Stochastic Cellular Automata in Vascularized Tissue Regeneration Model

submitted by

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1 Introduction

1.1 Cellular Automata in Biology

Tissue regeneration following a traumatic injury is a mechanistically controlled biological process that involves cell proliferation, migration, angiogenesis, and remodeling of the extracellular matrix at its location. Failure of this successful regeneration often results in necrosis or scar formation (also called keloid when present on the surface of a skin). To understand how cellular decisions interact spatially to produce emergent tissue architecture, the rules of Cellular Automata (CA) can be used.

A Cellular Automaton is a discrete, rule based dynamics in which each one of the spatial element evolves according to its current states and also takes into consideration of its local neighbors. Although biological tissue contain various complex highly regulated multi-state continuous entities and factors which determine the fate of re-development of the injured tissue, CA can be used to offer a biologically interpretable abstraction which captures the local interaction rules while preserving the spatial structure and temporal evolution. This project replicates the process of tissue regeneration and angiogenesis (blood vessel formation) in higher order animals following a traumatic injury.

1.2 The Vascular Regeneration Model

The vascular regeneration model is constructed as a two dimensional stochastic cellular automaton in which each of the lattice site represents a discrete tissue element corresponding to a small spatial unit of a limb cross section. The grid itself approximately represents a mesoscopic tissue organization, where local cell cell interactions determine survival, proliferation and degeneration.

Each lattice site (i, j) is assigned to one of the state variable :

$$S_{ij}(t) \in \{B, M, S, V, N, Sc\}$$

- **Bone (State B):** The central support structure. In this model, it is spatially fixed at the center by radial anatomical constraints.
- **Muscle (State M):** The primary tissue requiring high oxygen. These muscle sites are capable of participating in regenerative expansion, given that the adjacent tissue exists and probabilistic growth conditions are satisfied.
- **Skin (State S):** The outer protective layer. In this model, it defines the boundary of the anatomical domain and it doesn't exhibit vascular dependent necrosis within the simplified rule set.
- **Vessel (State V):** The source of oxygen and growth factors.Instead of modeling complex continuous oxygen diffusion, the system approximates vascular influence through local adjacency rules. A lattice site is considered vascularity supported if at least one neighboring site is in the Vessel State. Vessel sites can sprout into adjacent empty regions within the injury domain, mimicking angiogenic expansion and the presence of vessels reduces the probability of formation of necrotic sites in muscles and promotes regenerative recovery.

- **Necrosis (State N):** Dead tissue resulting from ischemia (lack of blood). Muscles lacking adjacent vascular support undergo transition to necrosis with a probability $p_{necrosis}$. Necrosis also represent a transient pathological state that may later transition into fibrotic tissue.
- **Scar (State Sc):** Fibrotic tissue replacing necrotic cells. This tissue is non functional and doesn't revert back to muscle in this system and the sites in necrotic state transition to scar tissue with probability p_{scar}.

2 Mathematical Framework

2.1 Lattice and Neighborhoods

The tissue is defined as a grid L of size 100×100. The state of a cell at location (x, y) at time t is $C^t_{(x,y)}$.

Von-Neumann neighborhood is utilized to compose the central cell and its four orthogonal neighbors (Up, Down, Left, Right). This type of 2D neighborhood is used to represent paracrine scale biological signaling where a cell senses only adjacent neighbors.

$$N_{(x,y)} = \{C^t_{(x,y-1)}, C^t_{(x,y+1)}, C^t_{(x-1,y)}, C^t_{(x+1,y)}\} \tag{1}$$

2.2 Initial Conditions

The initial condition establishes a biologically accurate cross-section. Concentric circles define the layers of Bone, Muscle, and Skin. Initial blood vessels are seeded randomly within the muscle tissue with a probability density of $\rho = 0.08$.

The anatomical geometry is encoded using radial distance from the center :

$$r = \sqrt{(x - x_c)^2 + (y - y_c)^2}$$

where (x_c, y_c) is the grid center. And the tissue layers are defined as:

$$C^0_{(x,y)} = \begin{cases} B & r \leq 15 \\ M & 15 < r \leq 38 \\ S & 38 < r \leq 42 \\ \emptyset & r > 42 \end{cases}$$

Where $\emptyset$ is the empty region. This equation establishes a biologically consistent cross section.

3 Rules of Evolution

The simulation evolves based on stochastic transition rules. In every time step, a random variable $R \in [0, 1]$ is generated.

