AOFAS Annual Meeting 2023

A Novel Application of Neural Networks to Identify Potentially Effective Combinations of Biologic Factors for Enhancement of Bone Fusion/Repair

Albert T. Anastasio, MD; Bailey S. Zinger, BS; Thomas J. Anastasio, PhD

Category: Basic Sciences/Biologics; Other

Keywords: basic; Autologous Bone Marrow Aspirate; Platelet Rich Plasma

Introduction/Purpose: The use of biologic adjuvants (orthobiologics) is becoming commonplace in orthopaedic surgery. Amongst other applications, biologics are often added to enhance fusion rates in spinal surgery and to promote bone healing in complex fracture patterns. Generally, orthopaedic surgeons use only one biomolecular agent (ie allograft with embedded bone morphogenetic protein-2) rather than several agents acting in concert. Bone fusion, however, is a highly multifactorial process and it likely could be more effectively enhanced using biologic factors in combination, acting synergistically. We used artificial neural networks to identify combinations of orthobiologic factors that potentially would be more effective than single agents.

Methods: Available data on the outcomes associated with various orthopaedic biologic agents, electrical stimulation, and pulsed ultrasound were curated from the literature and assembled into a form suitable for machine learning. The best among many different types of neural networks was chosen for its ability to generalize over this dataset, and that network was used to make predictions concerning the expected efficacy of 2400 medically feasible combinations of 9 different agents and treatments.

Results: The most effective combinations were high in the bone-morphogenic proteins (BMP) 2 and 7 (BMP2, 15mg; BMP7, 5mg), and in osteogenin (150ug). Some of the most effective combinations included bone marrow aspirate concentrate. In some others, electrical stimulation could substitute for osteogenin. BMP2 and BMP7 appear to have the strongest pairwise linkage of the factors analyzed in this study.

Conclusion: Artificial neural networks are powerful forms of artificial intelligence that can be applied readily in the orthopaedic domain, but neural network predictions improve along with the amount of data available to train them. This study provides a starting point from which networks trained on future, expanded datasets can be developed. Yet even this initial model makes specific predictions concerning potentially effective combinatorial therapeutics that should be verified experimentally. Furthermore, our analysis provides an avenue for further research into the basic science of bone healing by demonstrating agents that appear to be linked in function.
### Table 2.

The 10 best and 10 worst combinations of orthobiologic factors, as determined from the neural network. Combinations are ranked, best to worst, out of the total of 2400 combinations in the computational screen. BMP2 and BMP7 are at their highest levels in the 10 best combinations, while they are at their lowest levels in the 10 worst combinations. OG tends to be at its highest or lowest levels in the 10 best or worst, respectively, while PDGF tends in the opposite direction. The 10 best and worst combinations are presented in Table 2. ES and BMAC are present in some of the 10 best but in none of the 10 worst. PRP is absent from all of the 10 best and worst combinations. EGB is present in all 2400 combinations by design and is included only for completeness. Units: BMP2 and BMP7 are in milligrams, PDGF is in micrograms, and PU is in total treatment days; the other inputs are either present or absent. The levels (doses, intensities, amounts, etc.) of all inputs are in the ranges as reported in published studies.

![Diagram of the artificial neural network](image)

**Figure 1.** Diagram of the artificial neural network used to predict the efficacy of 2400 combinations of orthobiologic factors. The feedforward network has two layers of hidden units. The first hidden layer receives the input not directly but only after it has been processed by a layer of autoencoder units. The 17 input units project to a layer of 50 autoencoder units, which project to the first layer of 100 hidden units, which in turn project to the second layer of 100 hidden units, which finally project to the set of 26 output units. The connectivity between layers is complete in that each unit in a previous layer projects to every unit in a subsequent layer. The weights from the input layer to the autoencoder layer are trained separately, and then held fixed while the other weights in the network are trained.
Figure 2. Desired and actual outputs of the neural network after training. The values of the 26 output units for each of the 225 input/desired-output patterns in the training dataset are shown as images, separately for the desired (left) and actual (right) outputs. The unscaled values of the outputs range from 2 (deep blue) to 277 (bright yellow). Close inspection reveals that the match between the desired and actual outputs is good but not perfect. This is expected due to ambiguity in the training dataset, which is derived directly from the experimental data of multiple labs that often reported different outputs for the same inputs. The pattern of agreement in general, with disagreement in detail, indicates that the neural network has learned to generalize from the data in the training dataset. The ability to generalize is central to the ability of the neural network to predict the outputs for combinations of inputs on which it has not been trained.

Figure 3. The efficacies of 2400 combinations of orthobiologic factors as predicted by the neural network. The scores are sorted from least to most effective. Effective combinations were defined as those that were high in 17/26 outputs (DR, BF3, BF6, MVTV, PLF, FR, ODI, FR, FH, OW, RO, HO, and IS), and low in 5/26 outputs (TWZ/CH, TRU, RBG, NH, and DY). The remaining 9/26 outputs were not included in the efficacy measure. For the purposes of ranking, the outputs that should be low were flipped, all outputs were scaled in the range [0, 1], and the output values were averaged. By this measure, which is relative to the maximal and minimal output values, the highest possible efficacy of 1 would be obtained if all of the outputs that should be high/low were at their maximal/minimal levels for that output, and vice versa for the lowest possible efficacy of 0. The predicted efficacies for the 2400 combinations in the screen varied widely over the [0, 1] range and nearly plateaued for the most effective several hundred.
Figure 4. The combinations of orthobiologic input factors ordered by predicted efficacy. The combinations are presented in descending order, so the combinations are most/least effective at the top/bottom of either plot. The plot on the left shows all 2400 combinations while the plot on the right shows the top 200 combinations. The factors ES, BMAC, and PRP are either present or absent; EBG is always present. The factor BMP7 takes 2 levels; BMP2, OGF, and PU each take 4 levels; and PDGF takes 5 levels. Input factor levels varied over a broad range but were normalized into [0, 1] for purposes of illustration. In the images, yellow and deep blue correspond to 1 and 0, respectively.