Mathematical model suggests mechanism of action for connexin mimetic peptide Gap27 to accelerate wound healing

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Introduction

- In the U.K., **wound care costs** the NHS around **£5 billion a year** – about 4% of total annual expenditure.
- Connexin mimetic peptide **Gap27** is a promising wound healing therapeutic, shown to **accelerate healing** in a number of experimental models [1,2].
- Gap27 works by binding to sub-components of cellular hemichannels and gap junctions, called **connexins**.
- The exact **mechanism of action** by which Gap27 can accelerate healing is unclear and **not yet established** in the experimental literature.
- We investigate how Gap27 might modulate cell migration behaviour during healing using **mathematical modelling** and computational simulations.

Aims:

- We propose a mathematical model to describe cell migration influenced by connexin-based cell-cell interactions and include Gap27 binding kinetics.
- We test the model within a 2-d domain inspired by the configuration of an experimental scrape wound assay and explore how Gap27 may work to influence wound closure through *in silico* simulation.

Methods

- The model is based on an **Ornstein-Uhlenbeck** process to describe cell migration.
- Cells within the domain **interact** based on **proximity** and a coupled dynamical model for **connexin 43 cycling** with Gap27 binding kinetics *(see Figure 1)*.

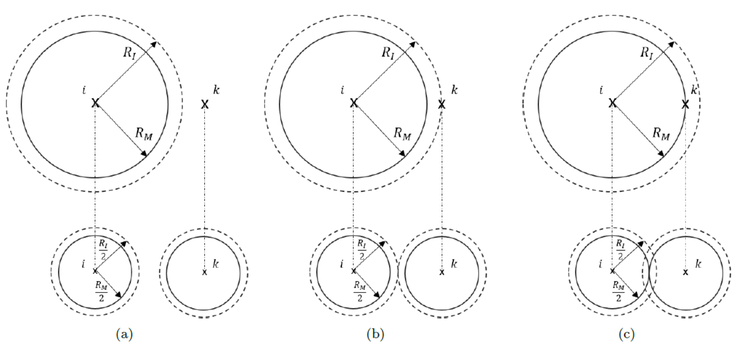

Figure 1: Cell-cell interaction scenarios considered in the model: (a) cells i and k are too distant to interact, (b) cells i and k interact and (c) cells i and k collide rather than interact.

Methods (cont'd)

- Model: $\boldsymbol{v}^i(t)$ is 2-d **velocity** for cell i at time t, with $\boldsymbol{f}^i(t)$ the associated position, *Eq. (1)*.
- $\boldsymbol{C}^i(p)$ is **directional bias** from interaction with cells from a surrounding population $k = 1, \dots, N$, $k \neq i$, *Eq. (2-3)*.
- $\mathbf{W}(t)$ is the 2-d **Wiener** process, α and β are parameters.

$$d\boldsymbol{v}^i(t) = \Big(\boldsymbol{C}^i(p) - \beta \boldsymbol{v}^i(t)\Big)dt + \sqrt{\alpha} d\boldsymbol{W}(t), \qquad (1)$$

$$\boldsymbol{C}^i(p) = \sum_{k=1, k\neq i}^{N} \boldsymbol{c}^k. \qquad (2)$$

$$\boldsymbol{c}^k = \begin{cases} \mathbf{0}, & \| \boldsymbol{f}^i(t) - \boldsymbol{f}^k(t) \| > R_I. \\ \boldsymbol{F}(p), & R_M < \| \boldsymbol{f}^i(t) - \boldsymbol{f}^k(t) \| \leq R_I. \\ \mathbf{0}, & \| \boldsymbol{f}^i(t) - \boldsymbol{f}^k(t) \| \leq R_M. \end{cases} \qquad (3)$$

- Cell-cell interaction strength depends on **total gap junction plaque concentration**, $p(\tau)$, derived from the coupled connexin 43 cycling model *(see Figure 2)*.

