Introduction to convolutional neural networks (CNN)

Advanced Topics in Machine Learning for Bioinformatics and Biomedical Engineering

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Institute for Research and Innovation in Health

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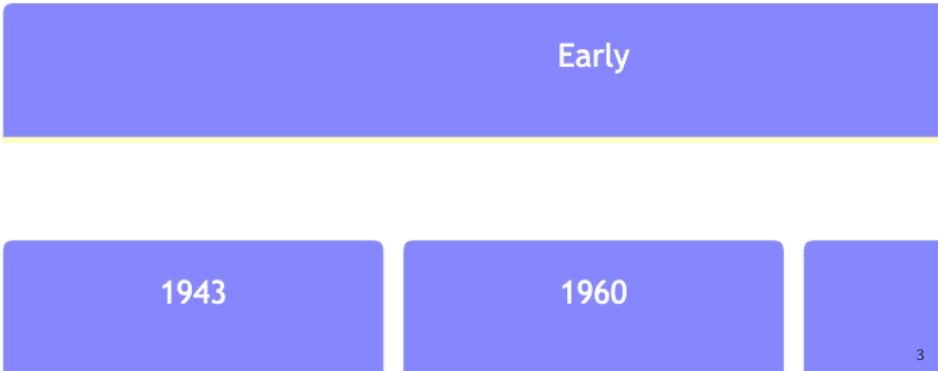
Introduction, historical view

Context:



From local features to deep feature hierarchies

1962: Hubel and Wiesel - Cat's visual cortex

1980: Neocognitron (shift-tolerant pattern recognition) (Fukushima 1980)

Late 80s / 90: LeNet for handwriting (convolution + pooling + backprop) (LeCun et al. 1989, 1998)

2012: AlexNet scales CNNs with GPUs + ReLU + dropout + data (Krizhevsky, Sutskever, and Hinton 2012)

2015–2016: BatchNorm, VGG-style depth, ResNets (Simonyan and Zisserman 2015; Ioffe and Szegedy 2015; He et al. 2016)

2015+: U-Net makes CNN segmentation practical for biomedicine (Ronneberger, Fischer, and Brox 2015a)

Architecure of visual cortex of the cat

David H. Hubel (1926–2013): Neurophysiologist. Canadian-born, trained in medicine/research (MD background) and became a leading experimental neuroscientist. Spent most of his career at Harvard Medical School (Department of Neurobiology), working on visual processing in cats and monkeys.

Torsten N. Wiesel (b. 1924): Neurophysiologist. Swedish-born, medically trained (MD background) and specialized in sensory neurophysiology. Also based at Harvard Medical School during the classic visual cortex work with Hubel.

- Together they ran landmark experiments on the cat's visual cortex (V1), and they received the 1981 Nobel Prize in Physiology or Medicine (shared) for discoveries about information processing in the visual system

