AI ASSISTED DIGITAL MICROSCOPY IN MICROBIOLOGY

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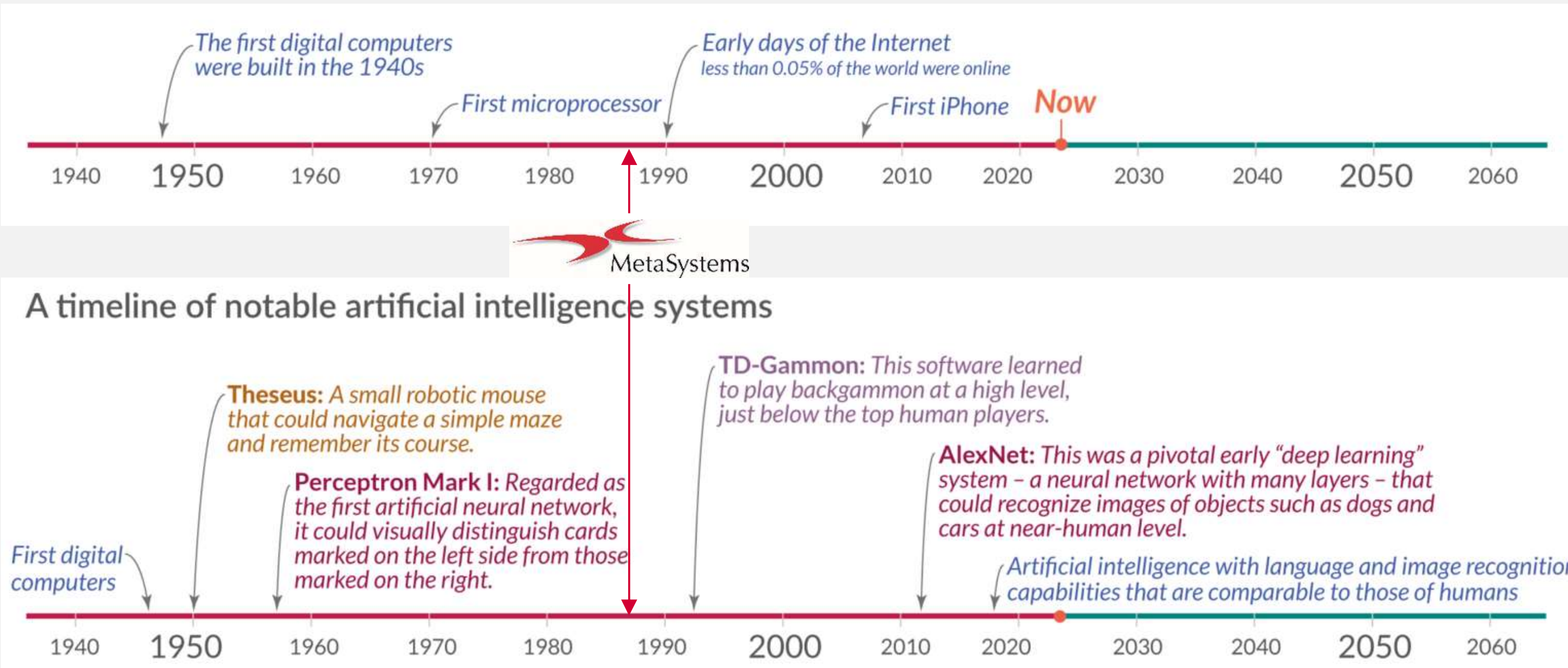
DNN Applications Engineer
MetaSystems Group, Inc.

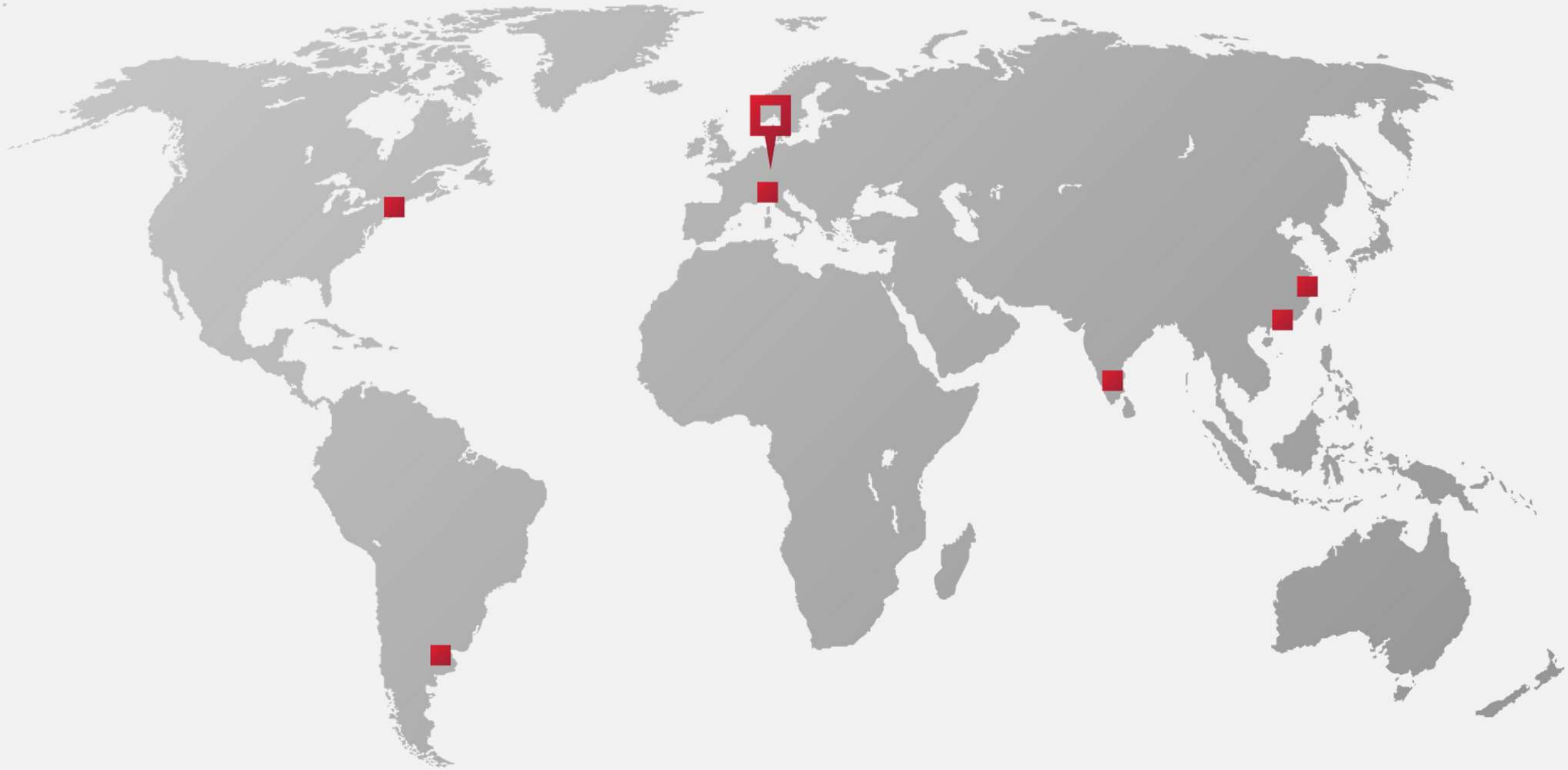
AI ASSISTED DIGITAL MICROSCOPY IN MICROBIOLOGY

- MetaSystems
- Automation in Microbiology and Microscopy
- Challenges & Limitations
- AI Assisted Microscopy
- Benefits, Challenges, Limitations

