A Continuum Based Morphoelastic Model for Skin Contraction

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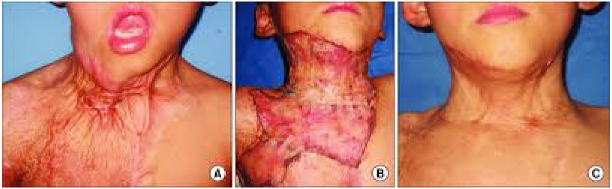
THANKS ! !

Sponsors:

- The Dutch Burns Foundation
- Foundation Animal Free Testing

The underlying problem

Burn injuries and their problems



- Ugly (hypertrophic) scars
- Serious dermal contraction

Skin contraction can render patients (partially) disabled and immobile.

Why do we need mathematics for burn injuries?

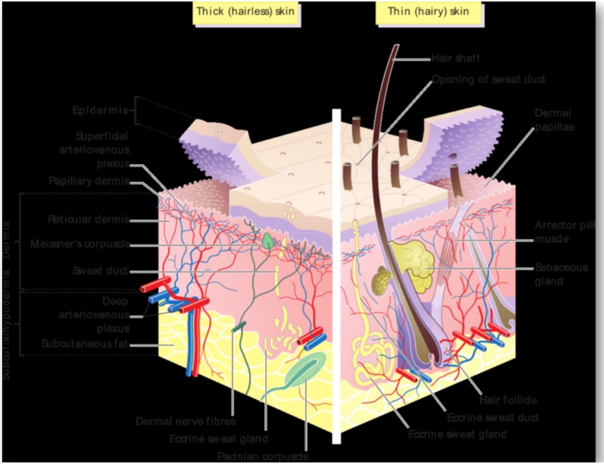
1. Therapy and treatment are necessary to minimize skin contraction and formation of hypertrophic scars
2. Quantitative insight is necessary for understanding biological processes in skin after burning and hencewith to optimize therapy
3. Many input variables in mathematical models are uncertain as a result of variation among patients
4. Like in weather forecasting, a single simulation is just a sample from a probability distribution
5. Simulations need to be interpreted in probabilistic sense
6. Estimation of the probability of successful treatmetn
7. The probabilistic approach (by large number of samples) requires computational power that is not feasible in a clinical environment

What do we want ...

... to simulate?

Contraction of skin: (poro)elastic material that shrinks and causes disabilities

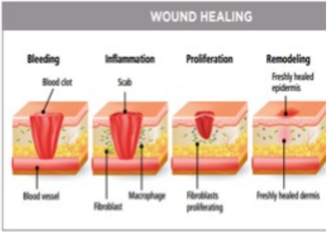
Major Issue: Many input parameters are unknown, hard to measure, or patient-specific $\Longrightarrow$ Uncertainty



Schematic of skin: epidermis, dermis and subcutis

Problem description

- Hemostasis: Blood clotting & formation of fibrin by platelets, release of platelet derived growth factor
- Inflammation: Ingress of immune cells (phagocytes, leukocytes, macrophages, ...) and clearance of debris, release of TG-beta
- Proliferation: Ingress of fibroblasts, angiogenesis and regeneration of collagen & fibronectin, reepithelialisation of epidermis
- Maturation: realignment of collagen, apoptosis of unneeded cells



(www.inovanewsroom.org)

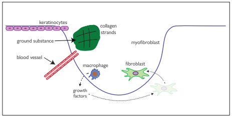
Continuum hypothesis-based mechano-bio-chemical model

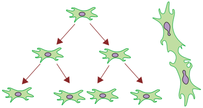
Mechanical Hall – Koppenol (2017)

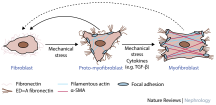
- Displacement of the dermis (u)
- Displacement velocity (v)
- Infinitesimal effective strain (ε)

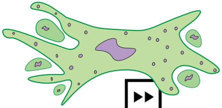
(bio)-Chemical

- Fibroblasts (produce collagen)
- Myofibroblasts (exert forces)
- Signaling molecules (inter-cellular communication)
- Collagen (skin integrity)