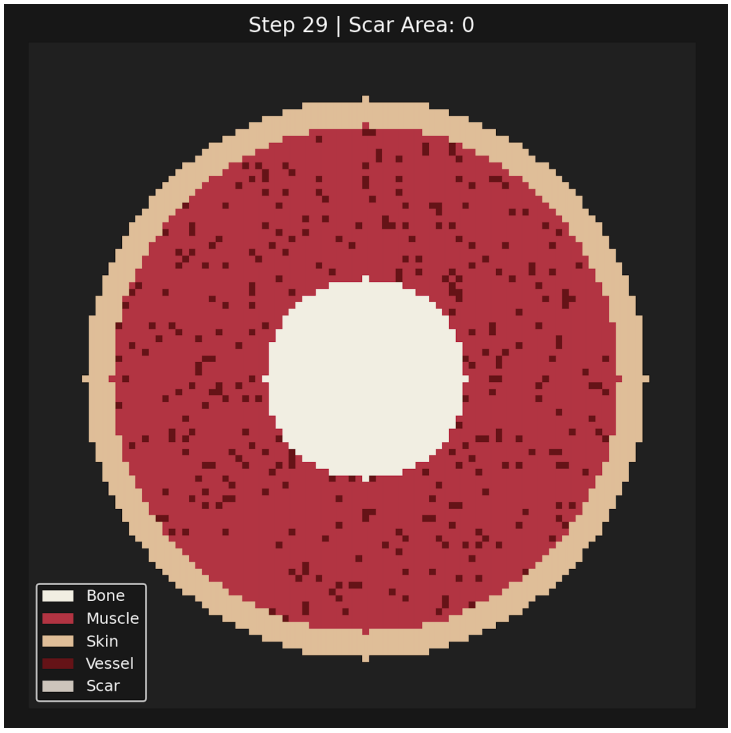


Figure 1: **Initial Condition:** The grid represents a limb cross-section. Central gray is Bone, Red is Muscle, Outer layer is Skin. Dark spots represent initial blood vessels.

3.1 Rule 1: Tissue Regrowth

Healing moves from the healthy edge to the wound.
The Cells divide to fill empty space caused by injury. This creates a moving boundary problem.

$$C_{(x,y)}^{t+1} = \text{Tissue} \quad \text{if } \exists n \in N_{(x,y)} \neq \emptyset \text{ and } R < P_{growth} \tag{2}$$

Where $P_{growth} = 0.55$. This simulates the biological contact guidance of mitosis.
If the conditions are met, then the cell differentiates based on its radial distance r from the center:

$$C_{(x,y)}^{t+1} = \begin{cases} B & r \leq 15 \\ M & 15 < r \leq 38 \\ S & 38 < r \leq 42 \end{cases}$$

3.2 Rule 2: Angiogenesis (Vessel Sprouting)

Hypoxic tissue release VEGF-mediated vessel expansion (Vascular Endothelial Growth Factor), hence new vessels branch from existing ones to oxygenate the regenerating tissue.

$$C_{(x,y)}^{t+1} = \text{Vessel} \quad \text{if } \exists n \in N_{(x,y)} == \text{Vessel and } R < P_{vessel} \tag{3}$$

Where $P_{vessel} = 0.10$. This is significantly slower (5.5 times) than tissue growth, creating a "lag" in oxygen supply. Thereby generating the ischemic zones.

3.3 Rule 3: Necrosis and Scarring

If muscle regenerates but blood vessels have not yet reached it, no ATP generates due to lack of oxygen and the tissue dies (Ischemia). Finally the dead tissue us replaced by

collagen.

$$C_{(x,y)}^{t+1} = \text{Necrosis} \quad \text{if } \forall n \in N_{(x,y)} \neq \text{Vessel and } R < P_{necrosis} \tag{4}$$

Given that, $p_{necrosis} = 0.04$. Although the rate is small, the cumulative survival probability over T (let T=50) steps is:

$$(1 - P_{necrosis})^T$$

$$(0.96)^{50} \approx 0.13$$

Hence, prolonged ischemia almost guarantees death. Subsequently, necrotic tissue converts to Scar tissue with probability $P_{scar} = 0.20$. This scar tissue formation is the final step and it doesn't revert.

4 Simulation Results

4.1 The Injury Event

At $t = 30$, an amputation event occurs, removing a wedge of tissue. This resets a portion of the grid to the Empty state ($\emptyset$).