COMPUTERS & ARTIFICIAL INTELLIGENCE



METASYSTEMS

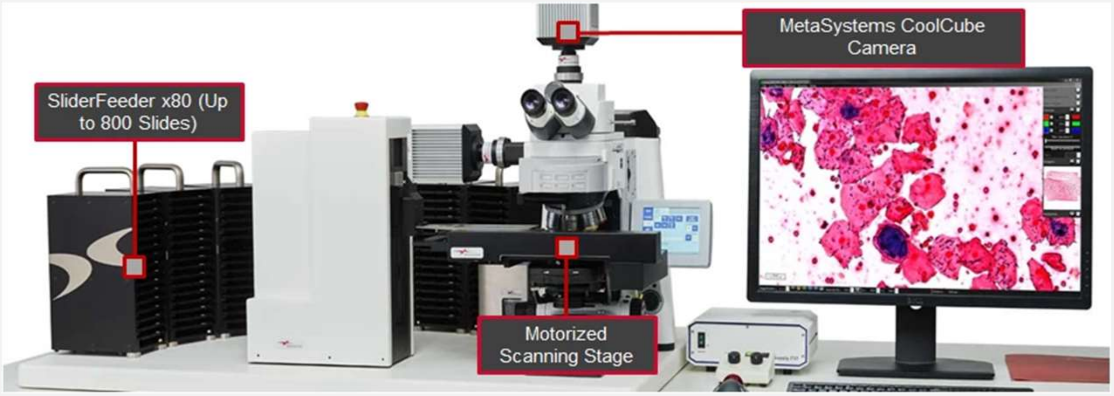


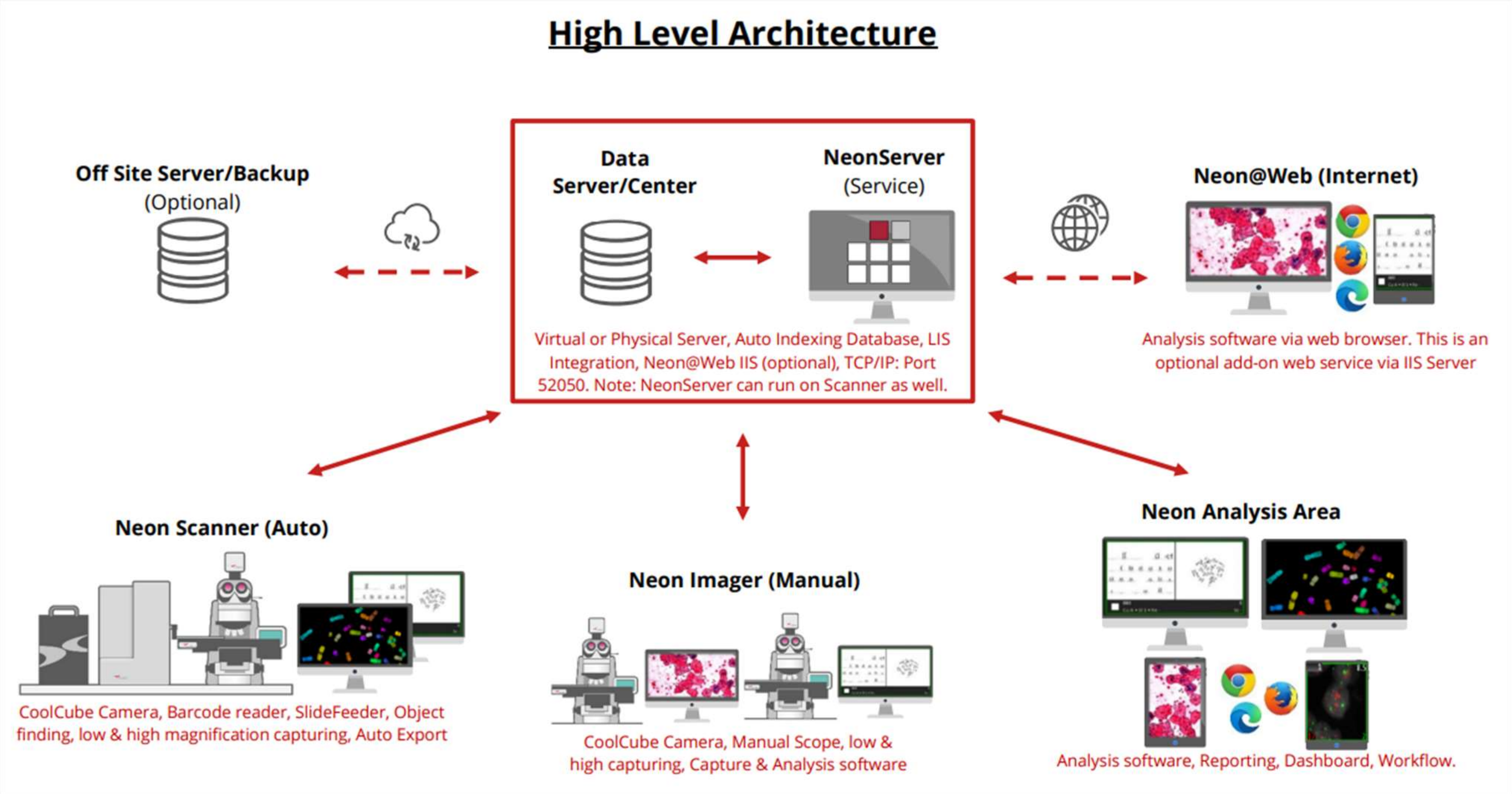
MetaSystems

A BRIEF HISTORY

- 1983 – How to Find Metaphases
- 1985 – Metafer
- 1986 – MetaSystems
- 1991 – Ikaros (Karyotyping software)
- 1995 – MetaSystems Boston Office
- 2002 – High throughput
- 2010 – Whole Slide Stitching
- 2013 – Collaboration with Copan, first microbiology application
- 2016 – Neon Database Management Software
- 2021 – Patented AI Assisted Karyotyping

METASYSTEMS SCANNER




High Level Architecture
Off Site Server/Backup
(Optional)
Data
Server/Center
NeonServer
(Service)
Virtual or Physical Server, Auto Indexing Database, LIS Integration, Neon@Web IIS (optional), TCP/IP: Port 52050. Note: NeonServer can run on Scanner as well.
Neon@Web (Internet)
Analysis software via web browser. This is an optional add-on web service via IIS Server
Neon Scanner (Auto)
CoolCube Camera, Barcode reader, SlideFeeder, Object finding, low & high magnification capturing, Auto Export
Neon Imager (Manual)
CoolCube Camera, Manual Scope, low & high capturing, Capture & Analysis software
Neon Analysis Area
Analysis software, Reporting, Dashboard, Workflow.

DIGITAL MICROBIOLOGY

Aspects of digital microbiology in the diagnostic process

Process	Aspect	Example
Pre-analytics	Quality control	What is the sample quality? – Automated measurement and feedback regarding the correct filling of blood culture bottles. – Automated assessment of sample contamination including species and clinical score
	Diagnostic stewardship	Which additional diagnostic test should be ordered? – Suggestion based on a digital twin, smartphone app, or chatbot
Analytics	Quality control	How reliable is the analytical performance of a test? – Surveillance of reagent lots performance with internal and external controls and automated reporting in connection to specific used lots of time
	Imaging	Are there bacteria on the microscope slide? – Automated image acquisition with a microscope and scan for pathogen-like structures and category
	Plate reading	Is there bacterial growth on the plate? – Automated image acquisition and scan for colonies and subsequent identification (telebacteriology)
	Expert system	Does the detected resistance profile make sense? – Medical validation of antibiotic resistance profiles with expert database
	Public Health	Is there a potential outbreak? – Automated screening for pathogen similarities, e.g., resistance profile or automated bioinformatics
Post-analytics	Highlight important data	Is there a potential bacterial phenotype? – Detection of resistance by analysing MALDI-TOF spectra
	Sepsis treatment	What is the best treatment for the patient? – Prediction of sepsis, and best treatment, e.g., volume and antibiotics for the patient

Source: Egli, A., Schrenzel, J., & Greub, G. (2020). Digital Microbiology. *Clinical Microbiology and Infection*, *26*(10), 1324–1331. https://doi.org/10.1016/j.cmi.2020.06.023

CHALLENGES OF AUTOMATION

HISTORICAL IMPEDIMENTS TO AUTOMATION IN MICROBIOLOGY

- Microbiology is too complex to automate.
  - Specimen types: blood, sterile body fluids, tissues, urine, catheter tips, other prosthetic devices, respiratory tract specimens
  - Transportation, variety of vessels
  - Processing: concentrated, macerated, digested, decontaminated, sonicated prior to being plated, or plated directly;
    - plating can be quantitative, semiquantitative, or nonquantitative
- No machine can replace a human in the microbiology laboratory.
  - Machines cannot operate fast enough
  - Decision-making, critical-thinking
- Cost of automation can be too high.
- Microbiology laboratories are too small for automation.

Bourbeau, P. P., & Ledeboer, N. A. (2013a). Automation in clinical microbiology. *Journal of Clinical Microbiology*, *51*(6), 1658–1665. https://doi.org/10.1128/jcm.00301-13

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Driving forces for automation

- Increasing test volumes
- 24/7 labs
- Staff shortages
- Advancement of technology

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WHOLE > $\sum(PARTS)$

- Sample collection
- Accessioning
- Sample preparation
- Processing
- Data acquisition
- Analysis/identification
- Resulting/reporting

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$\left.\begin{array}{l} \\ \\ \\ \\ \\ \\ \\ \end{array}\right\}$ Interoperability & Standardization

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Interoperability
&
Standardization

⇓

Quality
Accuracy
Speed

⇓

Better work environment
Better healthcare
Lower cost

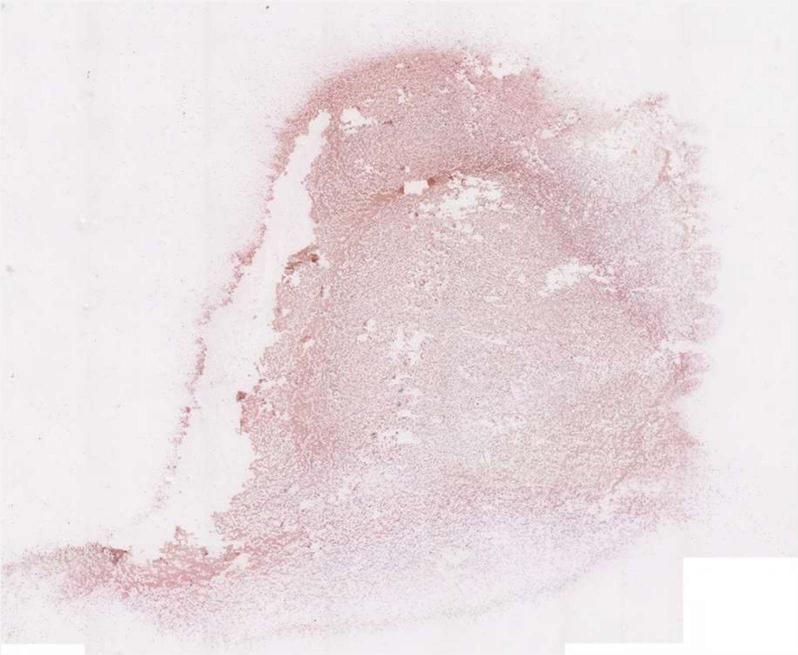
DIGITAL MICROSCOPY

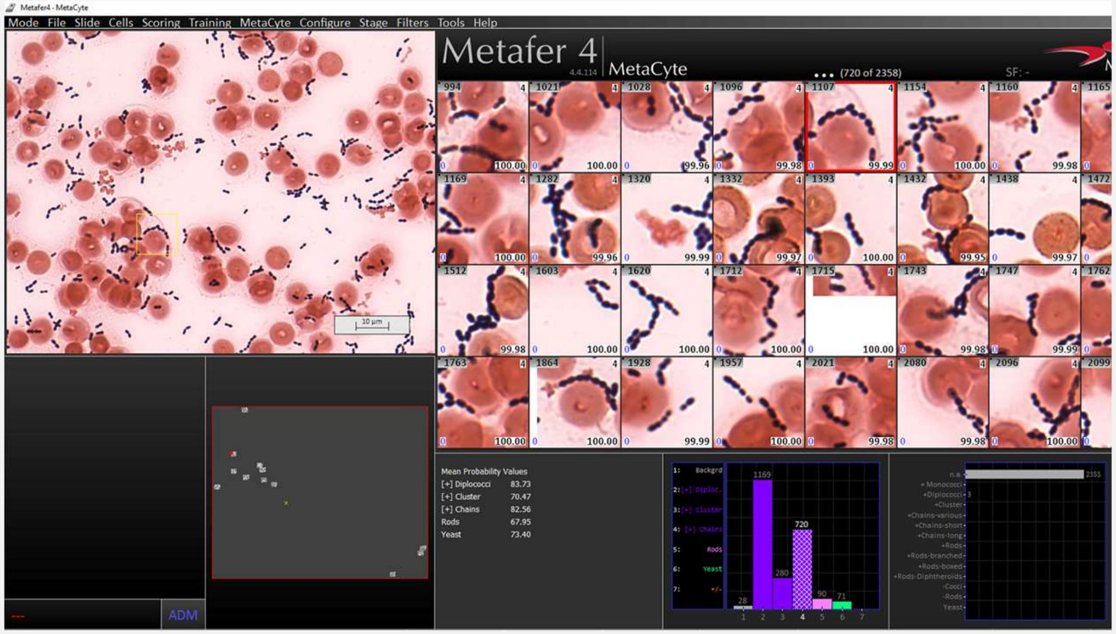
- Data acquisition
- Storage
- Quality control
- Analysis
- Security and protection
- Interoperability/interconnection
- Reporting and visualization