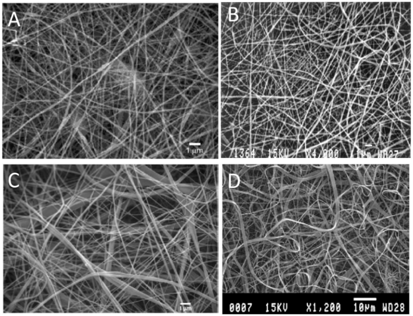




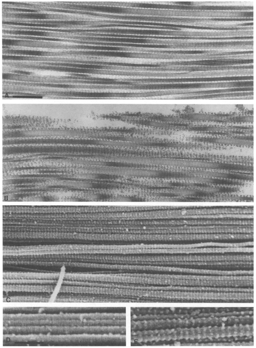


UHASSELT KNOWLEDGE IN ACTION

Collagen: isotropic or non-isotropic?



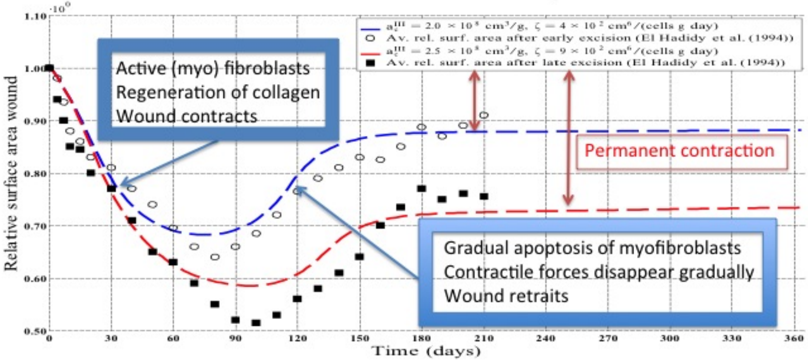
Type 1 collagen



Type 3 collagen

Incorporation of collagen I and III in the simulations because of their different properties regarding stiffness and isotropy
$\Longrightarrow$ mechanical properties

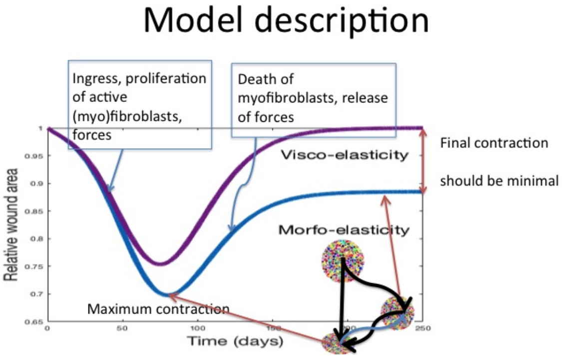
Simulation example



Thanks to Daniel Koppenol (2017)

Morphoelasticity: Elastic growth / shrinkage

Problem: Scar texture evolves over time,
$\Longrightarrow$ need for permanent displacements.



Plasticity & Growth —— Application to burn injuries
Goriely, Moulton (2011–elastic growth, nice introduction)
Rodriguez et al (1994–first introduction, invention)

Model Equations

Biochemical part:

$$\frac{DN}{Dt} + N\ \nabla \cdot \mathbf{v} + \nabla \cdot [-D_F(N+M)\nabla N + \chi_F N \nabla c] =$$
$$r_F \left[1 + \frac{r_F^{\max} c}{a_c^{III} + c}\right] [1 - \kappa_F(N+M)] N^{1+q} - k_F c N - \delta_N N$$

$$\frac{DM}{Dt} + M\ \nabla \cdot \mathbf{v} + \nabla \cdot [-D_F(N+M)\nabla M + \chi_F M \nabla c] =$$
$$r_F \left[\frac{[1 + r_F^{\max}]c}{a_c^{III} + c}\right] [1 - \kappa_F(N+M)] M^{1+q} + k_F c N - \delta_M M$$

