**Title: Constructing computational models simulating burn wound healing.**

## Background:

Perfect skin regeneration of burn wounds remains a challenge. There is still a lack of fundamental understanding of the interactions between different cell types, complex cell signalling networks and mechanical feedback loops during the wound healing process. Previous efforts have focused on constructing dynamic computational frameworks simulating cutaneous wound healing [1,2,3], but have not focused on burn wound healing.

In addition, dynamic computational models have been used to study the inflammation process in wound healing. Presbitero et al. [4] constructed a validated numerical systemic inflammation model under clinical treatment conditions of the Alkaline Phosphatase enzyme. Alkaline phosphatase (AP) exhibits anti-inflammatory effects by dephosphorylating inflammation triggering moieties (ITMs) like bacterial lipopolysaccharides and extracellular nucleotides.

These models are all not burn wound specific, therefore adjustments or an expansion of these models are demanded, to simulate the burn wound procedure. The link between the AP model and the cutaneous wound healing models, has not been investigated/found yet. By first performing a literature review focused on possible connections, this will be investigated. Constructing a computational model simulating burn wound healing would be a step forward towards a better understanding of dynamical adaptation to heal burn wounds.

**Research Question:**

What are the main factors influencing the burn wound healing procedure and how well can this procedure be modelled?

**Subquestions:**

What causes a better healing of burn wounds?

What is the link between the AP model and the cutaneous wound healing model?

## Approach

A mechanistic computational model based on literature knowledge will be constructed, which will eventually be clinically validated. To accomplish this, a number of experimental burn models will be studied on cellular behaviour/pathways affected by burns. We aim to design an Agent-based model combining the AP with the adjusted cutaneous wound healing model (adjusted in a way to fit the burn wound healing procedure). All previous efforts were programmed in Python, so using the python language, combined models will be built. Agent-based modelling is an object-oriented, rule-based, and discrete event computational modelling technique well suited for modelling cellular behaviour.

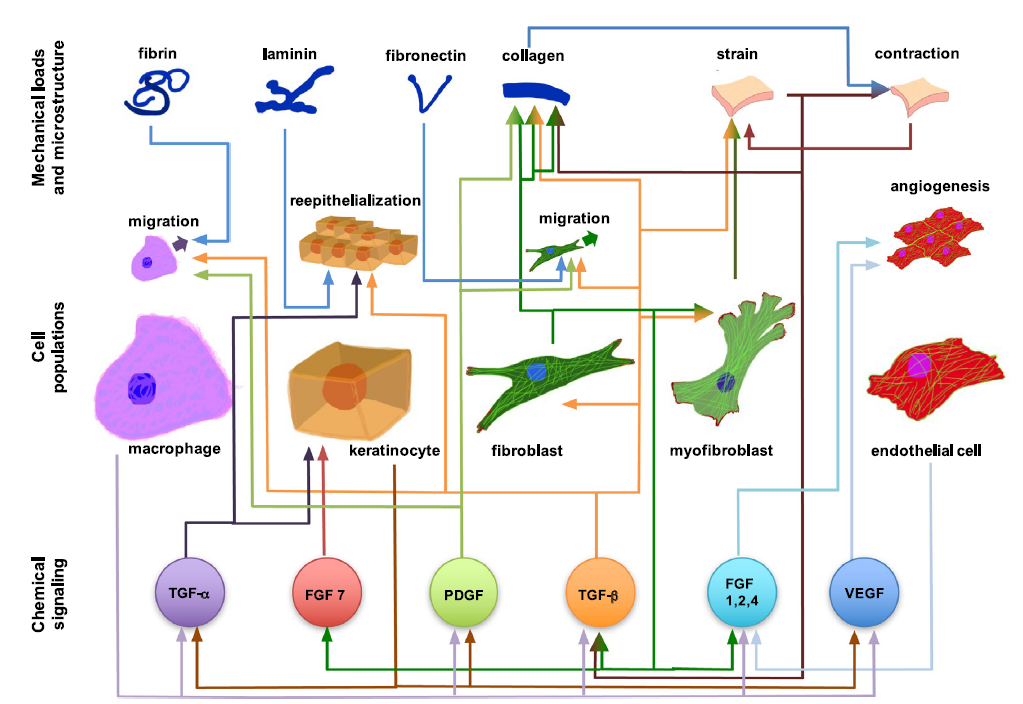
## Objectives

We hope to deliver a novel computational framework to simulate the healing of burn wounds. The model will bring together the found knowledge on continuum mechanics, growth and remodeling of cells. The model will be validated against clinical data from patient. Clinical trials will be performed with in cooperation with the ‘brandwondenstichting’. With this we hope to gain new insights in the influences of the different mechanics involved with burn wound healing.

**Difference with normal Wound Healing**

* Hemostasis:
* Inflammation:
* Proliferation:
* Remodeling:

What differences in this pathway?



### Model Spatio-temporal Wound Domain (Geometrical Considerations):

In order to examine the role that the wound shape or surface extent plays in the healing process, a 3d model will be constructed.

3 zones:

* Coagulation: This is the central part of burns with complete coagulative necrosis.
* Stasis: Zone of stasis is at the periphery of zone of coagulation. The circulation is sluggish in this zone but it can recover after early and adequate resuscitation, and proper wound care.
* Hyperemia: This is peripheral to zone of stasis. It is the result of intense vasodilatation as is seen in inflammatory phase after the trauma. This eventually recovers completely.

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Geometrical parameters:

* Length, width, Depth of burn (2nd – 0.12 to 2.0 mm), surface, volume
* Total Body surface area of burn (TBSA) (Wallace Rule of Nines)
* Burn Location/s

# Type of burns:

First-degree burn or epithelial burns - Skin is erythematic without vesication.

Second-degree burns - Involving epidermis and variable thickness of dermis. This is again divided into

* + Second-degree superficial –where vesication and inflammation is seen in skin as only papillary dermis is involved.
  + Second-degree deep -eschar formation is seen as it involves deep reticular dermis.

Third-degree burn - Also known as full thickness burns - eschar formation is present in these burns.

### Modeling Framework:

discrete vs. continuum

### Species to be included:

oxygen, inflammatory cells, VEGF, TGF-β, fibroblasts, ECM,

### Development of Model Equations:

### Estimation of Model Parameter Values:

**References:**

1. Buganza Tepole, A. (2017). Computational systems mechanobiology of wound healing. *Computer Methods in Applied Mechanics and Engineering*. <https://doi.org/10.1016/j.cma.2016.04.034>
2. Flegg, J. A., Menon, S. N., Maini, P. K., & McElwain, D. L. S. (2015). On the mathematical modeling of wound healing angiogenesis in skin as a reaction-transport process. *Frontiers in Physiology*. https://doi.org/10.3389/fphys.2015.00262
3. Ziraldo, C., Mi, Q., An, G., & Vodovotz, Y. (2013). Computational Modeling of Inflammation and Wound Healing. *Advances in Wound Care*. <https://doi.org/10.1089/wound.2012.0416>
4. Presbitero, A., Mancini, E., Brands, R., Krzhizhanovskaya, V. V., & Sloot, P. M. A. (2018). Supplemented alkaline phosphatase supports the immune response in patients undergoing cardiac surgery: Clinical and computational evidence. *Frontiers in Immunology*. https://doi.org/10.3389/fimmu.2018.02342