- Hardware
- Software
- Infrastructure
- Cybersecurity

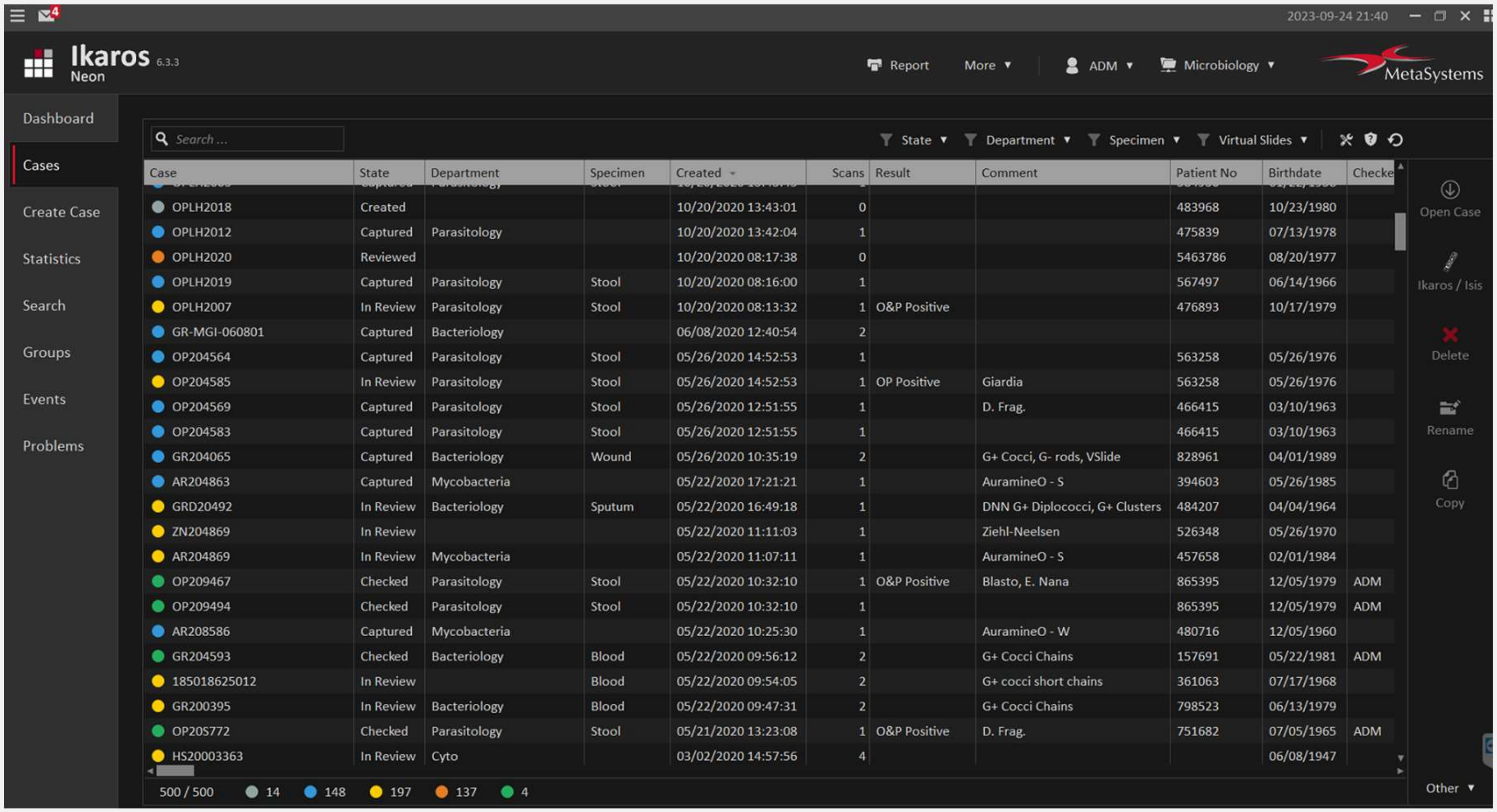
- 12 MP images
- Multiple focus planes (z-stack)
- Imaging 3 mins average
- ~ 500 MB – 1 GB raw data per slide
- Containing patient demographics

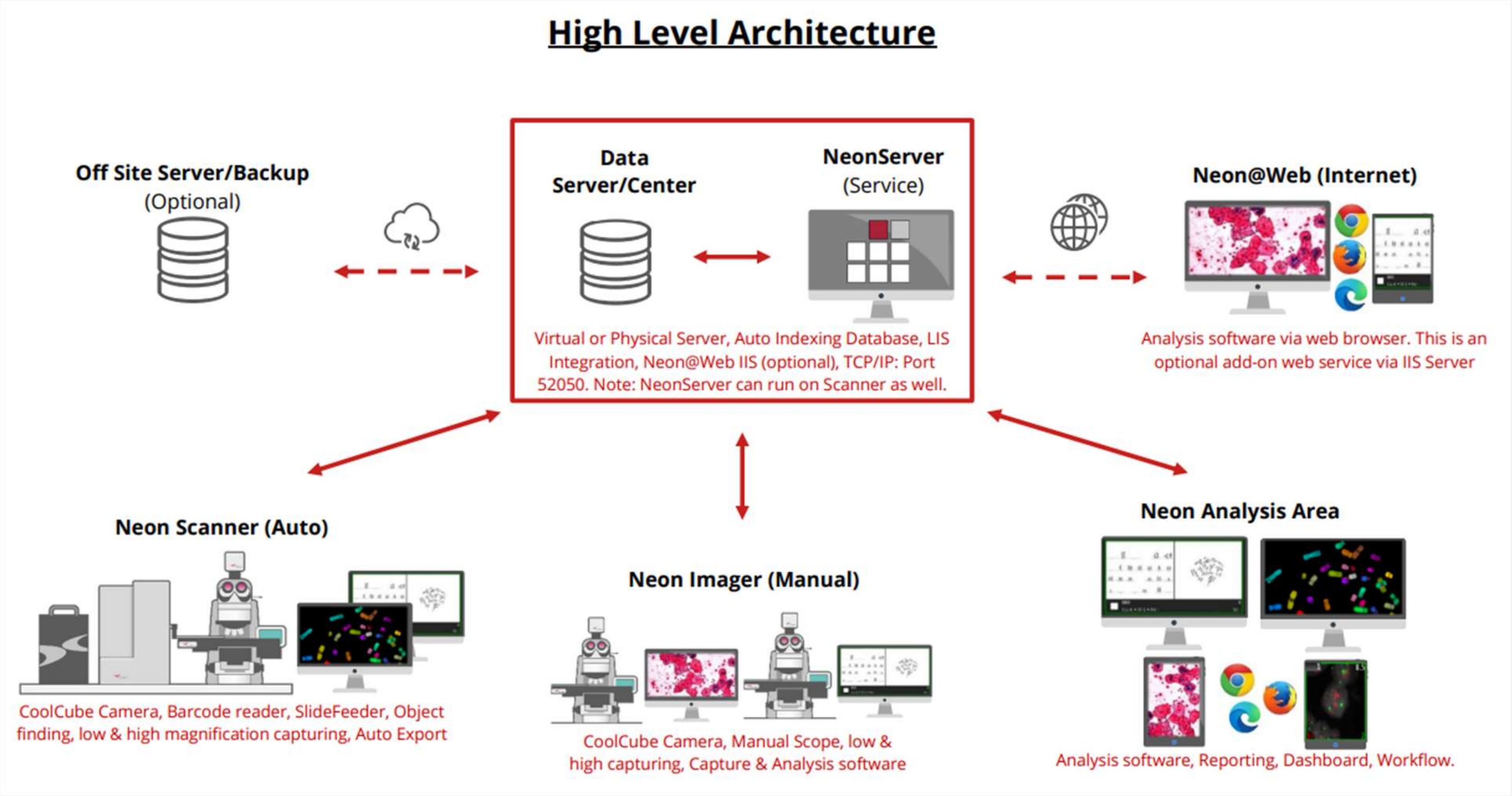
DIGITAL MICROSCOPY





DIGITAL MICROSCOPY

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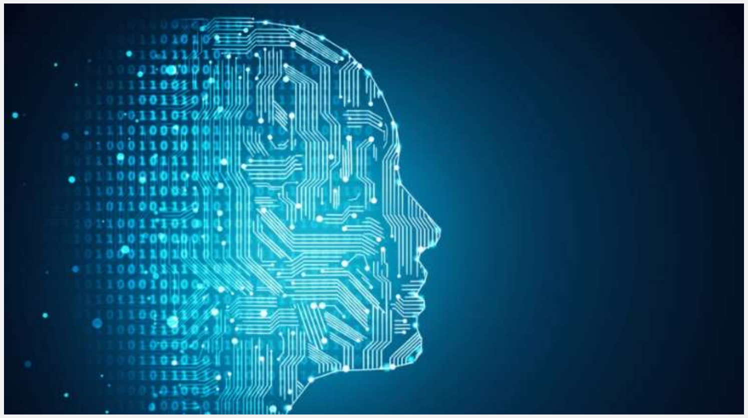
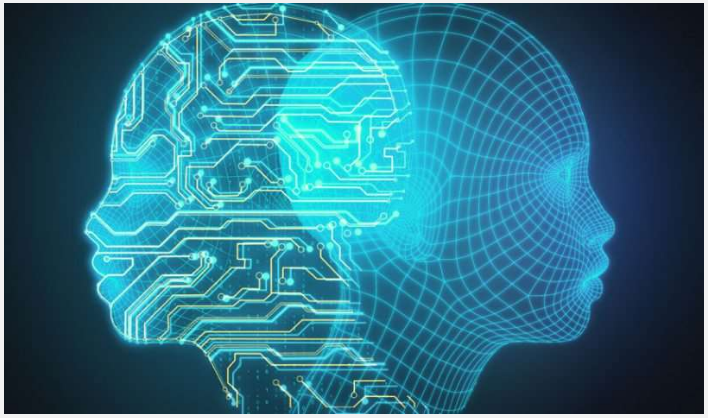
ARTIFICIAL INTELLIGENCE

ARTIFICIAL INTELLIGENCE (AI)

