tag{19}$$

using $Var[e_t]=E\left[e_t^2\right]-E\left[e_t\right]^2$ to provide the last equality in Eq. (19).

Consider $e_t>0$ (a separate analysis must be done for $e_t<0$):

$$\Delta V_t^S=\frac{N_t^R}{N^2}\left[p-p^2\right]+\left[e_t-\frac{N_t^R}{N}p\right]^2-e_t\left[e_t-\frac{N_t^R}{N}p\right] \tag{20}$$
$$+e_te_{t-1}-e_{t-1}^2$$

where N_t^R is now defined by Eq. (10). For stability, $\Delta V_t^S\leq 0$:

$$\frac{N_t^R}{N^2}p(1-p)-\frac{N_t^R}{N}e_tp+\left(\frac{N_t^R}{N}\right)^2p^2+e_{t-1}(e_t-e_{t-1})\leq 0 \tag{21}$$

which is a convex quadratic in *p* (assuming $N_t^R>1$) with roots:

$$p_{1,2}=\frac{\frac{N_t^R}{N^2}(Ne_t-1)\pm\sqrt{\alpha}}{2\frac{N_t^R}{N^2}\left[N_t^R-1\right]} \tag{22}$$

where

$$\alpha=\left(\frac{N_t^R}{N}\right)^2(Ne_t-1)^2-4\left[N_t^R-1\right]\frac{N_t^R}{N^2}e_{t-1}(e_t-e_{t-1}) \tag{23}$$

and admissible transition probabilities: $0\leq p\leq 1$.

Equations (21) and (22) are written for $e_t>0$, which means that either $0<e_t\leq e_{t-1}$ or $e_{t-1}\leq 0<e_t$ under assumption (8). Either way, the quantity $e_{t-1}(e_t-e_{t-1})\leq 0$, which means that the left root $p_2\leq 0$, and that the stable control law is governed by 0 and the right root: $0\leq p\leq \min(1,p_1)$. Stable policies for $N_t^R=0,1$ are apparent from Eq. (21).

The complete control law guaranteed asymptotically stable by the stochastic Lyapunov function while $e_t>0$ is

$$p=\begin{cases}0\leq p\leq \max(1,p_1) & N_t^R>1\\ 0\leq p\leq \max(1,\mu) & N_t^R=1, e_t<1/N\\ 0\leq p\leq 1 & otherwise\end{cases} \tag{24}$$

where $\mu=N^2e_t(e_t-e_{t-1})/(Ne_t-1)$.

The control law for $e_t<0$ can be developed similarly. Since a stable control law is available for every e_t and e_{t-1}, *m* is arbitrarily large and the probability of convergence is 1.

III. Cell Cloud Dispersion

A. Dispersion under Current Model

A key feature of our control strategy is that we are controlling the aggregate behavior of the cell cloud and we have no command authority over individual cells. Since each cell moves stochastically and independently, the cell cloud will be more likely to spread out the longer the cloud is allowed to behave stochastically. This idea can be quantified by considering the variance of the distance, d^{ij}, between any two cells *i* and *j*.

Assume that particle *i* has undergone R_t^i non-refractory, or *ready*, time steps and particle *j* has undergone R_t^j *ready* time steps at time *t*. Say that the cells start at a distance $d_0^{ij}=0$ at time $t=0$ and say that the random variable describing the change in distance from the motion of cells *i* and *j* are δ_k^i and δ_k^j, respectively where the *k* index denotes an instance

that each cell has been in the *ready* state. The distance between the cells at time *t* is given by

$$d_t = \sum_{k=1}^{R_t^i} \delta_k^i + \sum_{k=1}^{R_t^j} \delta_k^j \tag{25}$$

The probability mass function for δ_k while the control law broadcasts movement to the right, $q = 0$ and $p = const$, is given by Table I, where the lack of superscript indicates either cell under consideration.

Table I: Probability mass function of δ_k while $q = 0$, where *a* is 1 for the cell to the right and -1 for the cell to the left.

δ_k	0	a
$\Pr(\delta_k)$	1-p	p

From the probability mass function,

$$Var[\delta_k] = p - p^2 \tag{26}$$

regardless of *a*.