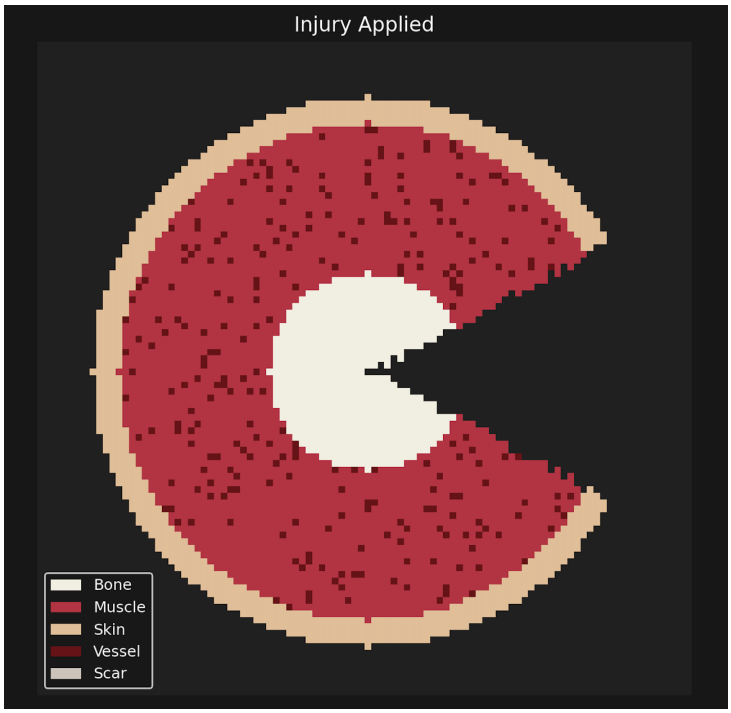
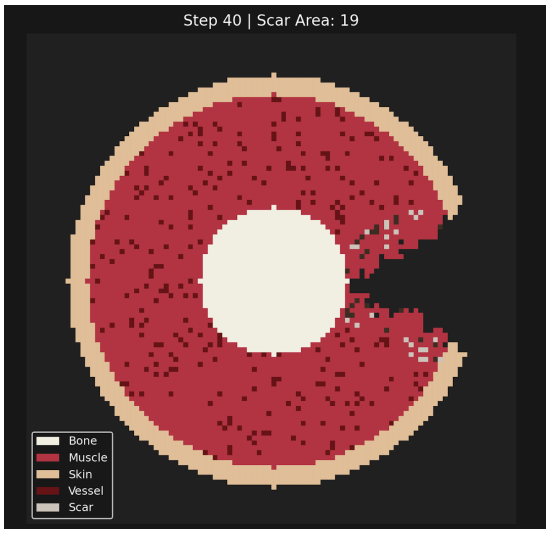


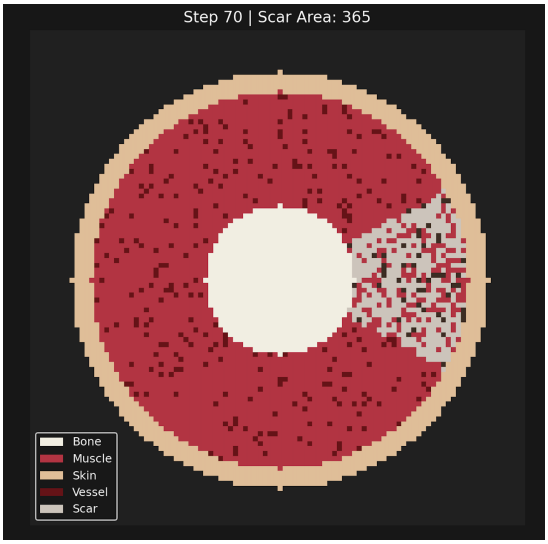
Figure 2: **Injury Event:** A wedge is removed from the tissue at $t = 30$, simulating a traumatic wound.

4.2 Progression of Healing

We observe the race between healthy regeneration and necrosis. The following figures show the state of the tissue at different time steps.