- Computer systems able to perform tasks that normally require human intelligence (visual perception, speech recognition, translation between languages, decision-making etc.)
- Theory and development of computers systems able to perform tasks that normally require human intelligence
- Computer Science, Statistics, Neuroscience, Psychology





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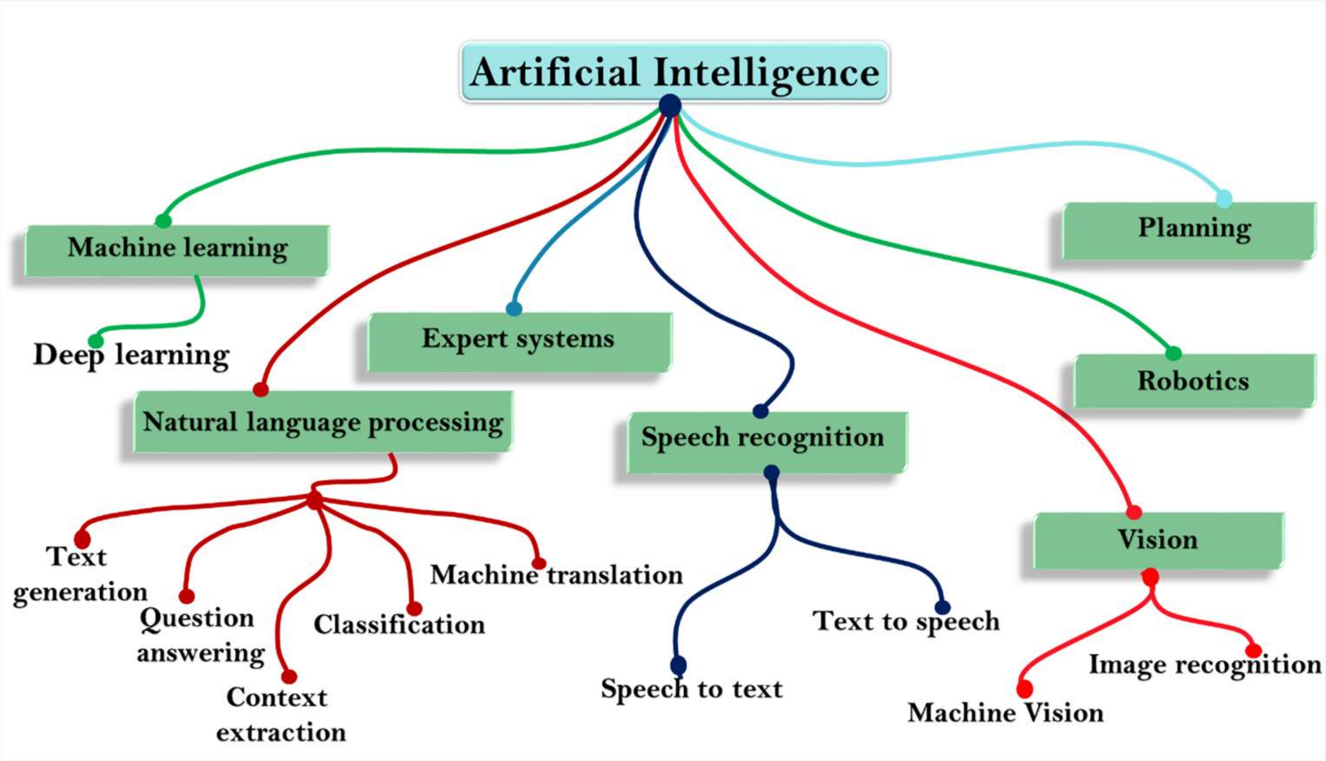

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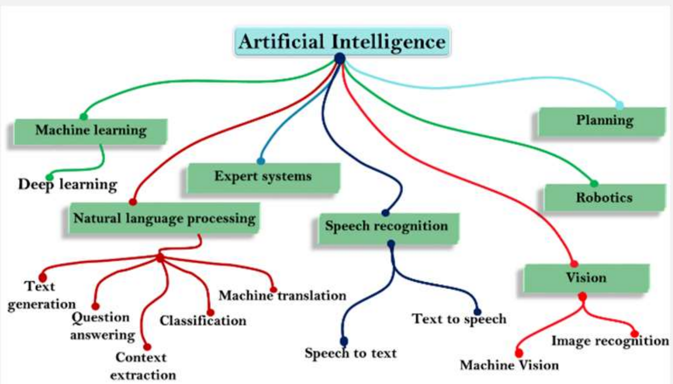

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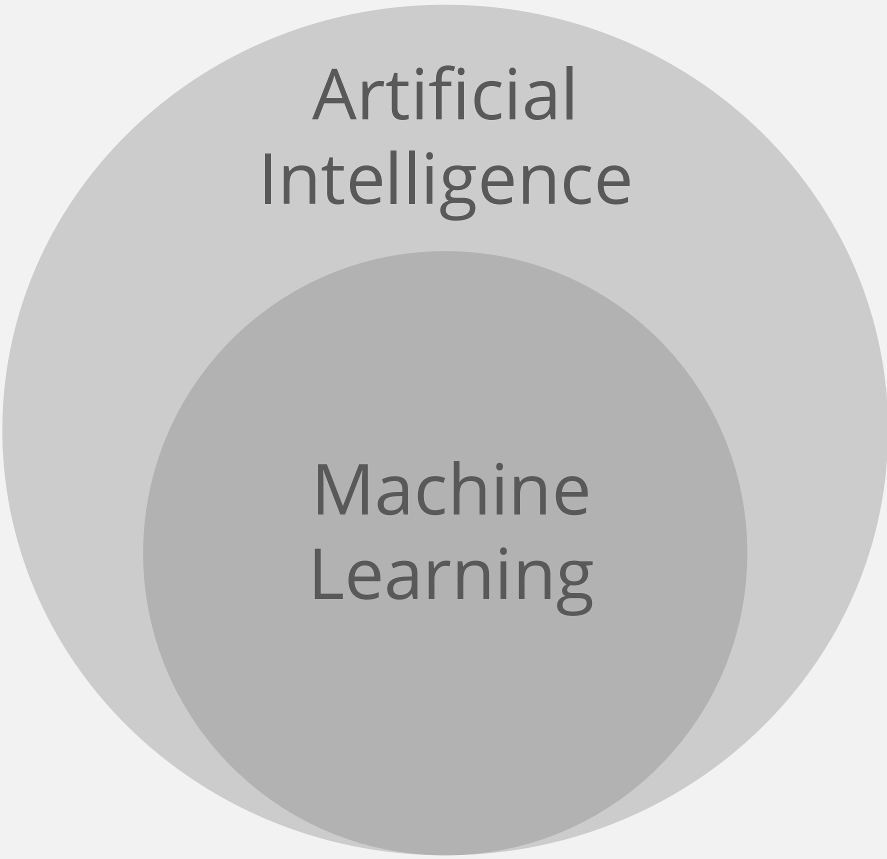
MACHINE LEARNING (ML)

- Computation learning using algorithms to learn from and make predictions on data
- Gives computers the ability to learn without bring explicitly programmed
- the use and development of computer systems that are able to learn and adapt without following explicit instructions, by using algorithms and statistical models to analyze and draw inferences from patterns in data.
- **In classical machine learning, an expert manually designs features that can be used to distinguish objects-of-interest by different parameters, e.g., shape, color, or texture. In this process called feature engineering, the expert transfers knowledge to the algorithm.**



