# GENETIC ALGORITHM TO CALIBRATE A MULTISCALE COMPUTER MODEL OF BONE FRACTURE HEALING

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## Introduction

In recent years the investigation of bone fracture healing progression with computational methods gained more and more interest[1]. The coupled dynamics of the (mechano)biological processes across different time- and length-scales makes experimental exploration challenging. This paved the way for *in silico* modeling to be used as a successful technique to unveil the hidden processes underlying bone regeneration. COMMBINI (COmputational Mechano-biological Model of Bone INjury Immunoresponse) has been created to investigate the inflammatory stage of bone healing. The parametric calibration of the model with experimental data needs an adequate methodology. Here, we present a machine learning approach for the parametric calibration of the computer model.

## Material & methods

COMMBINI is a multiscale model of the immune response in bone healing. An agent-based model simulates the biological environment by representing the macrophage populations (cellular level) and cytokine concentrations (molecular level) within the healing region. The multiscale mechanisms and interactions are regulated by parameter-based algorithms, of which equations and values are collected from specialized literature[2,3]. The possibility to use a discrete agent-based model permits a direct comparison with immunofluorescent images of macrophage distribution collected from early healing stages in mice bone fracture[4]. Quantitative comparison between the experimental data and model cellular environment (in silico immunofluorescence) was used to calibrate the model. In detail, we employed Genetic Algorithm (GA) to calibrate the multiscale interactions simulated by the model. In the first instance, we evaluate the model sensitivity to the different parameters varying the values between two levels: 50% or 100% of the original literature-based value. Analysis of variance (ANOVA) evaluates the impact of each single variable on the model outputs as percentage of the total sum of squares (%TSS). The values of the most impactful parameters (%TSS > 1%) have been calibrated with GA. This method iteratively compares the model quantitative outputs with experimental data (e.g. macrophage count from immunofluorescent images[4]) and adapts the variables to reduce the *in silico-in vivo* differences. Each parameter is calibrated within a range of +/- 50% of the literature-based value. The calibration spans through multiple iterations ("generations") until below-threshold improvements are obtained.

## Results

Model sensitivity analysis was run on the total number of macrophages predicted by the model at day 3 post-fracture. The most impactful parameters were "inactivated macrophages proliferation ratio" ($k_{p0}$, 77.2%), "pro-inflammatory macrophages doubling ratio" ($k_{p1}$, 11.0%) and "maximum macrophage recruitment ratio" ($k_{Rmax}$, 2.4%). GA analysis performed on the parameters required 7 generations to significantly reduce the quantitative difference with experimental images (yellow bars in Fig. 1). If compared with literature data, the GA converges to minor values for $k_{p0}$, while for the other parameters the tendency was to slightly increase the value (Fig. 1).

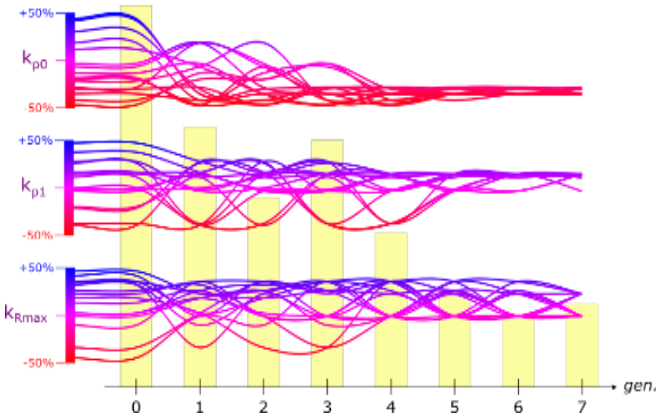


***Fig. 1*** *Value evolution of the most impactful parameters within +/-50% range during GA calibration. The in vivo-in silico macrophage count difference reduces with the calibration progression (yellow bars).*

## Discussion

The cellular level of the calibrated model showed a good agreement with experimental immunofluorescent data. Due to the efficiency of the presented calibration technique, its use will be extended to further calibrate the multiscale model when also mechano-biological modules will be included. The full calibration of the model with *in vivo* data, and its future validation for critical healing cases, will guarantee to COMMBINI a principal role in the preliminary planning of mechano-biological therapeutic strategies that supports bone fracture healing since the initial inflammatory response.

## References

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