Architecture of visual cortex of the cat

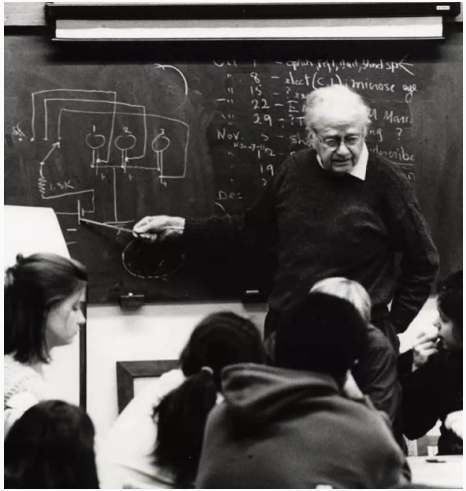


Figure 1: David Hubel

Figure 2: Torsten Wiesel

- Hubel and Wiesel: *Cat's visual cortex*

Cortex organization

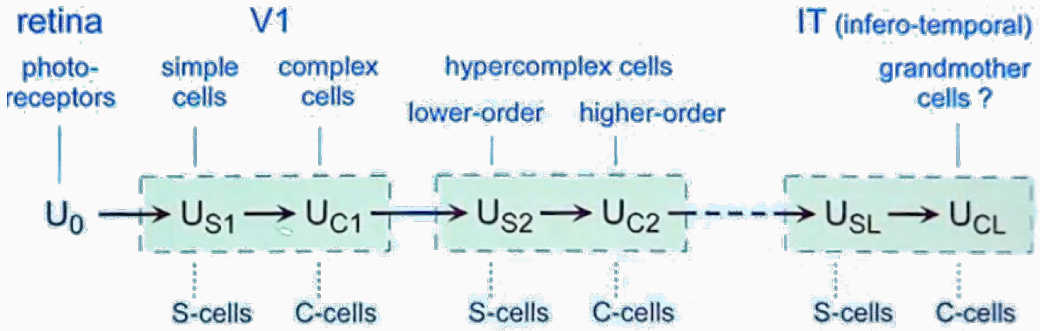
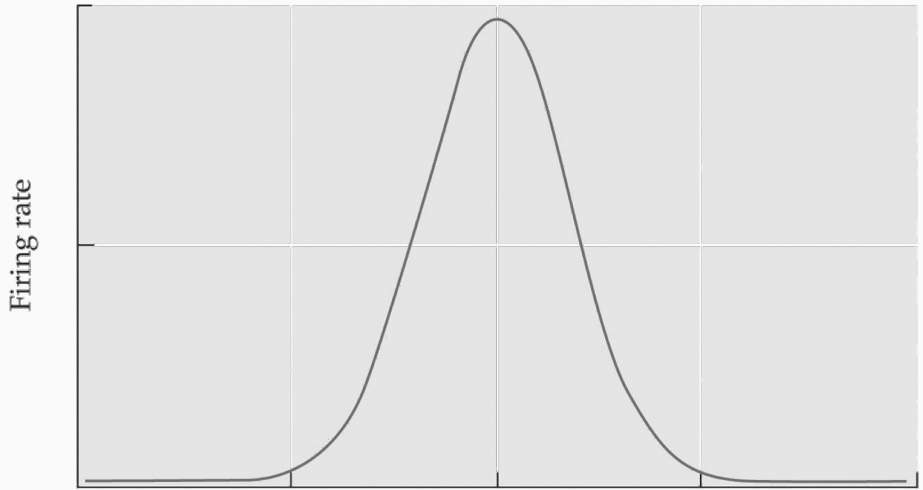
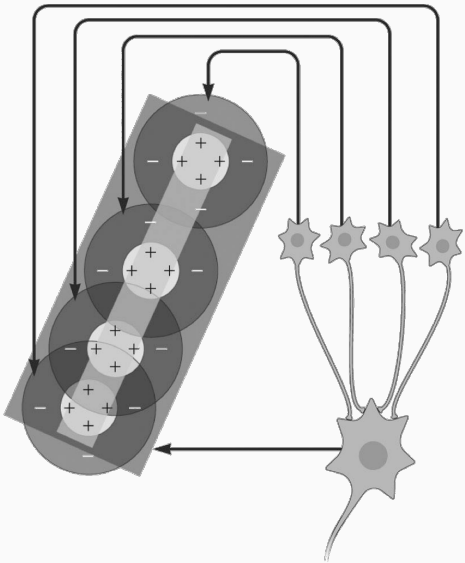


Figure 3: functional architecture of simple cells and complex cells in the early visual cortex

Orientation matters



Receptive fields



- A **receptive field** is the region of the visual field where a stimulus will change the firing rate of a neuron
- Receptive fields in V1 are small and retinotopic (map the visual field)
- Tend to grow in size with eccentricity, and become more complex through hierarchical pooling of earlier inputs
- V1 neurons respond best to specific local features, especially oriented edges/bars, at a particular location, orientation, spatial frequency, and often motion direction

Receptive fields

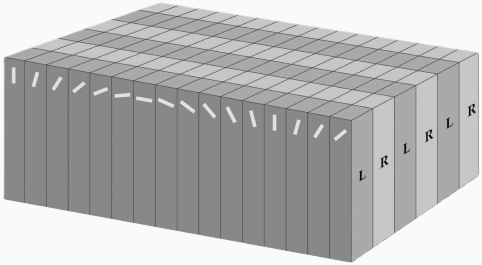


Figure 6: Receptive Fields in Striate Cortex

orientation column: vertical arrangement of neurons – systematic, progressive change in preferred orientation; all orientations were encountered in a distance of about 0.5 mm

hypercolumn: 1-mm block of striate cortex containing:

all the machinery necessary to look after everything the striate cortex is responsible for, in a certain small part of the visual world (Hubel, 1982)