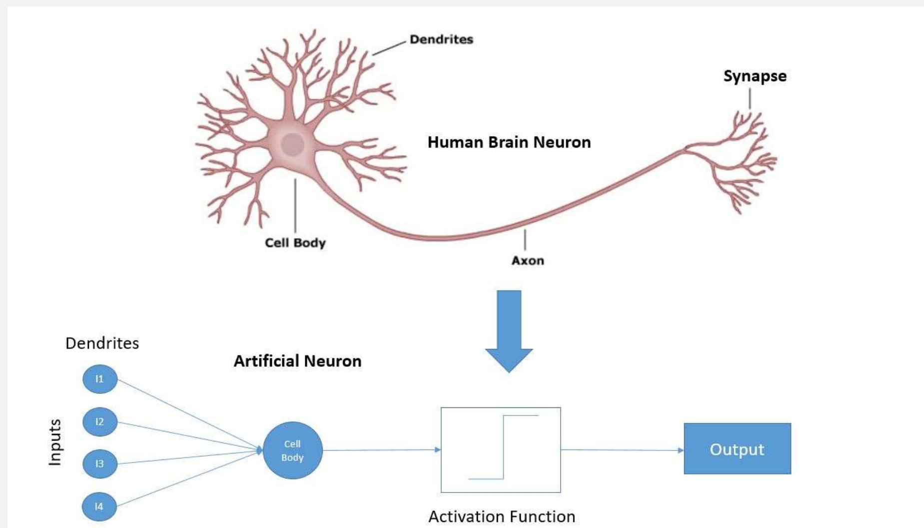
DEEP LEARNING

Artificial Intelligence
Enables a machine to mimic human behavior

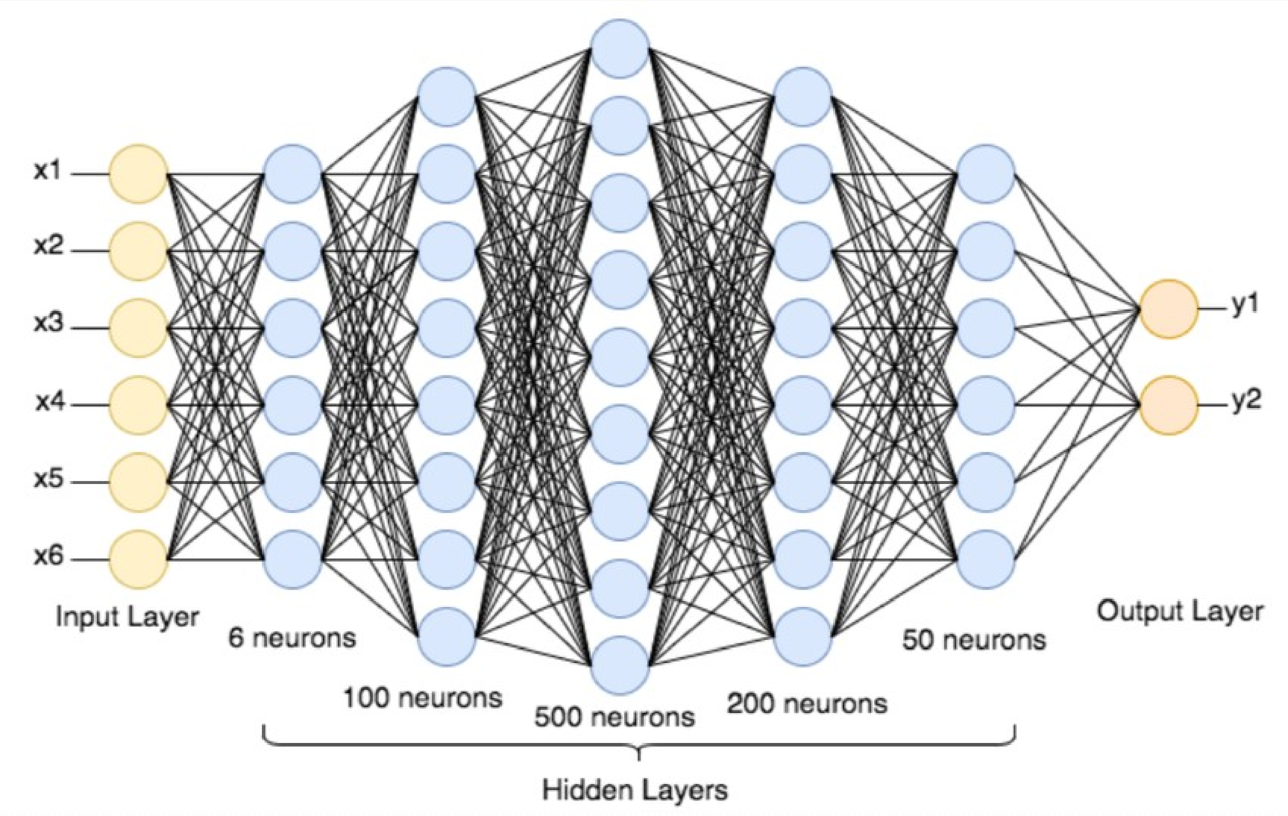
Machine Learning
Distinguishing features engineered by human developer

Deep Learning
Distinguishing features acquired by Deep Neural Network (DNN)

- Machine learning algorithms with brain-like logical structure of algorithms called artificial neural networks
- Biomimetics



DEEP LEARNING



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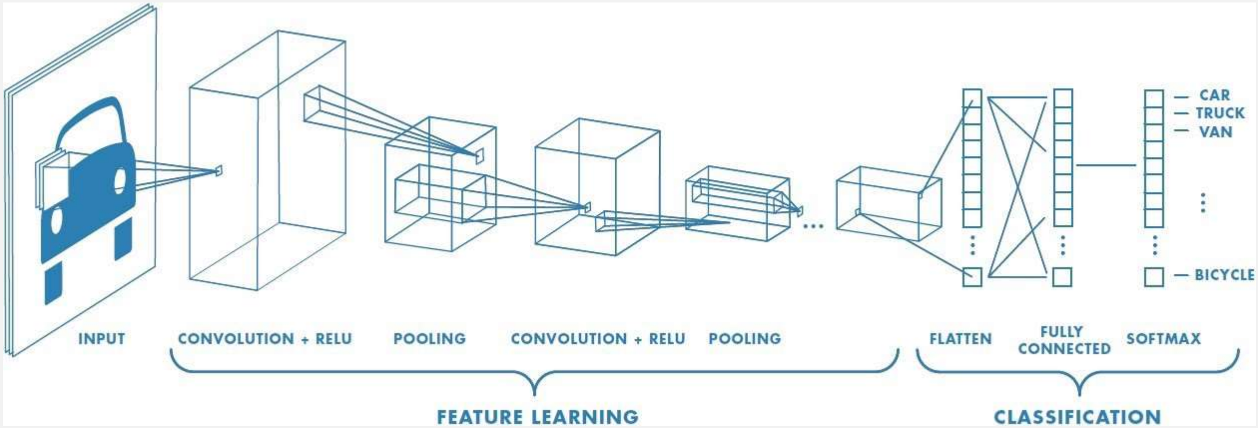
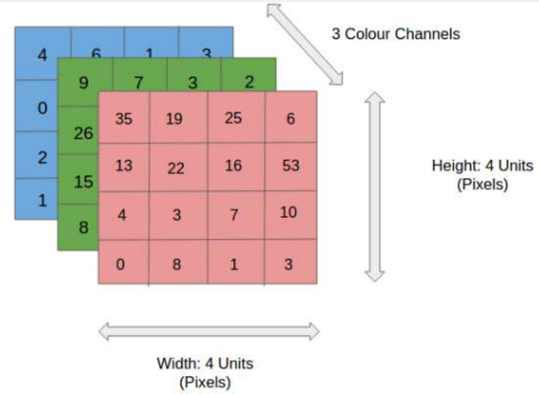
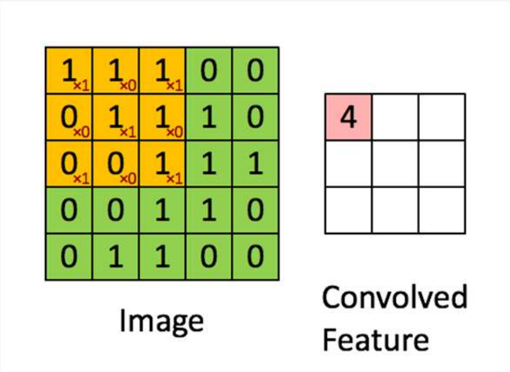




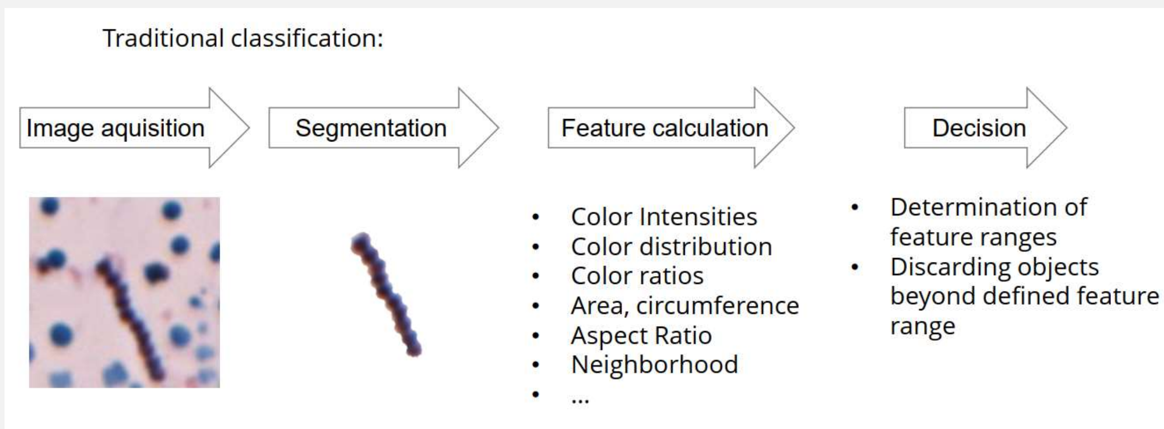


MACHINE LEARNING

Traditional classification:

Feature engineering
- Dark
- Elongated
- Made of small round objects
- Certain size
- …

The programmer “describes” the object, transfers knowledge to the algorithm.

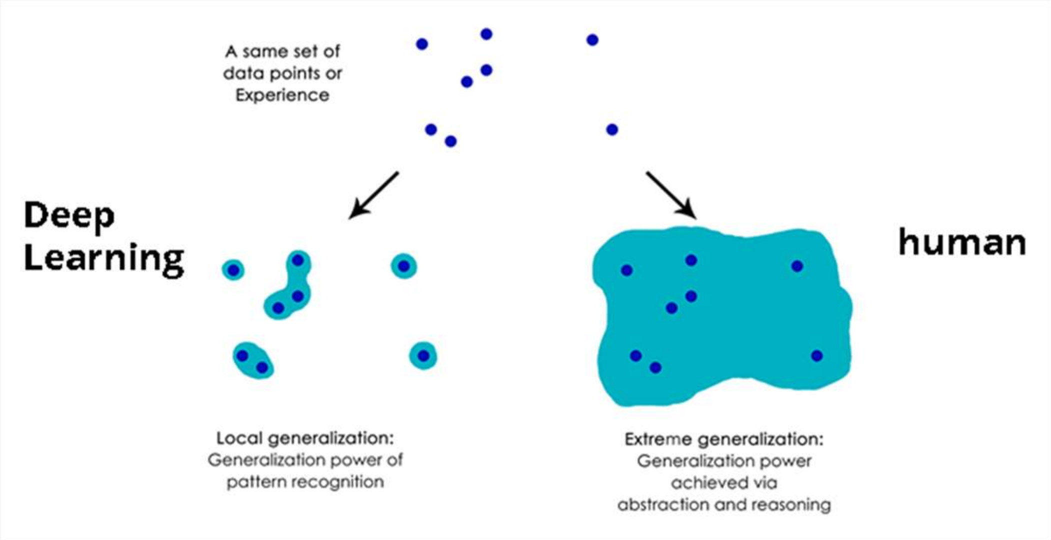


DEEP LEARNING

Deep Learning:
“Neuronal net” just learns that THIS image HAS TO BE “Gram-positive Chain“ = Learning by examples.

Problem: It does not know why. Is it the dark Rod? The blue clouds? The pink background? The noise? ....