Model Equations

Biochemical part (continued):

$$\frac{Dc}{Dt} + c\ \nabla \cdot \mathbf{v} - D_c \Delta c = k_c \left[\frac{c}{a_c^I + c} \right] [N + \eta^I M] - \delta_c \frac{[N + \eta^{II} M]\rho}{1 + a_c^{II} c} c$$

$$\frac{D\rho}{Dt} + \rho\ \nabla \cdot \mathbf{v} = k_\rho \left[1 + \left[\frac{k_\rho^{\max} c}{a_c^{IV} + c} \right] \right] [N + \eta^I M] - \delta_\rho \frac{[N + \eta^{II} M]\rho}{1 + a_c^{II} c} \rho$$

Mechanics:

$$\frac{D}{Dt}(\rho \boldsymbol{v}) + \rho\ (\nabla \cdot \boldsymbol{v})\boldsymbol{v} - \nabla \cdot \boldsymbol{\sigma} = \boldsymbol{F}_c$$

$$\boldsymbol{\sigma} = \frac{E(\rho)}{1 - \nu}(\varepsilon + \frac{\nu}{1 - 2\nu}\text{tr}(\varepsilon)\boldsymbol{I}) + \mu_1 \text{sym}(\boldsymbol{L}) + \mu_2 \text{tr}(\boldsymbol{L})\boldsymbol{I}$$

$$\frac{D\varepsilon}{Dt} + \varepsilon\ \text{skw}(\boldsymbol{L}) - \text{skw}(\boldsymbol{L})\ \varepsilon + (\text{tr}(\varepsilon) - 1)\ \text{sym}(\boldsymbol{L}) = -G$$

Evolution of strain

Conventional models (linear elasticity – infinitesimal strain)

$$\varepsilon = \frac{1}{2}(\nabla \mathbf{u} + \nabla \mathbf{u}^T),$$

which is symmetric.

Is ε symmetric for morphoelasticity?

Morphoelasticity sees

$$\frac{D\boldsymbol{\varepsilon}}{Dt} + \boldsymbol{\varepsilon}\ \mathrm{skw}(\nabla \boldsymbol{v}) - \mathrm{skw}(\nabla \boldsymbol{v})\ \boldsymbol{\varepsilon} + (\mathrm{tr}(\boldsymbol{\varepsilon}) - 1)\ \mathrm{sym}(\boldsymbol{L}) = -\boldsymbol{G}.$$

Assume that $\boldsymbol{G} = \alpha\ \boldsymbol{\varepsilon}$.

Evolution of strain

Then

$$\frac{D\varepsilon}{Dt} + \varepsilon \ \mathrm{skw}(\nabla \boldsymbol{v}) - \mathrm{skw}(\nabla \boldsymbol{v}) \ \varepsilon + (\mathrm{tr}(\varepsilon) - 1) \ \mathrm{sym}(\boldsymbol{L}) = -\alpha\varepsilon.$$

and taking transpose ($(AB)^T = B^T A^T$ and $\mathrm{skw}(A)^T = -\mathrm{skw}(A)$)

$$\frac{D\varepsilon^T}{Dt} + \varepsilon^T \ \mathrm{skw}(\nabla \boldsymbol{v}) - \mathrm{skw}(\nabla \boldsymbol{v}) \ \varepsilon^{\boldsymbol{T}} + (\mathrm{tr}(\varepsilon) - 1) \ \mathrm{sym}(\boldsymbol{L}) = -\alpha\varepsilon^T.$$

Setting $\boldsymbol{w} = \varepsilon - \varepsilon^T$ gives

$$\frac{D\boldsymbol{w}}{Dt} + \boldsymbol{w} \ \mathrm{skw}(\nabla \boldsymbol{v}) - \mathrm{skw}(\nabla \boldsymbol{v}) \ \boldsymbol{w} + \alpha \boldsymbol{w} = 0.$$

Hence $\boldsymbol{w}(.,0) = 0 \Longrightarrow \varepsilon - \varepsilon^T = 0$ for $t > 0$.
We will demonstrate that the cross terms vanish.

