## Group members

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<tr>
<th>Name</th>
<th>Title</th>
<th>Publications</th>
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<tr>
<td>Péter HORVÁTH</td>
<td>Senior Research Associate</td>
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<td>Krisztina BUZÁS</td>
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<td>Krisztián KOÓS</td>
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<td>Ede MIGH</td>
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<td>József MOLNÁR</td>
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<td>Tamás BALASSA</td>
<td>Junior Research Associate</td>
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<td>Edina GYUKITY-SEBESTYÉN</td>
<td>Junior Research Associate</td>
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<td>Mária HARMATI</td>
<td>Junior Research Associate</td>
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<td>Dávid BAUER</td>
<td>Scientific Administrator</td>
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<td>Attila BELEON</td>
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<td>István GREXA</td>
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<td>Tímea BÖRÖCZKY</td>
<td>Undergraduate Student</td>
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<td>Filippo PICCININI</td>
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Overview

Recent technological advancements in systems biology, lab automation, and high-throughput microscopy have opened the door to systematic discovery of complex biological systems using high-throughput light microscopy. Modern equipments produce massive amounts of data which cannot be analyzed manually.

Automating the analysis process poses several challenges related to computational cell biology. Our group dedicated to finding computational solutions to biological problems. Our research focuses on the intersection of biology and computer science, and combine wet-lab and light microscopy with image analysis and machine learning methods.

I. Image analysis

**Illumination Correction**
For quantitative measurements based on light microscopy and especially fluorescent intensities, it is essential to normalize the image data to correct for aberrations inherent in the acquisition process. One common source of error is the result of a non-ideal illumination field produced by the objective. Our novel algorithms addresses these issues using energy minimization. The corrected field resulting from our approach is extremely flat, and we can achieve this level of quality without requiring a calibrated reference sample.
Reconstruction
We developed an algorithm based on energy minimization to convert differential interference contrast (DIC) images to phase images to make them easier to analyze.

- Related publications: Piccinini et. al. ISBI 2013, Smith et. al. Nat. Meth. 2015
- Contributors: F. Piccinini, P. Horvath, K. Smith
- GitHub code: CIDRE

- Related publications: Koos et. al. Scientific Reports 2016
- Contributors: K. Koos, J. Molnar, P. Horvath
Tracking
We are interested in developing methods for identifying and tracking cells or sub-cellular structures on live cell images. We have developed a software the CellTracker, which corrects illumination problems, finds alignments, as well as automatically and manually tracks cells, mainly on phase contrast images. The program is available with MatLab GUI.
[Download CellTracker]

- Related publications: Piccinini et. al. Bioinformatics 2015
- Contributors: F. Piccinini, P. Horvath, A. Kiss
- Webpage: CellTracker

Segmentation of overlapping cells (the 'gas of circles' model)
Variational methods for shape modeling to extract near-circular objects (e.g. nuclei). The multi-layered 'gas of near-circles' model is capable of segmenting touching or even overlapping cells on high confluency images.
Selective Active Contours
The selective active contours utilize simple shape characteristics such as area and perimeter, to describe objects that can provide computationally efficient shape selective segmentation.

Related publications: Molnar et. al., IEEE WACV 2016
Contributors: E. Tasnadi, C. Molnar, I. Grexa, P. Horvath
Selective Active Contours in 3D
3D extension of the selective 2D active contours.

- Computationally expensive
- Utilizing GPU-s to achieve high enough performance for practical use

Cells in pseudohyphae and in normal form. Finding the pseudohyphae form.

- Related publications: Molnar et. al., DICTA, IEEE 2017
- Contributors: E. Tasnadi, T. Danka, J. Molnar, P. Horvath

Splitting touching cells
Segment individual cell nuclei by splitting touching ones. The two-step approach merely based on energy minimization principles using a higher-order active contour framework.

- Related publications: Molnar et. al., ISVC, IEEE 2016
- Contributors: C. Molnar, J. Molnar, P. Horvath
II. Machine learning

Phenotyping - Advanced Cell Classifier
Advanced Cell Classifier is a data analyzer program to evaluate cell-based high-content screens and tissue section images developed at the Biological Research Centre, Szeged and FIMM, Helsinki (formerly at ETH Zurich). The basic aim is to provide a very accurate analysis with minimal user interaction using advanced machine learning methods. ACC was used to analyze some of the first large whole genome scale RNAi screens and all together for more than 300.000.000 images and several billion single cell-based machine learning decisions.

- most accurate analysis
- minimal user interaction
- intelligent modules
- performance feedback
- advanced machine learning

Related publications: Piccinini et. al., Cell Systems 2017
Contributors: F. Piccinini, T. Balassa, C. Molnar, A. Szkalisy, P. Horvath
Webpage: Advanced Cell Classifier

Deep Learning
We developed a fast and fully automated tools that assesses the number and location of cells using Deep Convolutional Neural Networks (DCNN). Our methods highly outperforms state-of-the-art machine learning models and provides comparable detection accuracy to human field experts.
Microenvironment-based phenotyping
We research how various microenvironmental features contribute to identifying a cell and how such additional information can improve single-cell-level phenotypic image analysis.

III. Single Cell Analysis Methods

CAMI - Computer Aided Microscopy Isolation system
We develop a high-throughput, non-disruptive, and cost-effective isolation methods that is capable of capturing individually targeted cells using widely available techniques. Using high-resolution microscopy, laser microcapture microscopy, image analysis, and machine learning, our technology enables scalable molecular genetic analysis of single cells, targetable by morphology or location within the sample. Cell data along with the location and contour of each cell is sent to our interactive online database CAMIO.
**AutoPatcher**
We are building an automated patch clamp system to analyze the electrophysiological properties of neurons in vitro. The system automatically selects a cell in label-free microscopy and performs patch clamping on it using image processing and deep learning.

- Related publications: unpublished
- Contributors: K. Koos, J. Molnar, P. Horvath

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**Microscopy**

**High content screening**
The HCS technology employs different automated microscopes in a high throughput format to extract quantitative information from cells or tissue samples based on various parameters such as spatial distribution or the morphology changes of the target cells. To address these various cellular phenotypes, both widefield and confocal microscopes are used in the BIOMAG group:

- Related publications: Brasko et. al., Nature Communications 2018
- Contributors: C. Molnar, T. Balassa, A. Szkalisity, P. Horvath
PerkinElmer Operetta

Main features:
- laser-based autofocus system
- objectives ranging from low to high magnifications (2-100X)
- objectives with high numerical aperture
- live cell imaging

Analysis of cellular phenotypes:
- apoptosis and cell cycle studies
- cell differentiation and cell migration assays
- cell proliferation and cell shape changes
- cytoskeletal rearrangement and cytotoxicity
- protein expression and translocation experiments
- wound healing assays

Leica SP8-digital light sheet

- DMi8 series with a motorized objective revolver
- automated image acquisition for mosaic or multiwell applications
- super-sensitive photon detection making it ideal for low light and live cell imaging
- the platform can be turned into a light sheet microscope
Laser microdissection systems
During LDM, a laser is focused on the tissue and it cuts the sample alongside a predefined trajectory. After the cutting process, the required elements can be extracted and collected for further analysis. The dissected material is then available for further downstream applications such as genomics, transcriptomics, next generation sequencing, proteomics or other analytical techniques. Based on the movement of the laser and sample collection, two main approaches have been used:

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**Leica LMD6**
- the movement of the laser beam is achieved via optics
- the specimen is collected via gravity
- fully automated upright research microscope

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**Zeiss Palm Microbeam**
- motorized microscope stage
- laser catapulting
- standard microscopic slides can also be used