AI-ASSISTED DIGITAL MICROSCOPY



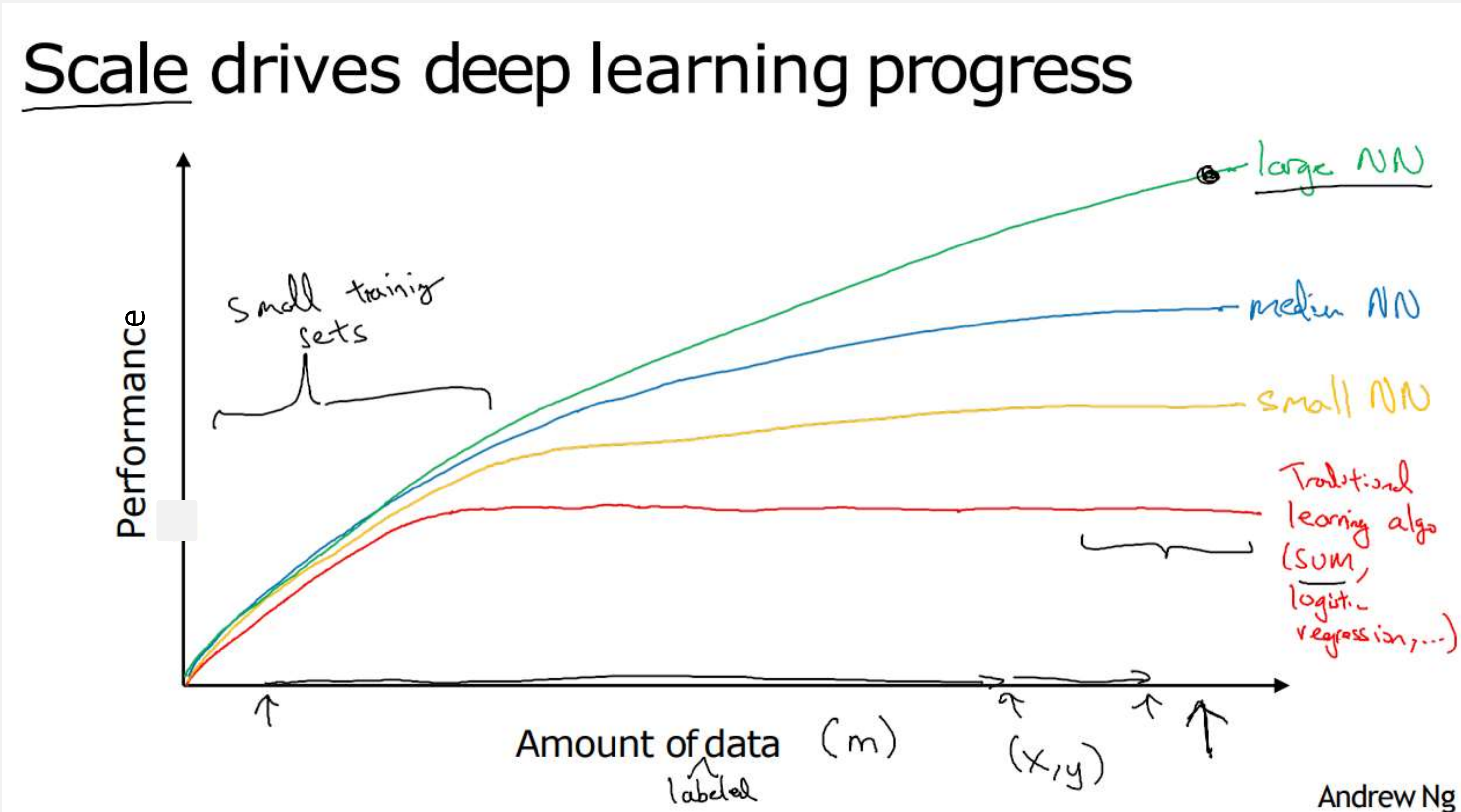
AI-ASSISTED DIGITAL MICROSCOPY

- **Solution**: Show a huge amount of example images of the object in all variations. This is the main reason why deep learning needs big data!

- The "intelligence" **comes from the people** who initially labeled all the images

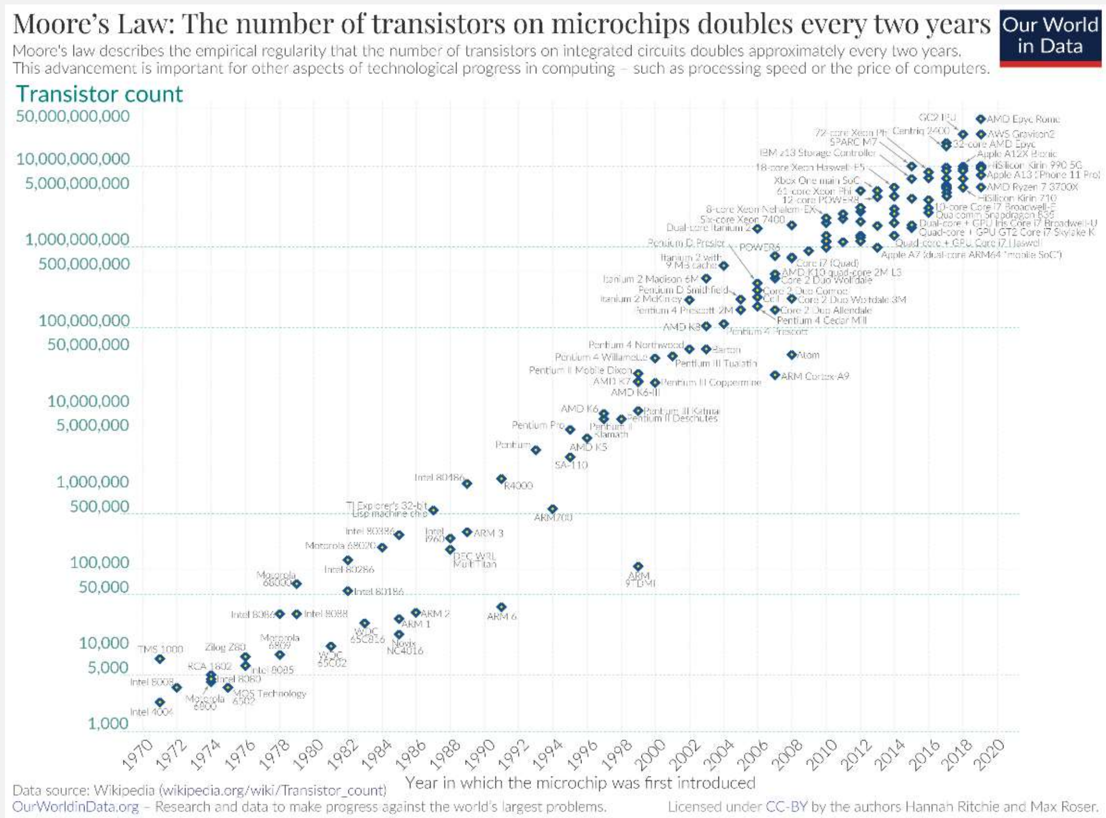
- This has to be done for every class!

WHY NOW?



Source: deeplearning.ai

WHY NOW?



Moore's Law: The number of transistors on microchips doubles every two years
Our World in Data
Moore's law describes the empirical regularity that the number of transistors on integrated circuits doubles approximately every two years.
This advancement is important for other aspects of technological progress in computing – such as processing speed or the price of computers.
Transistor count
50,000,000,000
10,000,000,000
5,000,000,000
1,000,000,000
500,000,000
100,000,000
50,000,000
10,000,000
5,000,000
1,000,000
500,000
100,000
50,000
10,000
5,000
1,000
1970 1972 1974 1976 1978 1980 1982 1984 1986 1988 1990 1992 1994 1996 1998 2000 2002 2004 2006 2008 2010 2012 2014 2016 2018 2020
Year in which the microchip was first introduced
Data source: Wikipedia (wikipedia.org/wiki/Transistor_count)
OurWorldinData.org – Research and data to make progress against the world's largest problems.
Licensed under CC-BY by the authors Hannah Ritchie and Max Roser.

HARDWARE

- CPU: Central Processing Unit
  - Basic arithmetic, logic, input/output processes specified by the instructions in a program
- Processor Core: an individual processor within a CPU

HARDWARE

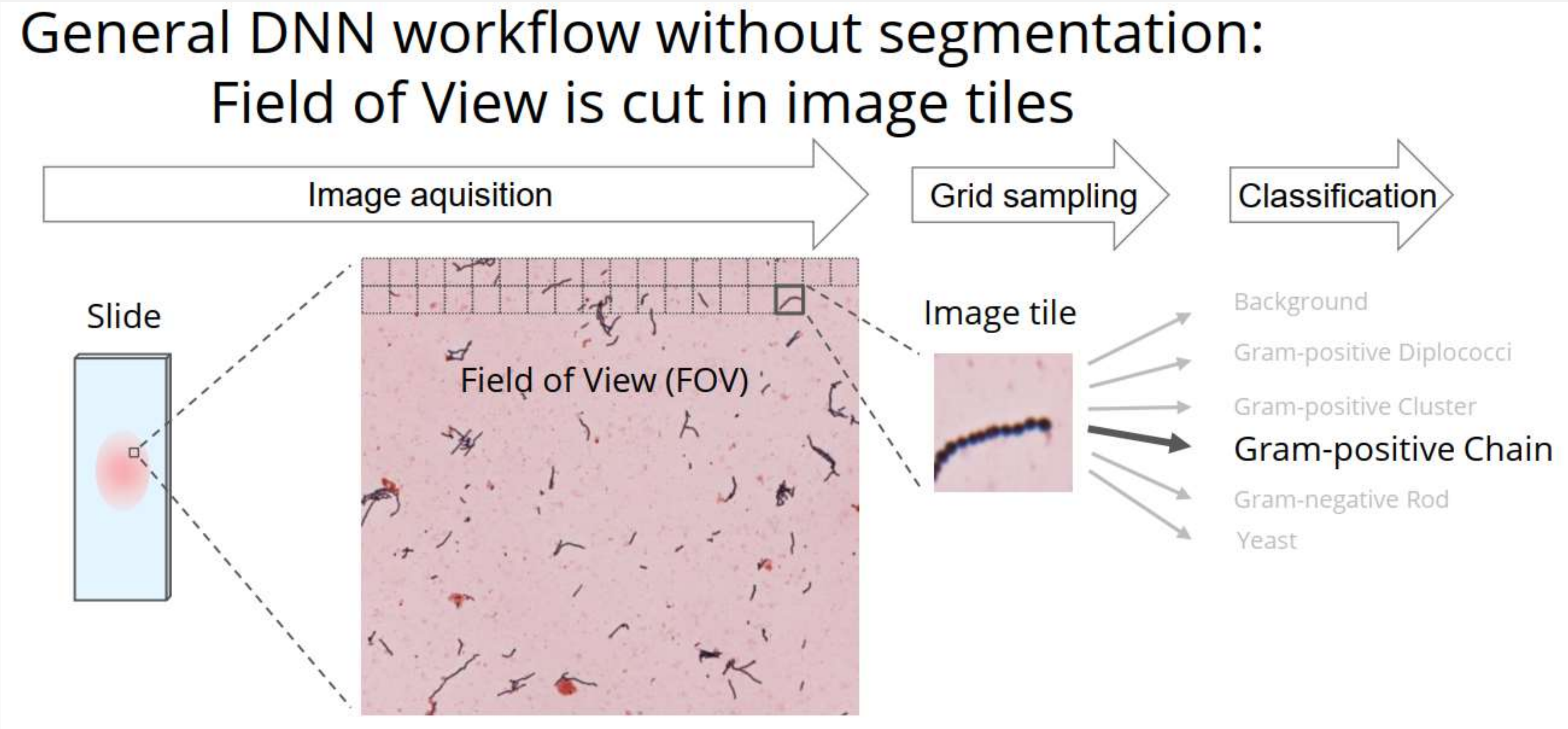
- GPU: Graphics Processing Unit
- CUDA: Compute Unified Device Architecture (NVIDIA)