Feature detectors

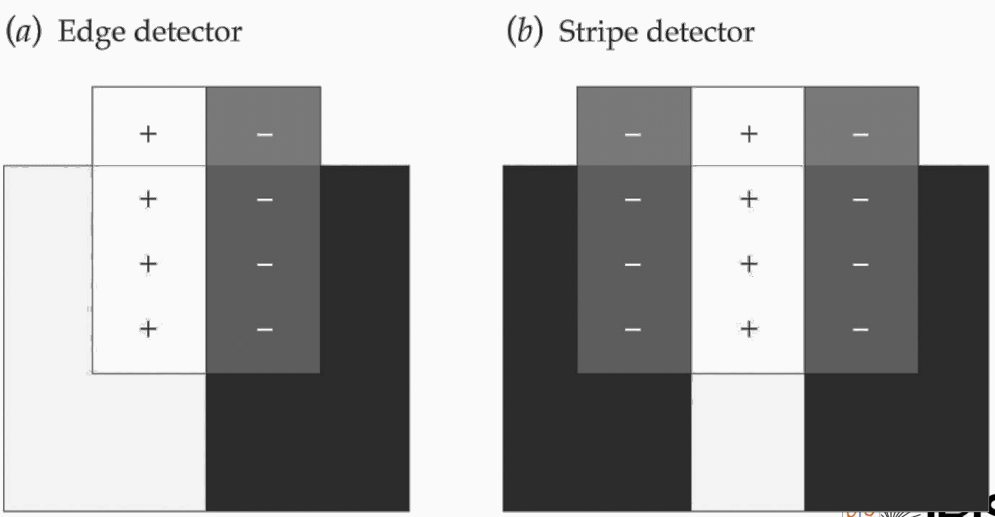


Figure 7: edge end stripe detectors

Feature detectors

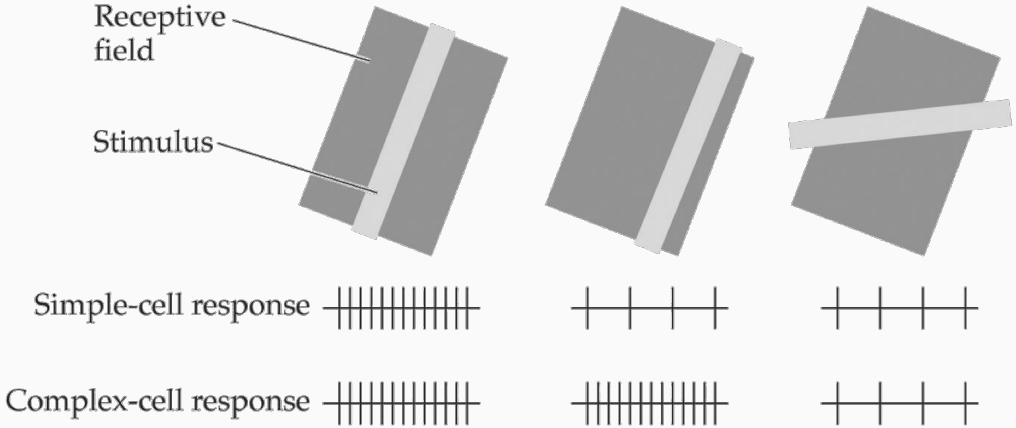
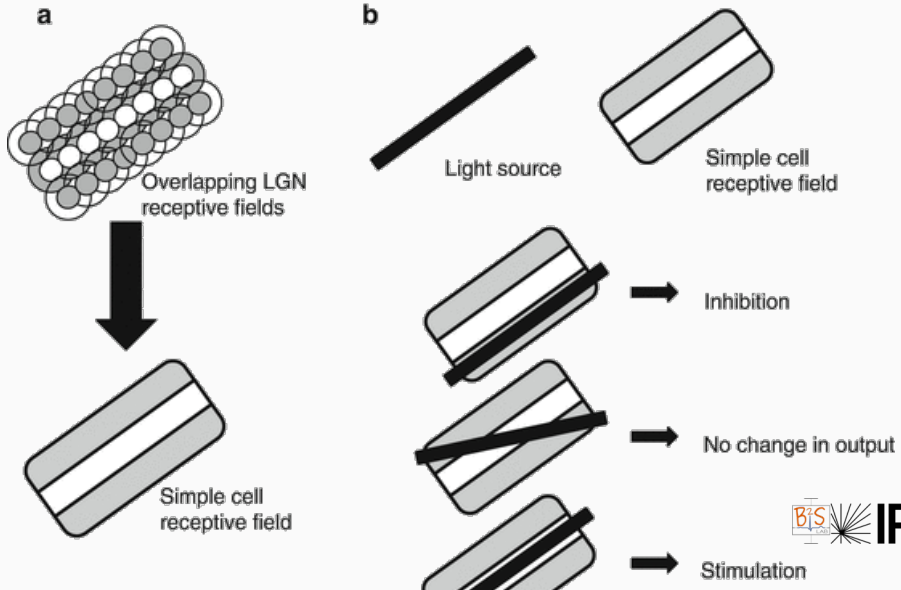


Figure 8: receptive fields vs stimulus

Feature detectors



Main findings (V1 / striate cortex)

- Feature-selective receptive fields: many V1 neurons respond best to oriented edges/bars (not spots).
- Cell types:
  - Simple cells: distinct ON/OFF subregions; tuned to position + orientation.
  - Complex cells: orientation-selective but more position-invariant; often direction selective.
- Hierarchical building blocks: more complex tuning can be explained by pooling simpler inputs (LGN[1] -> simple -> complex).
- Columnar organization: nearby neurons share preferences, forming orientation columns.

[1] lateral geniculate nucleus

Cortex organization (maps + columns)

- Retinotopy: V1 contains an orderly map of visual space.
- Ocular dominance: alternating bands biased to left vs right eye input; cells range from monocular to binocular.
- Systematic orientation map: preferred orientation changes smoothly across cortex (later visualized as pinwheel-like patterns).
- Cortex is a structured, modular feature extractor—a blueprint that shaped computational vision and CNN intuition.

Neocognitron: (Fukushima)

NEOCOGNITRON: A NEW ALGORITHM FOR PATTERN RECOGNITION TOLERANT OF DEFORMATIONS AND SHIFTS IN POSITION

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(*Received* 15 *May* 1981, *in revised form* 27 *October* 1981, *received for publication* 23 *December* 1981)

Abstract—Suggested by the structure of the visual nervous system, a new algorithm is proposed for pattern recognition. This algorithm can be realized with a multilayered network consisting of neuron-like cells. The network, "neocognitron", is self-organized by unsupervised learning, and acquires the ability to recognize stimulus patterns according to the differences in their shapes. Any patterns which we human beings judge to be alike are also judged to be of the same category by the neocognitron. The neocognitron recognizes stimulus patterns correctly without being affected by shifts in position or even by considerable distortions in shape of the stimulus patterns.

