MetaSystems White Paper

INTELLIGENT KARYOTYPING WITH IKAROS

MetaSystems – Innovative Solutions for Automated Imaging

In clinical cytogenetics, laboratory professionals analyze numerical and structural aberrations in chromosomes to diagnose genetic diseases or cancer. With over 30 years of experience in the cytogenetic field, MetaSystems offers comprehensive solutions for karyotyping and fluorescence in situ hybridization (FISH) that are adapted to time critical and precise routines. Innovations in artificial intelligence assist Ikaros users in achieving significant advances in accurate and efficient karyotyping.

Introduction

What is Deep Learning?

Deep learning is a subfield of machine learning and part of artificial intelligence. In machine learning, an expert manually designs features to distinguish objects-of-interest. Such features might be shape, color, or texture. By engineering features to distinguish images, the expert transfers knowledge to the algorithm. Previous chromosome classifiers in Ikaros have been based on such machine learning.

In **deep learning**, the expert prepares a high amount of classified example images, also called training images. The deep learning algorithm then finds useful features without further human interaction to distinguish the images based on the expert classification.

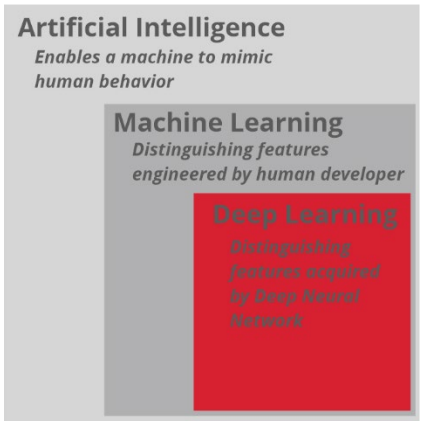

Figure 1: Deep learning is a subfield of artificial intelligence. The Deep Neural Network (DNN) acquires features without human interaction to distinguish images.

While the principles of deep learning are decades-old, the recent availability of big data and computational power have pushed the method to breakthrough. Prominent examples for deep learning are facial recognition in smartphone cameras and language recognition in spoken phrases or translations.

The deep learning algorithms implemented in Ikaros are called **Deep Neural Networks (DNNs)**, which solve advanced computer vision tasks. The architecture of DNNs is modeled on the network of neurons in the human brain. More precisely, DNNs are large statistical models with millions of adaptable parameters. The huge number of parameters enables a DNN to learn abstract features for image differentiation.

DNNs for computer vision are built on several layers of **convolutional filters** that process the image. While early layers often detect basic image properties, e.g., edges or colors, deeper layers combine basic information with more task-relevant features, e.g., "looks like a chromosome".

During the DNN's training period, the prediction given by the DNN for every training image is compared to the

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actual, correct output (ground-truth). In a process called back-propagation, the parameters of the DNN are then changed incrementally to progressively approach the ground-truth.

As the training images are the only source of knowledge, they must not only be correctly pre-classified, but also show the object-of-interest in all relevant variations. Thereby, the DNN learns robust features for image differentiation.

Training a DNN can easily take days to weeks and is computationally intensive. Once the training and validation process of the DNN is finished, the resulting Ikaros Classifier for chromosome separation or classification is ready to use.

Intelligent Karyotyping with Ikaros

For karyotyping, metaphase chromosomes are processed to visualize distinct banding patterns. Subsequently, the stained chromosomes are sorted and analyzed to detect chromosomal aberrations. Thereby, cytogeneticists diagnose genetic diseases, developmental defects, and cancer.

Previously, the MetaSystems' product Ikaros used machine learning algorithms to separate and classify chromosomes.

As MetaSystems continuously seeks to improve the performance of Ikaros, our aim was to further reduce the frequency of errors to ultimately minimize the time spent with karyotyping.

Therefore, MetaSystems has implemented state-of-the-art deep learning algorithms in Ikaros to support chromosome separation and classification.

Results
Chromosome Separation in Ikaros

By testing the new DNN-based algorithms for chromosome separation and classification on test datasets, the following results were obtained.