  (AMD's "Stream Processors")

  - is a specialized programming language that can leverage the GPU in specific ways to perform tasks with greater performance

	RTX 2080	**GTX 1650**
Pipelines / CUDA cores	2944	896
Number of transistors	13600 million	4700 million

AI-ASSISTED DIGITAL MICROSCOPY



AI-ASSISTED DIGITAL MICROSCOPY

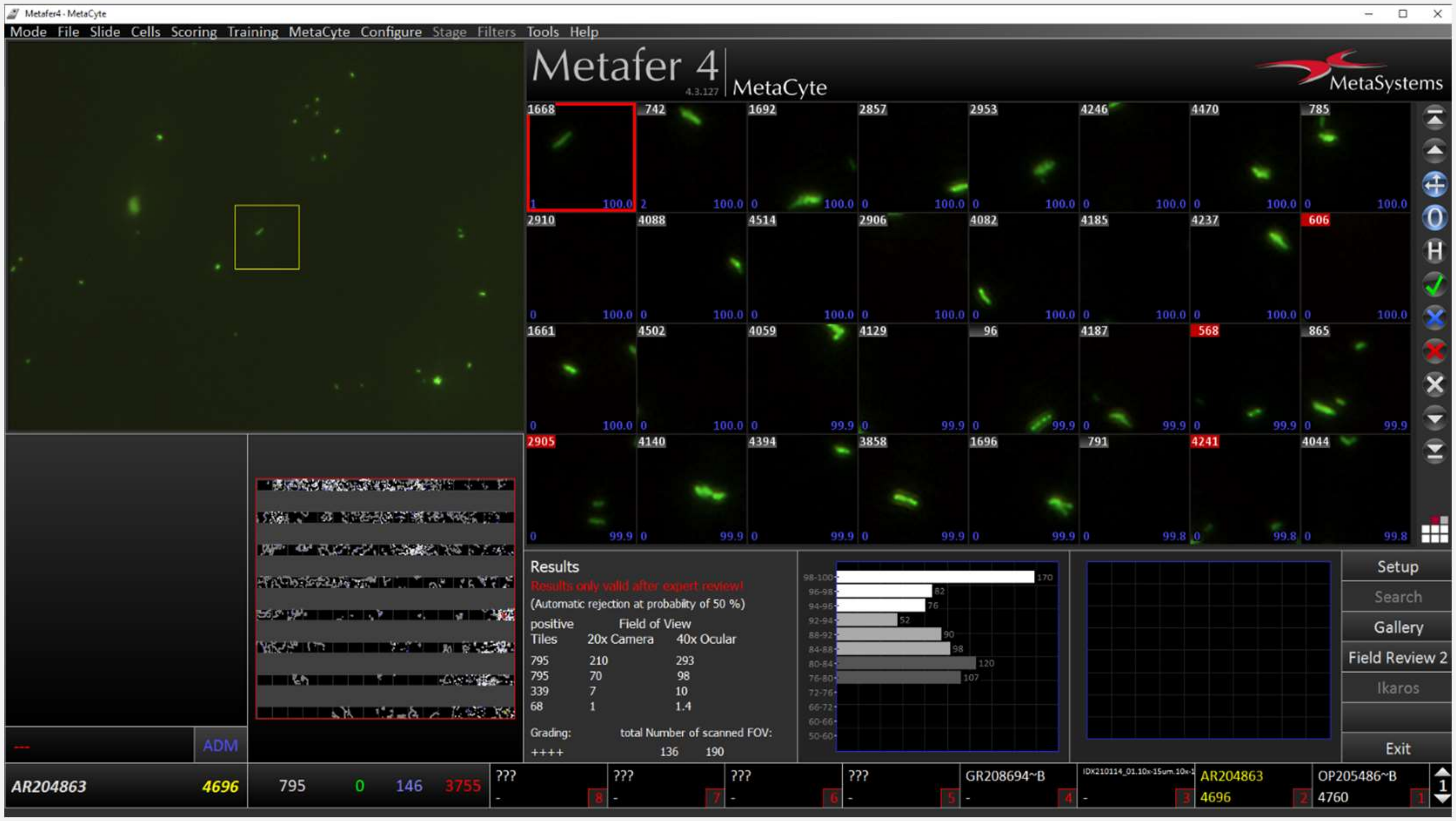
Why automation?

- Less hands-on microscope time
- Higher sensitivity
- Faster results

Challenges for imaging & analysis

- Focusing
  - Negative slides
  - Thick/dense samples
- Stain/slide prep consistency

AFB (AURAMINE-O STAIN)



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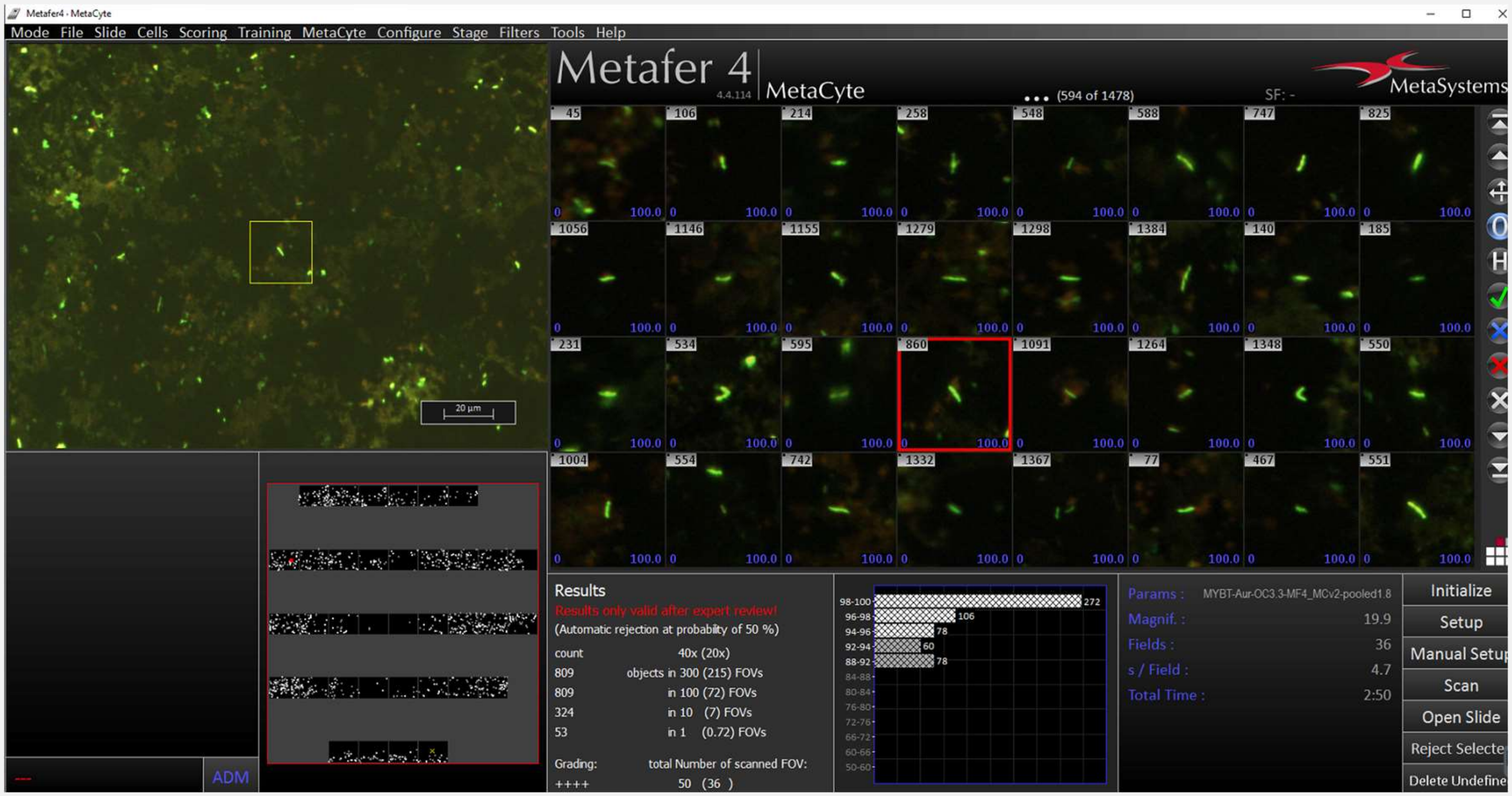

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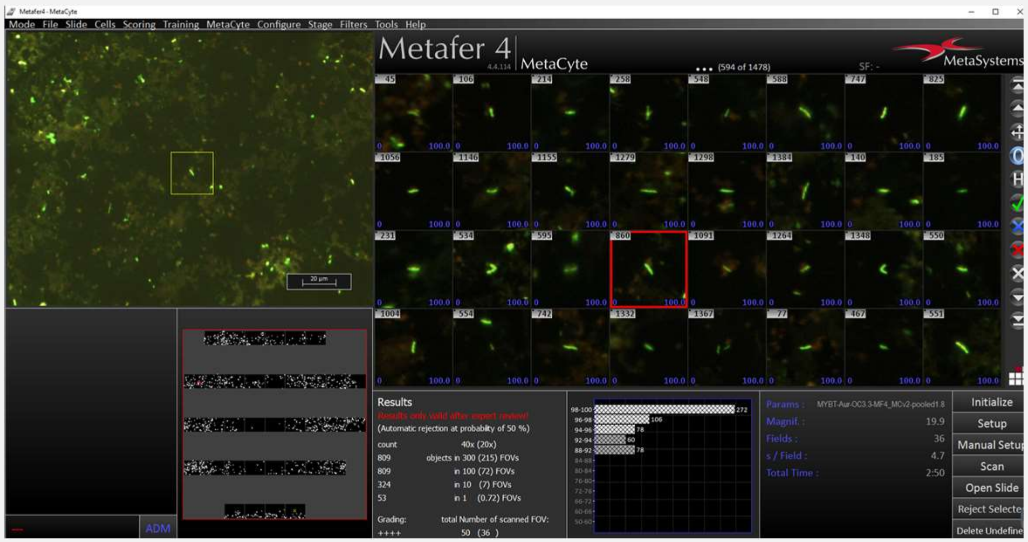