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Evolution of strain

Let $A, B \in \mathbb{R}^{n \times n}$, then

$$A : B = \sum_{i,j=1}^{n} A_{ij} B_{ij}. \tag{1}$$

The trace operator for tensors is defined by

$$\mathrm{tr}(A) = \sum_{i=1}^{n} A_{ii}.$$

Multiplication of the matrices A^T and B gives component-wisely

$$(A^T B)_{ij} = \sum_{k=1}^{n} A_{ki} B_{kj}.$$

Hence using equation (1), the trace is obtained from

$$\mathrm{tr}(A^T B) = \sum_{i=1}^{n} \sum_{k=1}^{n} A_{ki} B_{kj} = A : B. \tag{2}$$

Lemma:

Suppose $\mathbf{v} \in \mathbb{R}^{d\times d}$ and $\mathbf{L} \in \mathbb{R}^{d\times d}$ are 2D-tensors, and let $\mathbf{L}$ be skew (anti)–symmetric ($\mathbf{L}^T = -\mathbf{L}$), then for all $\mathbf{v} \in \mathbb{R}^{d\times d}$, the tensorial scalar product satisfies

$$\mathbf{v} : (\mathbf{L}\mathbf{v}) = \mathbf{v} : (\mathbf{v}\mathbf{L}) = 0.$$

Proof. Choose any $\boldsymbol{v} \in \mathbb{R}^{d\times d}$, use $\mathbf{L}^T = -\mathbf{L}$, $(AB)^T = B^T A^T$, and equation (2), then we arrive at

$$\boldsymbol{v} : (\boldsymbol{L}\boldsymbol{v}) = \mathrm{tr}(\boldsymbol{v}^T \boldsymbol{L}\boldsymbol{v}) = -\mathrm{tr}(\boldsymbol{v}^T \boldsymbol{L}^T \boldsymbol{v}) = -\mathrm{tr}((\boldsymbol{L}\boldsymbol{v})^T \boldsymbol{v}) = -\boldsymbol{v} : (\boldsymbol{L}\boldsymbol{v}). \quad (3)$$

Hence $\mathbf{v} : (\mathbf{L}\mathbf{v}) = 0$. Furthermore, since $A : B = A^T : B^T$, take $\boldsymbol{w} = \boldsymbol{v}^T$, and we use $\mathbf{L}^T = -\mathbf{L}$, we get using the above relation:

$$(\boldsymbol{w}\boldsymbol{L}) : \boldsymbol{w} = (\boldsymbol{w}\boldsymbol{L})^T : \boldsymbol{w}^T = (\boldsymbol{L}^T \boldsymbol{v}) : \boldsymbol{v} = -(\boldsymbol{L}\boldsymbol{v}) : \boldsymbol{v} = 0.$$

This proves the lemma.

Evolution of strain

Recall that $\boldsymbol{w} = \boldsymbol{\varepsilon} - \boldsymbol{\varepsilon}^T$ satisfies

$$\frac{D\boldsymbol{w}}{Dt} + \boldsymbol{w}\ \text{skw}(\nabla \boldsymbol{v}) - \text{skw}(\nabla \boldsymbol{v})\ \boldsymbol{w} + \alpha \boldsymbol{w} = 0.$$

Let $\boldsymbol{L} = \text{skw}(\nabla \boldsymbol{v})$, then

$$\boldsymbol{w} : \frac{D\boldsymbol{w}}{Dt} + \boldsymbol{w} : (\boldsymbol{w}\boldsymbol{L}) - \boldsymbol{w} : (\boldsymbol{L}\boldsymbol{w}) + \alpha \boldsymbol{w} : \boldsymbol{w} = 0.$$

Using the Lemma gives

$$\frac{1}{2}\frac{D}{Dt}||\boldsymbol{w}||^2 = -\alpha||\boldsymbol{w}||^2.$$

Integration implies that symmetry is stable iff $\alpha \geq 0$. Hence

Theorem:

If ε is initially symmetric, then ε remains symmetric for $t > 0$ and small perturbations around symmetry remain small iff $\alpha \geq 0$ (stability).