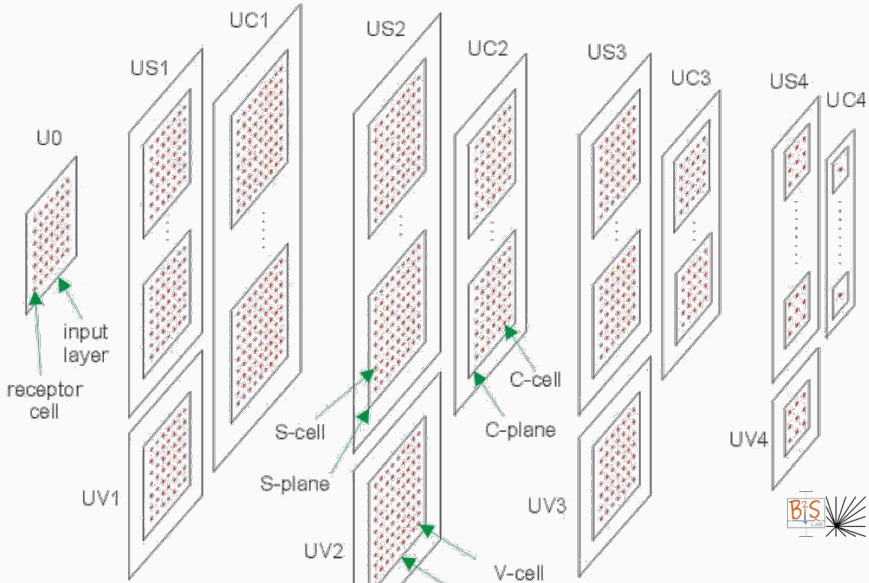
Visual pattern recognition
Unsupervised learning
Neural network model
Deformation-resistant
Self-organization
Visual nervous system
Position-invariant
Multilayered network
Simulation

(Fukushima 1980)

Neocognitron: (Fukushima)

- Architecture inspired by the mammalian visual cortex
- A hierarchical, multilayer neural network originally proposed for handwritten character recognition.
- Core promise: recognize learned patterns even when they are partially shifted, rotated, or otherwise distorted.
- Two classical variants are often described:
  - *self-organized* learning (without a teacher)
  - *supervised* learning (with a teacher; easier to explain for the core mechanism)

Neocognitron Network Structure



S Layer

S layer

- Feature Detector
- Each cell in the layer detects the presence of a different feature in the layer's input data
- Adaptable Weights
- Each S-cell is accompanied by a V-cell

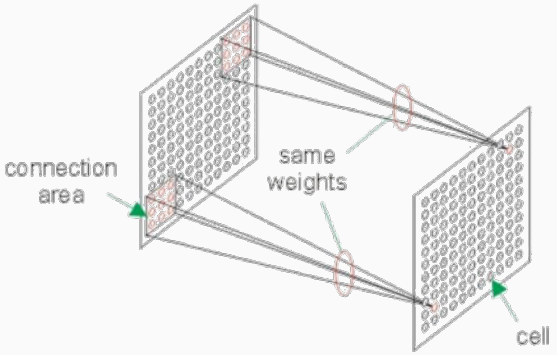
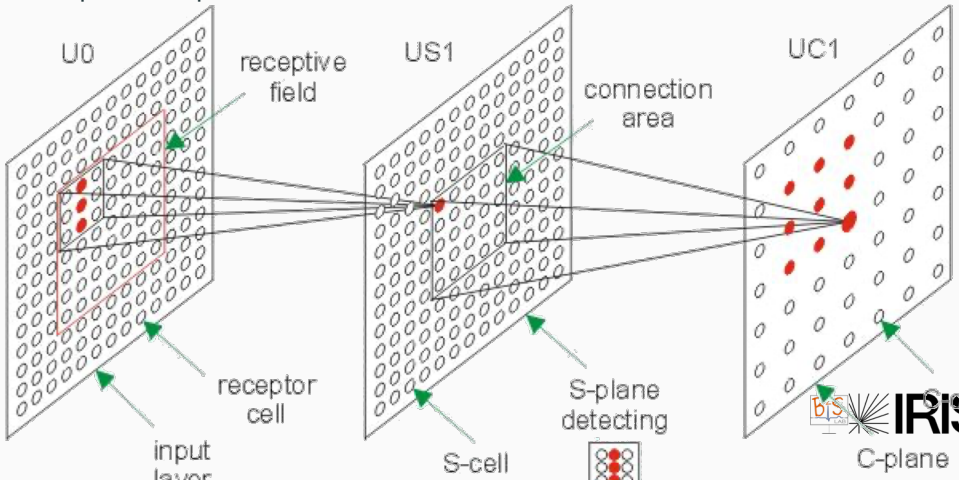


Figure 11: s-layer

C Layer

- hiding the exact position of the detected feature
- Improves the network robustness to deformations of the pattern - scaling, shifting of the pattern's position, or noise

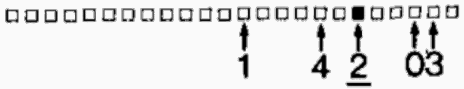


Training

- Weights get initialized with small positive values
- For each training instance, if a cell is the most active in its region and in its plane, then its active weights get reinforced
- Show the same few training instances over and over again
- Math works out so that an S-cell's weights directly correspond to the feature it is recognizing and activation

Deformation-tolerant recognition

- Unsupervised handwritten character recognition
- The model is designed to output category responses (e.g., “0” vs “1”) even when inputs are not identical to training examples.
- Input - Unlabeled Images
- Output:



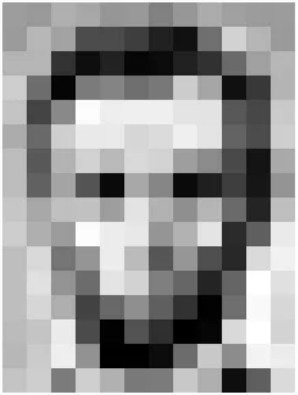
Showtime

vids/neocogst.mp4

From https://www.youtube.com/watch?v=oVYCjL54qoY

The “C”

About Images



157	153	174	168	150	152	129	151	172	161	155	156
155	182	163	74	75	62	33	17	110	210	180	154
180	180	50	14	34	6	10	33	48	106	159	181
206	109	5	124	131	111	120	204	166	15	56	180
194	68	137	251	237	239	239	228	227	87	71	201
172	105	207	233	233	214	220	239	228	98	74	206
188	88	179	209	185	215	211	158	139	75	20	169
189	97	165	84	10	168	134	11	31	62	22	148
199	168	191	193	158	227	178	143	182	106	36	190
205	174	155	252	236	231	149	178	228	43	95	234
190	216	116	149	236	187	86	150	79	38	218	241
190	224	147	108	227	210	127	102	36	101	255	224
190	214	173	66	103	143	96	50	2	109	249	215
187	196	235	75	1	81	47	0	6	217	255	211
183	202	237	145	0	0	12	108	200	138	243	236
195	206	123	207	177	121	123	200	175	13	96	218

157	153	174	168	150	152	129	151	172	161	155	156
155	182	163	74	75	62	33	17	110	210	180	154
180	180	50	14	34	6	10	33	48	106	159	181
206	109	5	124	131	111	120	204	166	15	56	180
194	68	137	251	237	239	239	228	227	87	71	201
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188	88	179	209	185	215	211	158	139	75	20	169
189	97	165	84	10	168	134	11	31	62	22	148
199	168	191	193	158	227	178	143	182	106	36	190
205	174	155	252	236	231	149	178	228	43	95	234
190	216	116	149	236	187	86	150	79	38	218	241
190	224	147	108	227	210	127	102	36	101	255	224
190	214	173	66	103	143	96	50	2	109	249	215
187	196	235	75	1	81	47	0	6	217	255	211
183	202	237	145	0	0	12	108	200	138	243	236
195	206	123	207	177	121	123	200	175	13	96	218

Figure 12: CS representation of an image

Convolutions

A convolution (denoted by $*$) is an operation on two functions f and k that produces a third function $(f * k)$.

In machine learning:

- f is the **input**
- k is a **kernel**
- output is a **feature map**

A **convolutional neural network (CNN)** uses convolution in place of general matrix multiplication in at least one layer. (Goodfellow, Bengio, and Courville 2016) It's main purpose is not dimensionality reduction but feature extraction.

Convolution definition

Definition (continuous and discrete)

Continuous (1D)

$$(f * k)(t) = \int_{-\infty}^{\infty} f(\tau)\, k(t - \tau)\, d\tau$$

Discrete (1D)

$$(f * k)[n] = \sum_{m=-\infty}^{\infty} f[m]\, k[n - m]$$

2D (images)

$$(f * k)[i, j] = \sum_{u} \sum_{v} f[u, v]\, k[i - u, j - v]$$

In CNNs, f is typically a tensor (e.g., height $\times$ width $\times$ channels), and k is learned.

Convolution properties

Commutativity (but. . .)

Mathematically (under standard conditions):

$$(f * k) = (k * f)$$

But: many deep-learning libraries implement **cross-correlation**:

$$(f \star k)[n] = \sum_m f[m]\, k[n+m]$$

Cross-correlation differs from convolution by a flip of the kernel index. CNNs still *learn* filters effectively, but the strict commutativity property doesn't directly apply to the implemented operator.

Convolution properties

Linearity (superposition)

Convolution is **linear** in each argument:

- $(af_1 + bf_2) * k = a(f_1 * k) + b(f_2 * k)$
- $f * (ak_1 + bk_2) = a(f * k_1) + b(f * k_2)$

This is one reason convolutions pair naturally with linear algebra operations in neural nets: they preserve additivity and scaling.

Convolution properties

Associativity (stacking filters)

Convolution is **associative**:

$$(f * k_1) * k_2 = f * (k_1 * k_2)$$

Interpretation for CNNs:

- If you stack *linear* convolution layers **without** nonlinearities, the result is equivalent to a **single convolution** with an "effective kernel" $k_{\text{eff}} = k_1 * k_2$.
- In practice, CNNs insert nonlinearities (ReLU, GELU, etc.), so depth adds expressive power beyond a single convolution.

Convolutions properties

Distributive property:

$$f * (k_1 + k_2) = (f * k_1) + (f * k_2)$$

Identity element: the (Dirac/Kronecker) delta acts like "do nothing".

- Continuous: $f * \delta = f$
- Discrete: $f[n] * \delta[n] = f[n]$ where $\delta[0] = 1$, $\delta[n \neq 0] = 0$

In CNN terms, an "identity-like" kernel (e.g., a 2D kernel with a 1 in the center and 0 elsewhere) passes features through unchanged.