Requirements for automation:

- Focusing on negative slides
    - Use of counter-stain
    - Slides with printed/etched patterns
- Consistent staining
- Consistent slide prep

OVA & PARASITE

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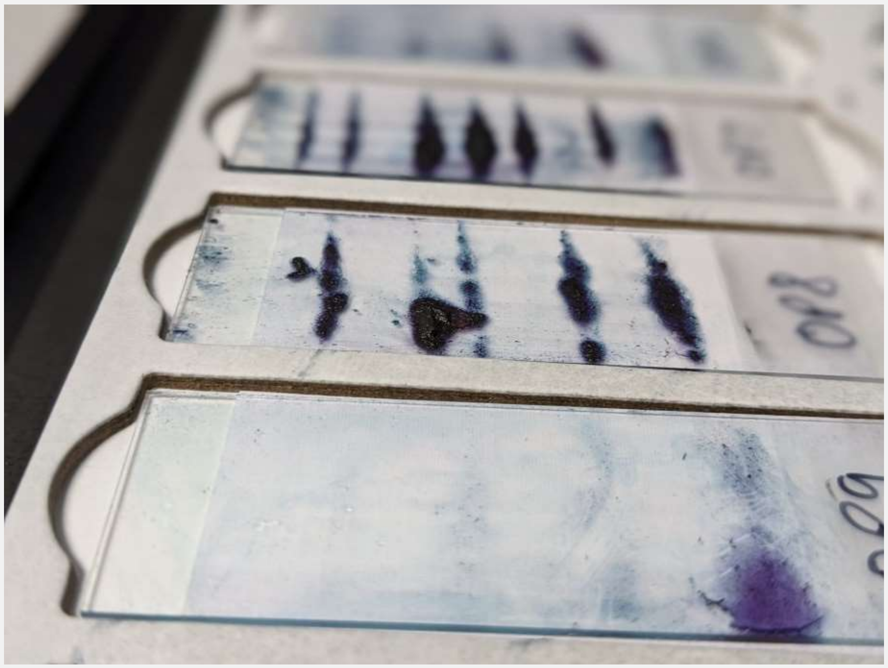
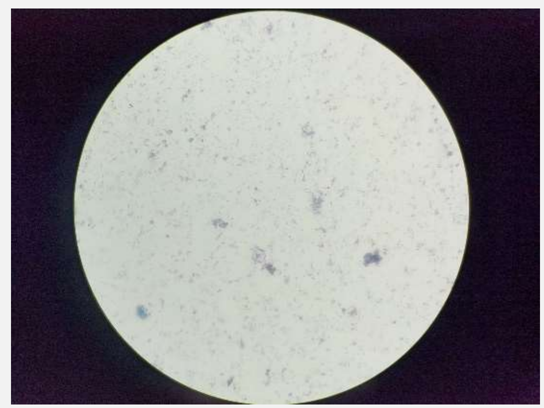
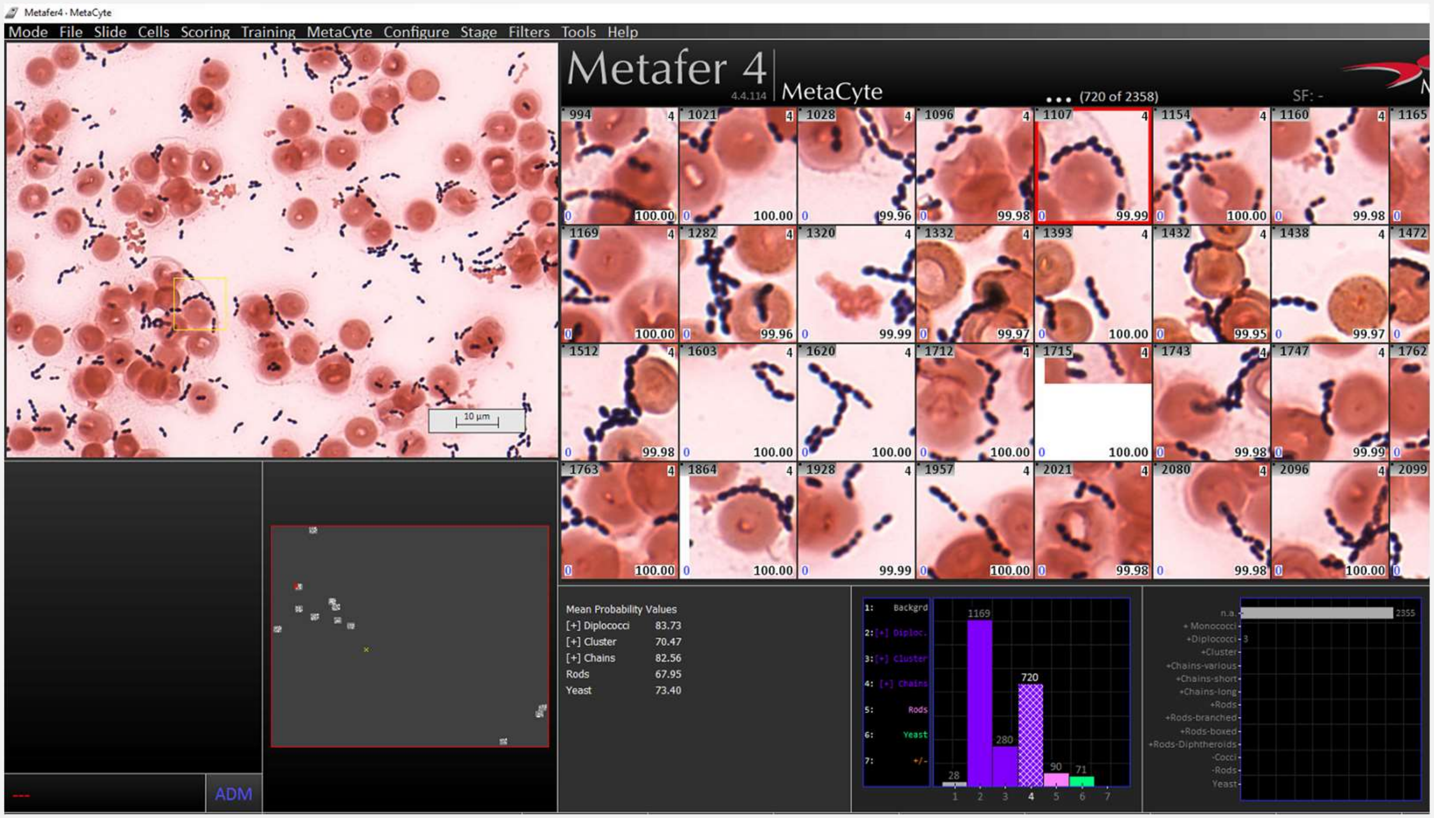
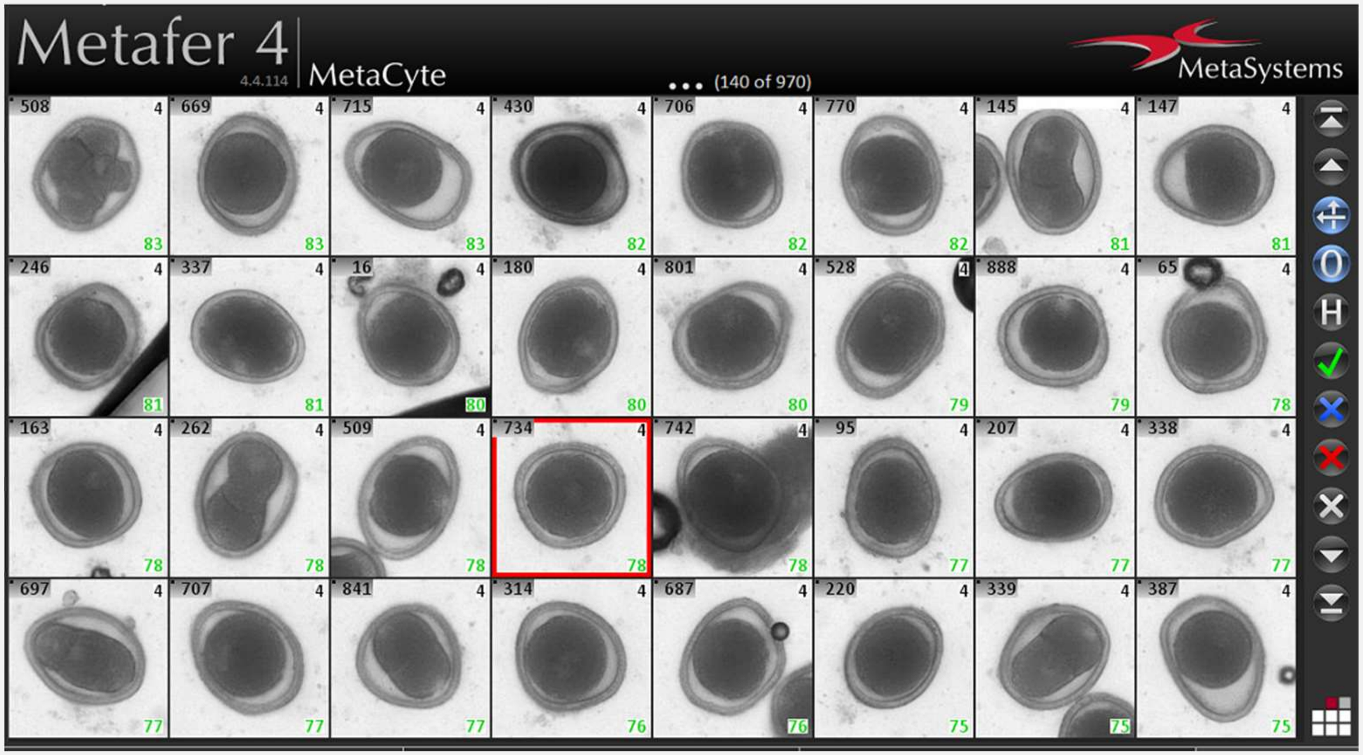




GRAM STAIN


Metafer4 - MetaCyte
Mode File Slide Cells Scoring Training MetaCyte Configure Stage Filters Tools Help
Metafer 4
MetaCyte
(720 of 2358)
Mean Probability Values
[+] Diplococci 83.73
[+] Cluster 70.47
[+] Chains 82.56
Rods 67.95
Yeast 73.40
ADM

OVA & PARASITE



FUTURE OUTLOOK

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- Sample preparation
- Processing
- Data acquisition
- Analysis/identification
- Resulting/reporting