Linear Stability Analysis

Steps:

- Determine the equilibria $\{\overline{N}, \overline{M}, \overline{c}, \overline{\rho}, \overline{v}_1, \overline{v}_2, \overline{\varepsilon}_{11}, \overline{\varepsilon}_{12}, \overline{\varepsilon}_{22}\}$
- Linearize around the equilibria
- Apply Fourier series $z = \overline{z} + \hat{z}$

$$\hat{z}(\mathbf{x}, t) = \frac{1}{|\Omega|} \sum_{j,k \in \mathbb{Z}} c^z_{j,k}(t) e^{\frac{2i\pi jx}{L_x}} e^{\frac{2i\pi jy}{L_y}}$$

  with $z \in \{N, M, c, \rho, v_1, v_2, \varepsilon_{11}, \varepsilon_{12}, \varepsilon_{22}\}$.
- Use orthonormality
- Use algebraic decoupling between biochemistry and mechanics

Linear Stability Analysis

One arrives at

$$\frac{d\mathbf{c}}{dt} + A\mathbf{c} = \mathbf{0},$$

where $A \in \mathbb{R}^{9\times 9}$,

$$A = \begin{pmatrix} a_{11} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ a_{21} & a_{22} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ a_{31} & a_{32} & a_{33} & 0 & 0 & 0 & 0 & 0 & 0 \\ a_{41} & a_{42} & 0 & a_{44} & 0 & 0 & 0 & 0 & 0 \\ 0 & a_{52} & 0 & a_{54} & a_{55} & a_{56} & a_{57} & a_{58} & a_{59} \\ 0 & a_{62} & 0 & a_{64} & a_{65} & a_{66} & a_{67} & a_{68} & a_{69} \\ a_{71} & 0 & 0 & 0 & a_{75} & a_{76} & 0 & 0 & 0 \\ a_{81} & 0 & 0 & 0 & a_{85} & a_{86} & 0 & 0 & 0 \\ a_{91} & 0 & 0 & 0 & a_{95} & a_{96} & 0 & 0 & 0 \end{pmatrix}$$

Linear Stability Analysis

$$A = \begin{pmatrix} a_{11} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ a_{21} & a_{22} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ a_{31} & a_{32} & a_{33} & 0 & 0 & 0 & 0 & 0 & 0 \\ a_{41} & a_{42} & 0 & a_{44} & 0 & 0 & 0 & 0 & 0 \\ 0 & a_{52} & 0 & a_{54} & a_{55} & a_{56} & a_{57} & a_{58} & a_{59} \\ 0 & a_{62} & 0 & a_{64} & a_{65} & a_{66} & a_{67} & a_{68} & a_{69} \\ a_{71} & 0 & 0 & 0 & a_{75} & a_{76} & 0 & 0 & 0 \\ a_{81} & 0 & 0 & 0 & a_{85} & a_{86} & 0 & 0 & 0 \\ a_{91} & 0 & 0 & 0 & a_{95} & a_{96} & 0 & 0 & 0 \end{pmatrix}$$

For stability $\text{Re}(\lambda(A)) \geq 0$, hence $a_{ii} \geq 0$ for $i \in \{1, \ldots, 4\}$.
Consider block a_{ij} with $(i, j) \in \{5, \ldots, 9\}^2$.

Linear Stability Analysis

Consider 'mechanical' block a_{ij} with $(i,j) \in \{5,\dots,9\}^2$.

$$\tilde{A} = \begin{pmatrix} a_{55} & a_{56} & a_{57} & a_{58} & a_{59} \\ a_{65} & a_{66} & a_{67} & a_{68} & a_{69} \\ a_{75} & a_{76} & 0 & 0 & 0 \\ a_{85} & a_{86} & 0 & 0 & 0 \\ a_{95} & a_{96} & 0 & 0 & 0 \end{pmatrix}$$

$\lambda = 0$ is an eigenvalue. Setting $\bar{\varepsilon}_{11} = \bar{\varepsilon}_{22} = \frac{1}{2}$ and $\bar{\varepsilon}_{12} = 0$, gives $a_{i,j} = 0$ for $(i,j) \in \{7,8,9\} \times \{5,6\}$.