Convolutions properties

Shift / translation equivariance (key CNN inductive bias)

Let $(T_a f)(t) = f(t - a)$ be a shift operator. Then:

$$(T_a f) * k = T_a(f * k)$$

So, if the input shifts, the feature map shifts by the same amount: **equivariance**.

For our CNNs:

- Features (edges, textures) can be detected **anywhere** using the same kernel.
- Pooling/striding can trade equivariance for approximate **invariance** (e.g., small translations cause smaller output changes).

Convolutions properties

Differentiation and smoothing

Convolution interacts nicely with derivatives (when everything is well-behaved):

$$\frac{d}{dt}(f * k) = (f' * k) = (f * k')$$

Classic signal-processing intuition:

- Convolving with a smoothing kernel (e.g., Gaussian) reduces noise.
- Convolving with a derivative-like kernel highlights changes (edges).

CNN filters often learn patterns that resemble smoothing, edge detection, oriented gradients, and more—especially in early layers.

Convolutions properties

Convolution theorem (frequency-domain view)

Let $\mathcal{F}$ be the Fourier transform. Then:

$$\mathcal{F}\{f * k\} = \mathcal{F}\{f\}\,\mathcal{F}\{k\}$$

Meaning:

- Convolution in space/time becomes multiplication in frequency.
- k acts like a **frequency response** (low-pass, high-pass, band-pass).

Practical CNN angle:

- Some large-kernel convolutions can be computed faster via FFT-based methods, though many modern CNNs rely on highly optimized spatial-domain kernels on GPUs.

Convolutions properties

Separable, dilated, strided, and padded convolutions

Separable kernels: if $k(x, y) = a(x)b(y)$, then:

$$f * k = (f * a) * b$$

This can reduce compute (used in depthwise-separable convolutions). (we will see more about this later)

Dilation: increases receptive field without increasing parameters.

Stride: samples the output every s steps (downsampling).

Padding: controls boundary behavior and output size ("same" vs "valid").

These variants change *how* the convolution is applied, but they build on the same core operator.

Convolution properties

Backprop: gradients are (cross-)convolutions too

For a loss L and output $y = f * k$, the gradients have convolution structure:

- Gradient w.r.t. input resembles convolution of upstream gradient with a flipped kernel.
- Gradient w.r.t. kernel resembles convolution (or correlation) between the input and upstream gradient.

ok, but what is a convolution?

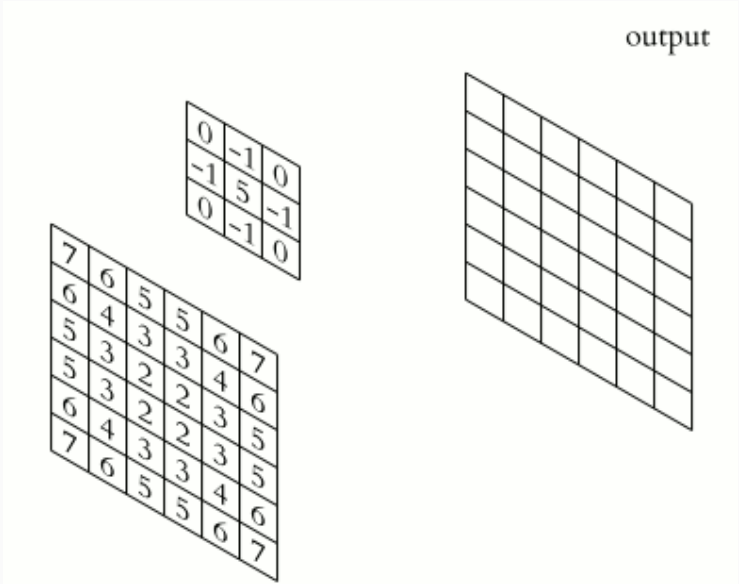
vids/convst.mp4

from https://www.youtube.com/watch?v=KuXjwB4LzSA

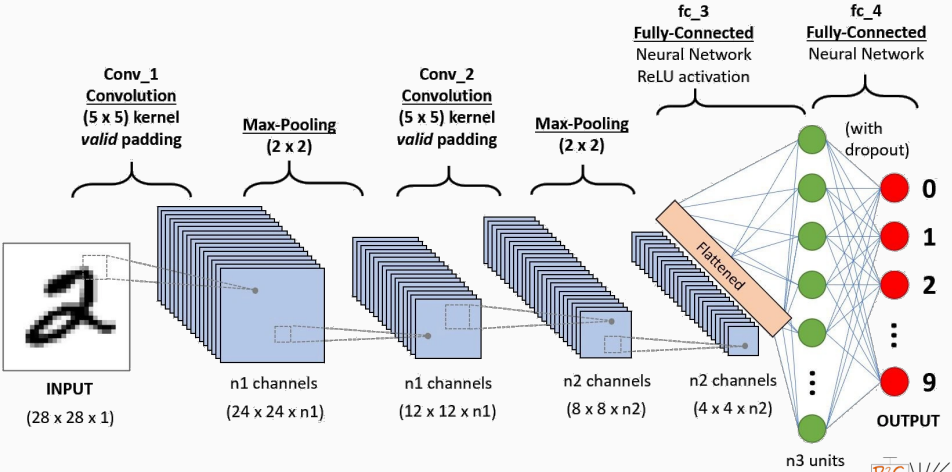
Why CNNs are efficient:

- **Parameter sharing**: one kernel is reused across positions.
- **Local connectivity**: kernels are small relative to the input.
- **Receptive field growth**: stacking layers increases the region of input each output depends on.