Thus the variance of the distance between two arbitrary cells is given by

$$Var[d_t] = (R_t^i + R_t^j)(p - p^2) \tag{27}$$

Note that Eq. (27) is still valid if the cells change place, (left-to-right) but that detail is omitted for simplicity. Since R_t^i and R_t^j are monotonically non-decreasing, a consequence of Eq. (27) is that the dispersion of the cell cloud is bounded only by the distance that the cloud must travel, or the number of time steps that the cells are behaving stochastically. Thus, while the output centroid of the cell cloud can be stably controlled, the cloud itself may be diverging.

Even though the cloud may be diverging, the global control framework is still useful. In general, when controlling the development of a vascular structure, or other biological structure, the exact location of all structural cells does not need to be controlled. It may be the case that the cellular structure only needs to propagate in a general direction. In controlling angiogenesis, for example, it may only be necessary that more vasculature is provided to a region of ischemic tissue. It is not necessary to pinpoint control the locations of the growing blood vessels.

B. Expected Time to Travel and Expected Dispersion

Two important questions regarding cell cloud control are how long will it take for the centroid to converge to the reference, and how much variance is there in the cloud at that time? Beginning with the first question, consider a reference at *r* and a cell cloud centroid beginning at position $Y = 0$. In the ensemble sense, then, the expected number of forward movements, Z, of a particular cell is

$$E[Z] = r \tag{28}$$

Then, the expected number of times that cell is in the *ready* state, N_R, before reaching the reference, *r*, can be found using the law of iterated expectations

$$E\left[E\left[\sum_{k=1}^{N_R} \delta_k \mid N_R \right] \right] = r \tag{29}$$

From Eq. (29) and knowing that δ_k are i.i.d.,

$$E[N_R] = \frac{r}{E[\delta_k]} \tag{30}$$

where $E[\delta_k] = p$ from Table I with $a = 1$. Finally, the expectation of the time, *T*, to convergence is approximated by

$$E[T] \approx \frac{r}{p} + r \tag{31}$$

where the additional *r* is due to the refractory time required after each cell transition. It should be noted that this is an approximation of the expected convergence time assuming that the controlled transition probability, *p*, is approximately constant during the majority of the cell travel. However, *p* is not constant as the centroid approaches the reference, as given by the control law (24). The answer to the second question follows from Eqs. (30) and (27) to yield that the variance (in the ensemble sense) of the distance between any two cells is approximated by

$$Var[d_T] \approx 2\frac{r}{E[\delta_k]}(p - p^2) = 2r(1 - p) \tag{32}$$

IV. SIMULATION

A. Control to Fixed Reference

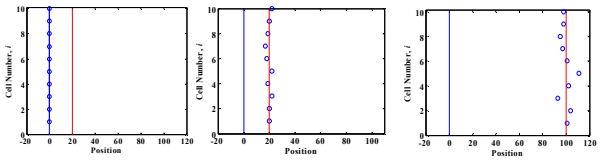
There are a number of different ways that we may wish to control the cell cloud. As one example, a region of ischemic tissue may require perfusion, and endothelial cells may need to travel from nearby existing vasculature. Thus, we simply want the cells to travel as quickly as possible from their current location to the ischemic site.

To see how our control scheme works, consider a cloud of $N = 10$ cells that need to be moved from a starting location to the ischemic site, and that do not possess any local regulatory mechanisms. It may seem strange to consider only 10 cells traveling from a previously existing vasculature. However, as previously mentioned, we are currently considering only the simple case of moving independent cells where they need to go. It may seem more realistic if the cells are thought of as vascular sprout tip cells, each acting independently of the other sprouts, and trying to make its way to the ischemic region.

One important point is that, in practice, it is not possible to control cell behavior deterministically. For example, if the reference location is to the right of the cell centroid, we cannot modulate the probability of moving to the right to $p = 1$. Thus, for these simulations, we will assume that the maximum attainable probability authority is 0.5 in either direction. Figure 4a shows the cloud of cells, all started at position $y_0^i = 0$. The cells are controlled to a static location $r = 20$ (Fig. 4b) and separately to $r = 100$ (Fig 4c) using the maximum stable transition probability guaranteed stable by Eq. (24).

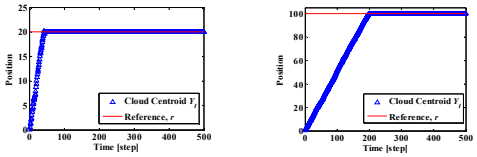
Figure 5 shows the behavior of the cell cloud centroid. Even though the cell cloud further disperses with greater the

distance the centroid has to travel, the centroid still converges to the correct reference.