$\lambda = 0$ (alg mult $= 3$), other λ's follows from eigenvalues of

$$\begin{pmatrix} a_{55} & a_{56} \\ a_{65} & a_{66} \end{pmatrix}$$

Analysis of Morpho-elasticity – Continuum based

Theorem (Ginger Egberts & FJV (2022))

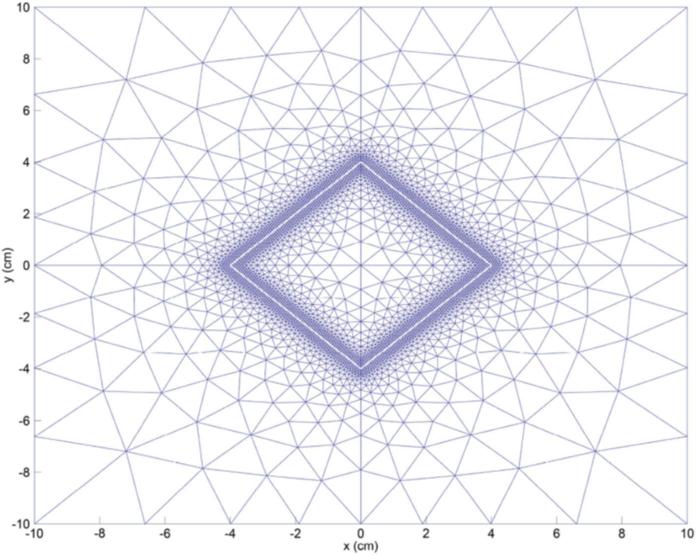
- The 'mechanical part' is stable if $\mu_1, \mu_2 \geq 0$ around the equilibrium $\varepsilon_{11} = \varepsilon_{22} = \frac{1}{2}$ and $\varepsilon_{12} = 0$;
- For $\delta_c \overline{\rho} \geq \frac{k_c}{a_c^l}$ and $q\delta_N \leq \kappa_F r_N \overline{N}^{1+q}$, the 'biochemical' part is stable.
- If the continuum problem is stable, then the semi-discrete problem is also stable (structured meshes).

Biological: Increased expression of signalling molecules can lead to increased myofibroblast migration and hence to increased collagen

This leads to instability, and wound fluctuations, to large wound contraction

Hence hypertrophic scarring and contracture

Finite Element Mesh (Initial)



Numerical Challenges and Methods

Nonlinearly coupled system of partial differential equations (multi-physics)

- Numerical time integration
- Moving finite element method (ALE approach)
- Mesh refinement and remeshing if mesh quality is bad
- Inner fixed point Picard iterations
- Segregated approach replaced with monolithic approach

Parameter estimation and uncertainty quantification

Reasons

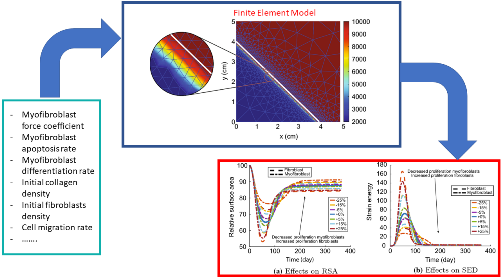
- Values of many input parameters are unknown or badly documented
- Values are Patient-specific age
  - recovery after stretching decreases
  - viscosity increases after turning 40

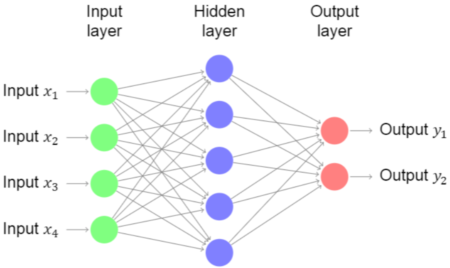
Studies

- Sensitivity analysis
- Feasibility study (age of patients)
- Analysis of stability of equilibria (healing versus scar – parameter range)

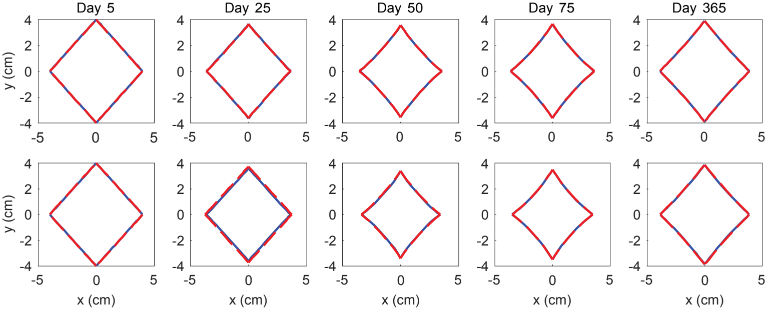
Deep Feed–Forward Neural Networks

- AdaMax stochastic gradient optimizer (varying learning rate)
- ReLu Activation function ($x_+ = max(0, x)$)
- Sigmoid activation at output nodes
- 2 hidden layers with 100 nodes
- 498 s per finite element sample
- 0.2744 ms per NN sample
- speed-up of $> 1,800,000$!