Conv 2D


output
0 -1 0
-1 5 0
0 -1 0
7 6 5 5 6 7
6 4 3 3 4 6
5 3 2 2 3 5
5 3 2 2 3 5
6 4 3 3 4 6
7 6 5 5 6 7

Basic CNN Structure

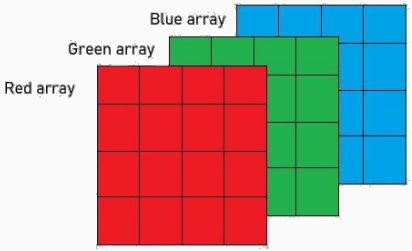


Three components

- channels
- strides
- padding

Channels

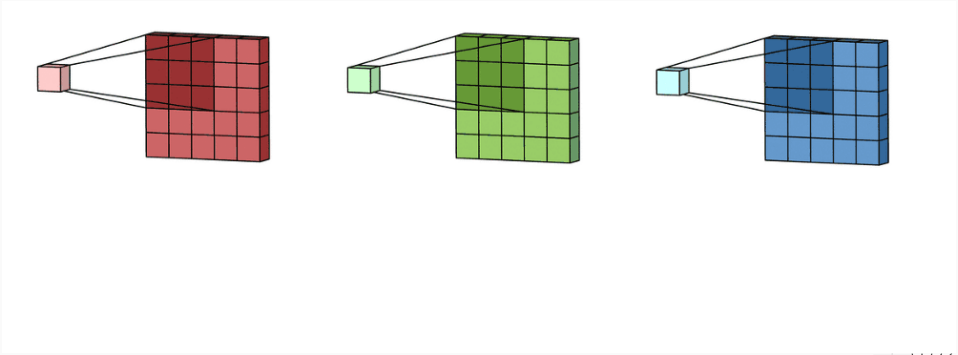
In color images, pixels intensity are represented a tensori RGB image are formed from the corresponding pixel of the three component



Arrrays stacked over each other to form a Digital Image.

Channels

In color images, pixels intensity are represented a tensori RGB image are formed from the corresponding pixel of the three component



Channels

- A convolution layer applies **multiple kernels (filters)** to the input.
- **Each kernel produces one output channel**, also called a **feature map**.
- The layer's **depth** (number of output channels) equals the **number of kernels** in that layer.
- The full output of the layer is the **stack of all feature maps**
- The shape: **(H_{out}, W_{out}, K)** where .
  - (H_{out}) = the height (number of rows) of each feature map after the convolution
  - (W_{out}) = the width (number of columns) of each feature map after the convolution
  - (K) = the number of feature maps, i.e., the number of kernels/filters in the layer So you can think of it as (K) separate 2D images, each of size ($H_{out} \times W_{out}$), stacked along the "channel" dimension.

Example: if a layer outputs (H_{out}=32), (W_{out}=32), and you use ($K = 64$) filters, the output shape is `(32, 32, 64)`: 64 feature maps, each 32×32.

Strides

- **Stride = step size** of the kernel as it slides across the input.
- If **S = 1**, the kernel moves **1 cell/pixel at a time** -> dense output (more positions).
- If **S = 2**, it moves **2 cells/pixels at a time** -> smaller output (downsampling).
- Bigger stride -> **fewer kernel positions** -> **smaller** H_{out}, W_{out} and less computation.

Padding

- **Padding = adding extra border cells** (usually zeros) around the input before applying the kernel.
- Main purpose: **control output size** and preserve information at the **edges** of the image.
- With $P = 0$ ("valid" conv): output shrinks because the kernel can't go outside the input.
- With $P > 0$ (often "same" conv when combined with $S = 1$): output can keep similar spatial size, and border pixels influence more outputs.

Convolution output size (1D)

$$\text{Output size} = \left\lfloor \frac{\text{Input size} + 2P - K}{S} \right\rfloor + 1$$

- **Input size**: number of positions in the input (e.g., width in 1D, or width/height in 2D).
- P **(padding)**: adds P cells on **each side**, so total added is $2P$.
- K **(kernel size)**: the kernel must "fit" inside the padded input, so we subtract K.
- S **(stride)**: step size of the kernel; dividing by S counts how many valid steps fit.
- $\lfloor \cdot \rfloor$ **(floor)**: if it doesn't divide evenly, we keep only the **complete** steps.
- $+1$: counts the **first** kernel position (at the start).

Convolution output size (2D)

It applies to 2D per dimension.