95.2 % of metaphase cells derived from bone marrow and 98.9 % of metaphase cells derived from lymphocytes could be corrected by the user with only two interactions, e.g., adding or deleting a chromosome or drawing a separation line between chromosomes.

The mean number of necessary user interactions for 10 metaphase cells was significantly lower with the DNN-based algorithm than with the previous conventional algorithm in Ikaros.

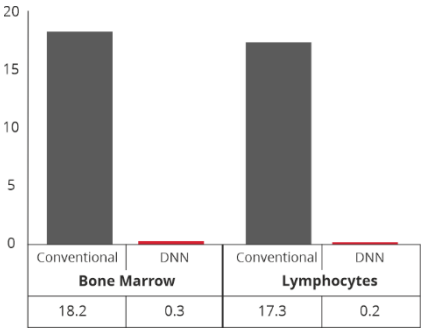

Figure 2: Mean number of interactions for 10 metaphase cells either derived from bone marrow or lymphocytes analyzed with the conventional, machine learning algorithm (grey) and the new DNN-based algorithm (red) in Ikaros.

Chromosome Classification in Ikaros

Classification of all common staining types for chromosome banding, e.g., G-Banding, R-Banding, and Q-Banding as well as different tissue types, e.g., lymphocytes, bone marrow, amniotic fluid, and chorionic villi, are supported.

The new DNN-based algorithms showed significant improvement for chromosome classification on both lymphocyte and bone marrow samples, compared to the previous machine learning algorithms.

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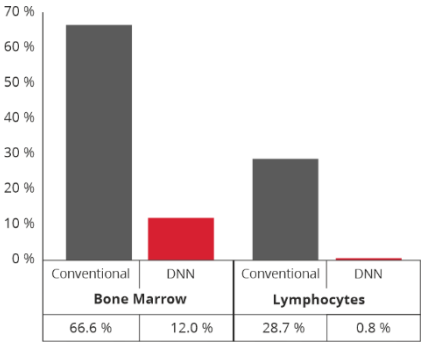

Figure 3: Mean error rates for chromosome assignment per metaphase in Ikaros using the conventional, machine learning algorithm (grey) and the new DNN-based algorithm (red). The graph shows the results for ~ 100,000 bone marrow metaphases and ~ 150,000 lymphocyte metaphases.

Conclusions

The advanced deep learning algorithms implemented in Ikaros simplify the whole process of karyotyping from chromosome separation to classification.

The number of required corrections in karyogram generation (i.e., separating and classifying the chromosomes) may be significantly reduced compared to the previous machine learning algorithms in Ikaros.

With the help of deep learning algorithms, Ikaros proposes a software-generated karyogram that just needs to be reviewed and evaluated by an expert. Corrections are possible at any point during karyotyping and easily realized with the intuitive software interface.

Please be aware that the quality of the sample is an indispensable factor for the generation of a karyogram proposal. If the metaphase images are systematically different from the images the DNNs were trained on, it might be necessary to develop another DNN.

With the smart scanning solution based on Metafer, MetaSystems is able to offer a fully automated workflow from automatic image acquisition of metaphases to processed karyogram proposals ready for expert review.

Highlights

- Deep learning algorithms are an advancement in the field of artificial intelligence.
- Deep Neural Networks (DNNs) represent such deep learning algorithms.
- DNNs in Ikaros separate and classify banded chromosomes to generate karyogram proposals.
- All common chromosome banding techniques are supported for karyotyping.
- Metaphase cells from different tissue types, e.g., lymphocytes, bone marrow, amniotic fluid, and chorionic villi can be analyzed.
- With the new DNN-based algorithms, the users perform fewer corrective interactions and karyotype faster.
- MetaSystems has been granted a US Patent for AI based chromosome analysis (U.S. patent no. 10,991,098).

We experienced a time gain of up to 50% in the karyotype analysis of bone marrow metaphases. This enormous gain in efficiency allows us to keep pace with the ever-increasing workload in times of shortage of personnel resources.

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Want to Know More?

MetaSystems offers innovative solutions for automated microscopy imaging for numerous applications with brightfield and fluorescence illumination.

Would you like to know more about how MetaSystems uses artificial intelligence? Please contact us at **info@metasystems.ai**.

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