Deep Neural Networks: $R^2 > 0.9969$



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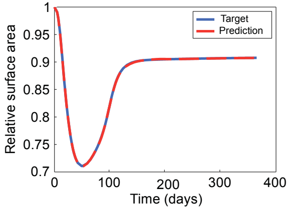
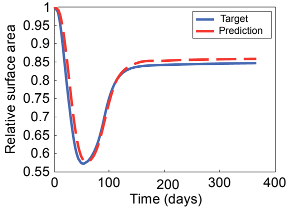
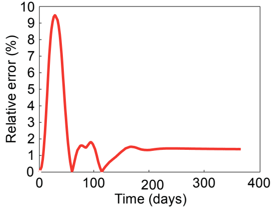
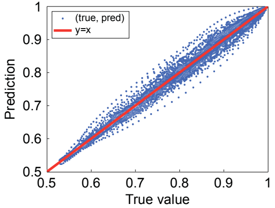


(a) Best prediction



(b) Worst prediction





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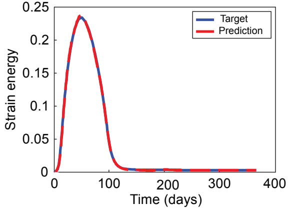

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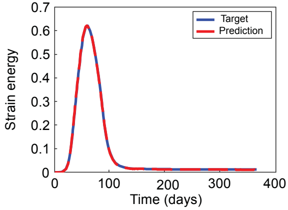
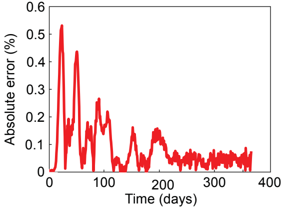
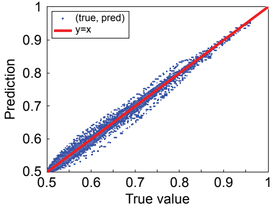


(b) Worst prediction





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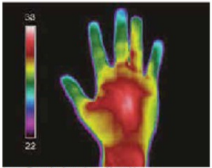
Onderzoeksidee op lange termijn



Laser Doppler Imaging of hand burns
Published in 2016
Management of Acute Hand Burns
C. N. Yogishwarappa, M. Ishwar, A. Vijayakumar

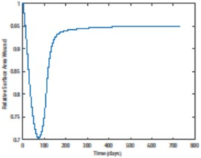
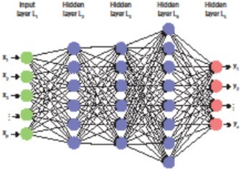
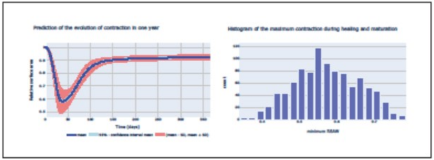


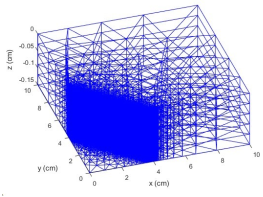
Image processing involves uncertainties and needs machine learning

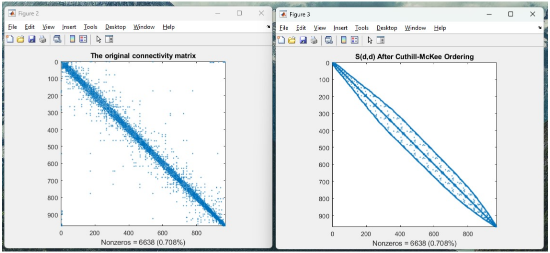




Reduced order model

Future and Current Work





1. Extension to 3D (first results available)
2. Application to hypertrophy (first results available)
3. Incorporation of collagen 3
4. Incorporation of wounds on curved body parts