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 more than 35 years of experience in automating slide scanning for medicine and life sciences, MetaSystems offers comprehensive karyotyping and fluorescence in situ hybridization (FISH) solutions adapted to time critical and precise routines. Innovations in artificial intelligence assist Ikaros users achieve significant advances in efficient karyotyping.

Highlights

- Deep learning algorithms are an advance in the field of artificial intelligence.
- Deep Neural Networks (DNNs) are such deep learning algorithms.
- DNNs in Ikaros separate and classify banded chromosomes to generate karyogram proposals.
- The most common chromosome banding methods 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, users perform fewer corrective interactions and karyotype faster.
- MetaSystems has been granted a U.S. 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.*
>
> **Prof. Claudia Haferlach**
> MD from MLL (Münchner Leukämielabor GmbH, Germany)
> www.mll.com

Deep Learning Moves Intelligent Karyotyping Forward

For karyotyping, chromosomes are processed in metaphase to visualize distinct banding patterns. The stained chromosomes are then sorted and analyzed to detect chromosomal aberrations. In this way, cytogeneticists diagnose genetic diseases, developmental disorders, and cancer.

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

As MetaSystems is constantly striving to improve the performance of Ikaros, our goal was to further reduce the frequency of errors in karyogram proposals, ultimately minimizing the time spent with preparations.

Deep learning pushes the frontiers in medicine and life sciences. Therefore, MetaSystems has implemented state-of-the-art deep learning algorithms in Ikaros to support chromosome separation and classification.

What Is Deep Learning?

Deep learning is a subfield of machine learning and belongs to artificial intelligence. In traditional machine learning, an expert identifies features that are suitable for distinguishing objects of interest. Such features can be shape, color, or texture. This is how the expert transfers knowledge to the algorithm. Chromosome classifiers in earlier versions of Ikaros were 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 to distinguish the images based on the expert classification without further human interaction.

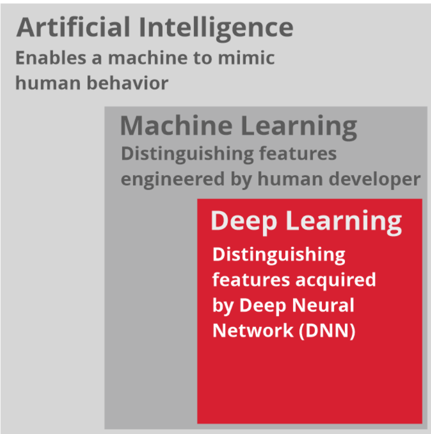

Figure 1: Deep learning is a subfield of artificial intelligence. The Deep Neural Network (DNN) acquires features without human interaction to distinguish images.

The principles of deep learning are decades-old, but the recent availability of big data and computational power have pushed the method to breakthrough. Deep learning is already in our everyday life, and you use it to unlock your phone with your face or to translate the menu in a foreign country's restaurant. Deep learning also pushes the frontiers in medicine and life sciences.

The deep learning algorithms implemented in Ikaros are called Deep Neural Networks (DNNs) that solve advanced computer vision tasks, such as object detection and image classification. Their design is broadly inspired by the network of neurons in the human brain.

More precisely, DNNs are large self-learning 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 multiple layers of convolutional filters that process the image. While early layers often detect basic image features, 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 each training image is compared to the actual, correct output (ground-truth). In a process called back-propagation, the parameters of the DNN are then incrementally changed to progressively approach the ground-truth.

Since 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 DNN training and validation process is finished, the resulting Ikaros Classifier for chromosome separation or classification is ready to use.

Chromosome Separation in Ikaros

When 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 manual operations, e.g., adding or deleting a chromosome or drawing a separation line between chromosomes.

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

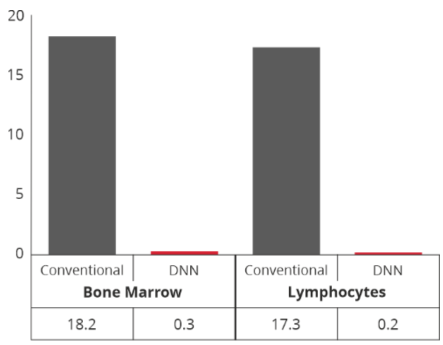

Figure 2: Mean number of user interactions for 10 metaphase cells derived from either bone marrow or lymphocytes analyzed with the conventional machine learning algorithm (grey) and the new DNN-based algorithm (red) in Ikaros.

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 for different tissue types, e.g., lymphocytes, bone marrow, amniotic fluid, and chorionic villi, is supported.

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

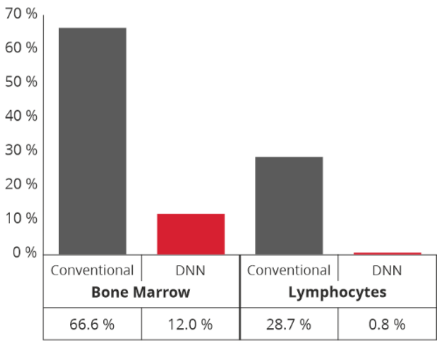

Figure 3: Mean error rates for chromosome classification per metaphase in Ikaros using the conventional machine learning algorithm (grey) and the new DNN-based algorithm (red). The graph shows results for ~ 100,000 bone marrow metaphases and ~ 150,000 lymphocyte metaphases.

Conclusion

The advanced deep learning algorithms implemented in Ikaros simplify the entire preparation process for karyotype analysis from chromosome separation to classification.

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

Using deep learning algorithms, Ikaros provides a software-generated karyogram proposal that only needs to be reviewed and evaluated by an expert. Manual operations are possible at any point in the karyotyping process and are easy to perform with the intuitive software interface.

Please consider that the quality of the sample is an indispensable factor for the generation of a karyogram proposal. If the metaphase images differ systematically from the images on which the respective DNN was trained, it may be necessary to adjust the existing DNN or train a specific, new DNN.

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

Further Reading

Vajen, B. et al. Classification of fluorescent R-Band metaphase chromosomes using a convolutional neural network is precise and fast in generating karyograms of hematologic neo-plastic cells. Cancer Genetics 260–261, 23–29 (2022).

https://doi.org/10.1016/j.cancergen.2021.11.005.

About MetaSystems

For 35 years, MetaSystems has been developing and producing innovative solutions for automated microscopy-based imaging for the healthcare and biotechnology sectors. Our headquarters are located in the southwest of Germany in the Rhine-Neckar metropolitan region near Heidelberg.

We are a global company with an international team working in Germany and in our subsidiaries in North and South America, Europe, India, and China. Our customers can be found in institutes, hospitals, and universities in over 100 countries around the world.

We continuously develop our products in close connection with our users, thus combining innovation with tradition. Our modern approaches include an advanced workflow management that grows with your requirements and the use of artificial intelligence. In many segments, this has enabled us to achieve an international top position on the market.

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.**

The described functions refer to the following software versions: Ikaros 6.3 | Metafer 4.3.
MetaSystems software and system products are classified as in vitro diagnostic medical devices (IVD) in the European Union in accordance with the Regulation (EU) 2017/746 or Directive 98/79/EC, respectively, and carry the CE label unless otherwise indicated. Use all MetaSystems products only within the scope of their intended purpose.
MetaSystems products are used in many countries worldwide. Depending on the regulations of the respective country or region, some products may not be used for clinical diagnostics.
Some hardware components supplied by other manufacturers are not included in MetaSystems IVD products and are therefore not IVD medical devices.

Document No.: WPC-MS-IKSDNN-EN-2022-06-02

MetaSystems

info@metasystems-international.com
www.metasystems-international.com