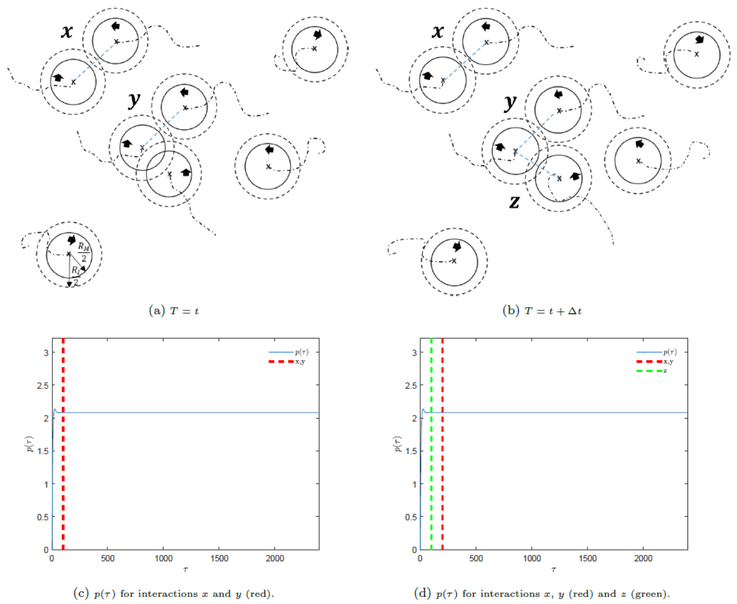

Figure 2: Time-dependency of $p(\tau)$ in the model. (c) shows $p(\tau)$ (red dash) for both interactions x and y at $T = t$ shown in (a). (d) shows $p(\tau)$ (red dash) for interactions x and y (red dash) and z (green dash) at $T = t + \Delta t$ shown in (b).

Results

- We organise the **spatial domain** to approximate the characteristic conditions of a 2-d **scrape wound assay** (central wound, high cell density).
- Results showed **cells** to **cluster** and the **wound** to remain **unpopulated** over time if total plaque concentration $p(\tau)$ was high *(see Figure 3, left)*.
- The introduction of **Gap27 significantly reduced cell clustering** and prompted full population **invasion of the wound** over time *(see Figure 3, right)*.

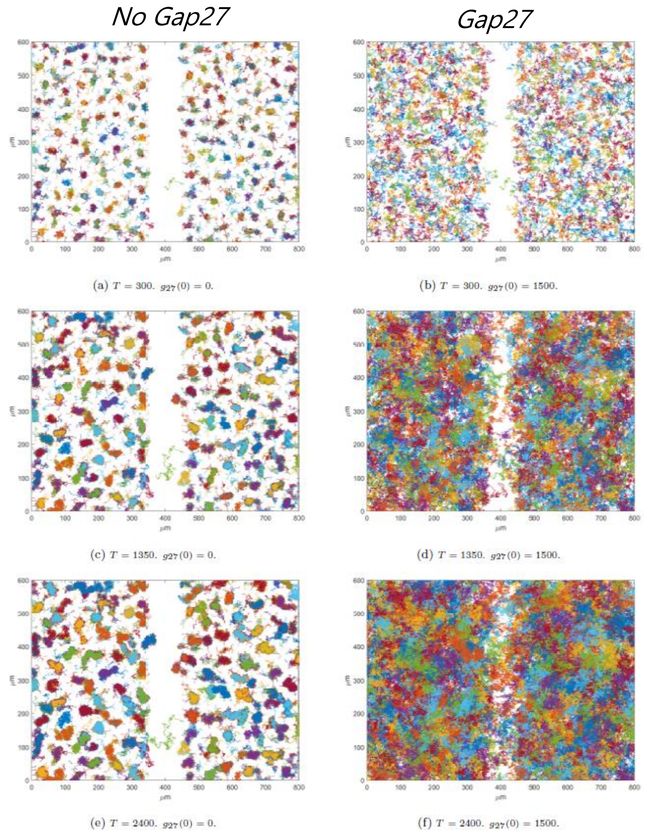

Figure 3: Model migration trajectories across the spatial domain at time points $T = 300$, $T = 1350$ and $T = 2400$ (rows) with no Gap27 (left) and with Gap27 (right), when $p(\tau)$ is large.

Conclusions:

- Simulations showed introduction of **Gap27 significantly improved population invasion** when total plaque concentration $p(\tau)$ was high.
- Study **suggests potential mechanism** for the preservation of chronic wound pathologies; gap junction plaque-based cell clustering.
- Also suggests introduction of **Gap27 could rescue healing** by blocking cell-cell interactions reducing plaque-based cell clustering, **prompting** cells to adopt a more **migratory phenotype**.

References:
[1] Pollok, et al., 2011. *Journal of cellular and molecular medicine, 15*(4), pp.861-873. [2] Wright, C.S. et al., 2009. *Wound repair and regeneration, 17*(2), pp.240-249.

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