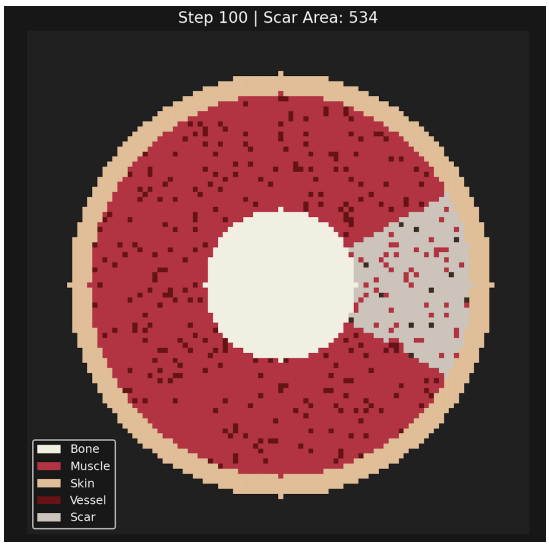


(a) Step 40: Initial Rapid Regrowth

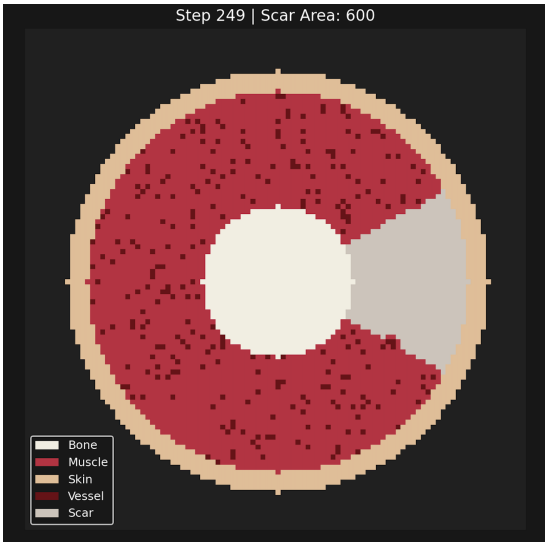


(b) Step 70: Regrowth of Tissues

Figure 3: **Evolution of the Wound:** (a) Tissue begins to close the gap, but vessels (dark red) lag behind. (b) Areas lacking vessel supply turn to Scar tissue (Grey)and presence of Necrotic Tissue (Black)



(a) Step 150: Formation of Scar



(b) Step 249: Completion of Healing

Figure 4: **Evolution of the Wound:** (a) The wedge is filled completely and scar tissue is rapidly forming (b) Total completion of healing only with scar tissue and no necrotic tissue is present.

5 Analysis

The stimulation demonstrates that the angiogenic growth rate parameter p_{vessel} acts as a primary limiting factor in successful tissue regeneration. While tissue regrowth occurs with probability $P_{growth} = 0.55$, vascular sprouting occurs more slowly at $P_{vessel} = 0.10$.

Because

$$P_{vessel} \ll P_{growth}$$

regenerating muscles advances spatially faster than the vascular network can oxygenate it. Hence, this mismatch produces the transient ischemic regions within the newly formed tissue.

Quantitatively, the five fold difference between growth and vessel probabilities implies that tissue outpaces oxygen delivery at a significant speed. This results in an imbalance where the newly formed muscles lack adjacent vascular support, thus triggering necrosis according to $P_{necrosis} = 0.04$.

In the following steps, scar formation emerges as a secondary effect of vascular insufficiency. When the regenerating muscles remain without vascular proximity, the cumulative survival probability decreases exponentially:

$$P(\text{survival over } T \text{ steps}) = (1 - P_{necrosis})^T$$

Necrotic tissue subsequently converts to scar with the probability of $P_{scar} = 0.20$. Hence, the scar patches represent the regions where metabolic demand exceeded oxygen supply and importantly it is the final stage of this model.
If in this model the P_{vessel} were to be increased which is analogous to the therapeutic VEGF enhancement, the vascular front should expand more rapidly to the injury zone and thus decreasing the rate of muscle sustainment and decrease the rate of formation of necrotic tissue and scar tissue.

Therefore, the "patchy" nature of the regeneration is a direct result of the Stochastic Cellular Automata method. Unlike differential equations which give smooth curves, CA captures the noisy and granular nature of biological growth. These fluctuations ultimately generate :

- Isolated necrotic islands
- Irregular scar clusters
- Nonuniform vessel penetration patterns

6 Conclusion

This cellular automaton framework captures the core spatial competition underlying tissue regeneration by coupling local tissue proliferation with vascular expansion. The simulation demonstrates that regenerative success depends not simply on the rate of mitosis but also on the temporal synchronization between the tissue growth and oxygen delivery. The discrete and stochastic architecture of the cellular automaton also reproduces the heterogeneous, patch morphology characteristic of real wound healing. These results provide both a visual and mathematical illustration that ischemic failure can be interpreted as a spatio-temporal synchronization problem between expanding tissue and its vascular support.
The code for the simulation is available at :
`https://github.com/BrometryDash/LaggingVessels_CA`

7 Limitations

This model makes several assumptions which simplifies the outcome but limits its biological realism. Vascular support is represented as a binary neighbour effect rather than a continuous oxygen diffusion field, and this model doesn't also involves reaction diffusion equations or any metabolic gradients. The complexity of the section of tissue is also reduced to only muscles and vessels whereas in real life conditions muscles don't even regenerate, the whole section preferably dedifferentiates and then rediffrentiates to make new cell types which eventually constitute the whole amputated section. Finally, the model is restricted to a two-dimensional lattice, whereas real tissues proliferate in a three-dimensional complex geometry.

References

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