(a) (b) (c)

Figure 4: Cell cloud started at position 0 (a); and controlled to centroidal positions $Y = 20$ (b); and $Y = 100$ (c).



(a) (b)

Figure 5: Cell cloud centroid vs. time controlled to $Y = 20$ (a); and $Y = 100$ (b).

Running the experiment 100 times for each reference, the average spatial variance of the cell cloud is 11.4 units squared for $r = 20$ and 47.8 for $r = 100$. Using Eq. (32), multiplied by a factor of ½ (to look at the spatial variance of a cell instead of the distance between two cells) the expected spatial variance of an ensemble of cells with centroid traveling 20 units and transition probability $p = 0.5$ is approximately 10, while the expected variance of traveling is approximately 100 units is 50. Thus the simulation matches with the analytical result. The simulation average result would converge to the analytical result as the number of trials is increased.

B. Trajectory Control

Another way we may wish to control the cell cloud is along a particular trajectory. For example, a new tissue bed may be growing, like an artificial muscle, that requires a vasculature to grow along with it. The vasculature cannot grow too slowly because the muscle will not be provided sufficient nutrients to keep growing or maintain health in the newly grown tissues. Additionally, the vasculature cannot attempt to grow beyond the bounds of the tissue because it will not form properly and may interfere with the tissue development.

Here we consider an exponential tissue growth requiring an exponential centroid trajectory starting at position 0 and terminating at 100 units. For the trajectory to be trackable, it is important that the rate of travel of the reference location is less than the maximum expected rate of travel of the cell centroid, which is given as

$$E\left[\frac{Y_{t+1}-Y_t}{\Delta t}\right]_{\max} = \frac{E[\delta_k]_{\max}}{E[\delta_k]_{\max}+1} \tag{33}$$

where δ_k is the random variable describing the movement of an arbitrary cell that is in the ready state. Our maximum transition probability is $p = 0.5$, so $E[Y_{t+1} - Y_t / \Delta t]_{\max} = 1/3$. The exponential trajectory tracking is shown in Fig. 6.

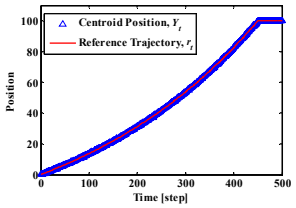


Figure 6: Reference trajectory and cell cloud centroid vs. time.

V. Interaction and Variance Control

A. Cellular Interaction

Cell dispersion is not something we would expect to see in a real biological system. Biological processes possess local regulatory mechanisms that guide cellular behaviors based on local requirements and conditions. For example, endothelial cells remain adjacent to each other and do not scatter when forming a new blood vessel. This chapter considers incorporating local control into the system model, but has to require that the location of each cell is directly measurable at each time step.

There are many mechanisms that locally regulate cell behavior. Here we consider laws for intercellular attraction. Cellular attraction is one way to moderate the spatial variance of a cell cloud developed by global randomness. In fact, it may be possible to harness the opposing forces of cell attraction and global randomness to control the spatial variance of a cell cloud in addition to its centroid. The theoretical development of Chapter II required a unilateral broadcast control scheme so that the number of *ready* cells could be determined from the aggregate output alone. However, if bilateral transitions (i.e. $p, q > 0$) were allowed in addition to intercellular attraction, it can be possible to control the variance of the cell cloud in addition to the centroid.

For the following development, we remove the cellular refractory period for simplicity. This means that all cells are ready at each time step. Also for simplicity, we will assume that cellular interactions add with the 'forces' broadcast from the local controller. Thus, the probabilities of transitioning right and left become

$$v_i = \begin{cases} \min(p+\xi,1), & \xi > 0 \\ p & otherwise \end{cases}$$
$$w_i = \begin{cases} \min(q-\xi,1), & \xi < 0 \\ q & otherwise \end{cases} \tag{34}$$

where ξ is the attractive 'force' due to cellular interactions. Here we consider both a linear attraction law

$$\xi = \gamma \sum_{j=1}^{N} \left(y_t^j - y_t^i\right) \tag{35}$$

were γ is a parameter and an inverse square law

$$\xi = \sum_{j=1}^{N} \frac{\upsilon}{\left(y_t^j - y_t^i\right)^2 - \beta} \tag{36}$$

where β and υ are parameters.

B. Variance Control

If we are considering cellular interactions in developing the control law, the aggregate output is not good enough and we need to know the location of each cell (which we assume can be directly measurable). We then define a new system state

$$\tilde{\mathbf{X}}_t = \begin{bmatrix} y_t^1 & \cdots & y_t^N \end{bmatrix}^T \tag{37}$$

which completely defines the system behavior during the next time step and we define the quantities we wish to control to zero:

$$\mathbf{Z}_t\left(\tilde{\mathbf{X}}_t\right) = \begin{bmatrix} (r - Y_t) & (u - S_t) \end{bmatrix}^T \tag{38}$$

where u is the desired spatial variance and the spatial variance is

$$S_t = \frac{1}{N}\sum_{i=1}^{N}\left(y_t^i - Y_t\right)^2 \tag{39}$$

From the work in [7], Theorem 1 can be generalized to guarantee asymptotic stability of $\mathbf{Z}_t$ if a Lyapunov function satisfying $V^S\left(\mathbf{Z}=\mathbf{0},\tilde{\mathbf{X}}\right)=0$ and $V^S\left(\mathbf{Z},\tilde{\mathbf{X}}\right)>0, \mathbf{Z}\neq 0$ can be obtained. We propose the function

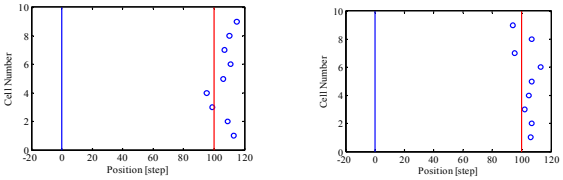
$$V_t^S = \left(r - Y_t\right)^2 + \left(u - S_t\right)^2 \tag{40}$$

and require $\Delta V_t^S < 0$, as in chapter II.

Unfortunately, it is not possible to obtain an analytically expressed control law for p and q because of the number of terms involved due to cellular interaction and the fourth moment of Y_t in ΔV_t^S due to squaring of a variance . Thus, p and q satisfying $\Delta V_t^S < 0$ have to be determined using a search algorithm. Whether a stable control law exists depends on the parameters in Eqs. (35) and (36).

C. Simulation

We will again consider the case of cells moving from a start location at 0 to a reference location $r = 100$. In addition, we choose a spatial variance reference $u = 30$. Figure 7a shows the cell cloud after 500 time steps with the linear control law and $\gamma = 0.00001$. The final centroid is $Y = 107.4$ and the variance is $S = 34.0$. Figure 7b shows the same simulation for the inverse square control law with $\nu = 0.0001$ and $\beta = 0.01$. The final centroid is $Y = 103.8$ and the variance is $S = 30.2$. Since the variance is controlled to a nonzero reference, p and q will always be positive and thus there will always be wander in all of the cell locations as well as centroid and variance.



(a) (b)

Figure 7: Cell cloud controlled to centroid location $Y = 100$ and variance $S = 30$ using linear attraction model (a); and inverse square attraction model (b).

VI. Conclusions and Future Work

This work has proposed a broadcast feedback control framework for controlling the position of a population of cells. The controller uses the aggregate output of the population, its centroid, to modulate the cellular transition probability, which is broadcast to the population. With broadcast control only, aggregate behavior is shown to be stably controllable even though the cell cloud is diverging. An approximate measure of expected cloud variance given distance to travel and transition probability authority was given. Theory validity was confirmed by simulation. Acknowledging that cell behavior is not divergent in real cell populations, we proposed intercellular attraction as a means of controlling spatial variance. By harnessing bilateral transitions it is possible to control the spatial variance of groups of attractive cells. However, to implement such a scheme, direct measurement of all cell locations is required.

The authors are currently working to extend the control framework presented in this paper in two ways. First, we are working to eliminate the unilateral transition requirement when only an aggregate output is available. Secondly, we wish to incorporate more realistic local regulatory dynamics into the behavioral model and stability analysis.

In the future, we will also extend the cell model to include cellular interactions, mechanical interactions in the form of shear forces, dividing, death, continuous motion in 3 dimensions, and the relationship between chemical stimulus and cell transitional behavior.

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