For an input of size $H \times W$ (height $\times$ width), kernel $K_h \times K_w$, padding P_h, P_w, stride S_h, S_w:

$$H_{\text{out}} = \left\lfloor \frac{H + 2P_h - K_h}{S_h} \right\rfloor + 1 \qquad W_{\text{out}} = \left\lfloor \frac{W + 2P_w - K_w}{S_w} \right\rfloor + 1$$

If you use the common symmetric case ($K_h = K_w = K$, $P_h = P_w = P$, $S_h = S_w = S$), it's the same formula applied to both H and W

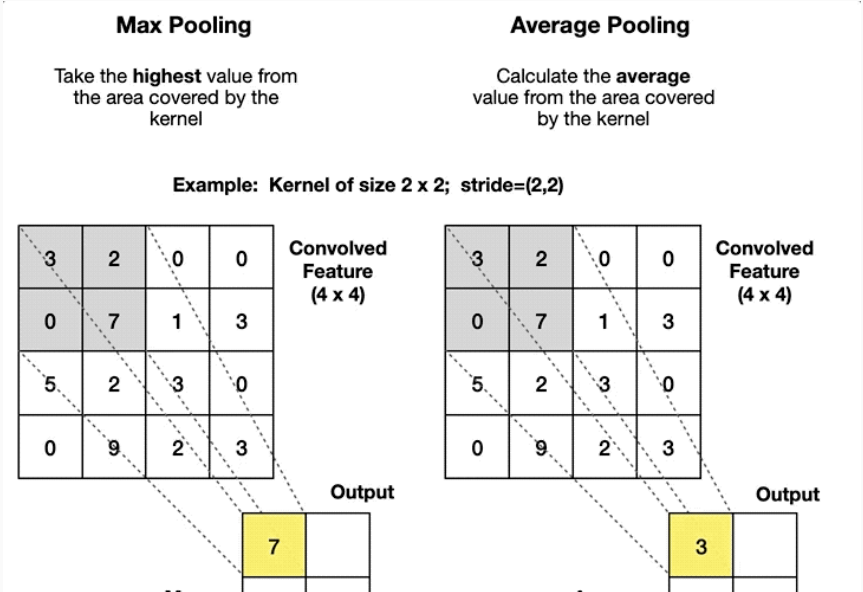
Better and image

Between the “C” and the “NN”

Pooling layers (Max/Average Pooling)

- Replaces each local window (e.g., 2×2) with **one value**
  - **Max pooling:** keeps the **largest** value
  - **Average pooling:** takes the **mean**
- They reduce spatial size (H, W):
  - **less computation**
  - **less overfitting**
  - **robustness to small shifts**.
- Pooling typically reduces H **and** W, but keeps the **number of channels** K the same.
- **Example:** with a 2×2 window and stride 2, an input $(32, 32, K)$ becomes $(16, 16, K)$.

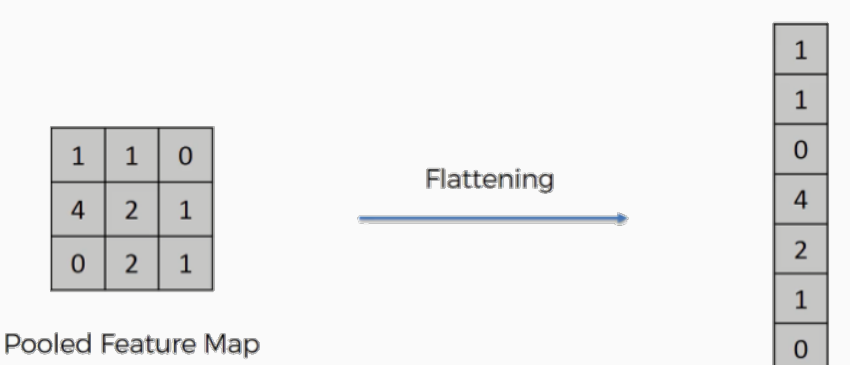
Pooling layer



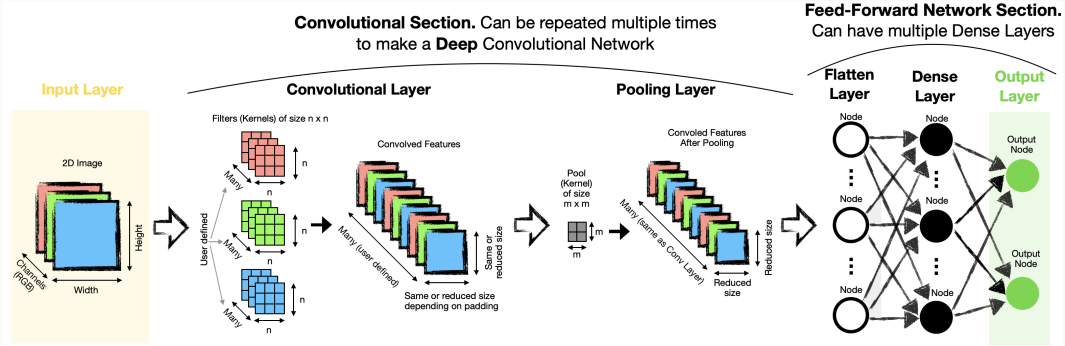
Flatten layer

- Converts a multi-dimensional tensor into a **1D vector** (per example), without changing the values.
- Typical use: between **convolution/pooling blocks** and a **fully connected (dense)** layer.
- Example shape change:
  - Input: $(H, W, K) = (8, 8, 32)$
  - Output: $(8 \cdot 8 \cdot 32) = (2048)$
- Flatten has **no learnable parameters** — it's just a reshape.

Flatten layer



All together



“The” CNNs

AlexNet (ImageNet Contest 2012)

- Winner of ImageNet Large Scale Visual Recognition Challenge (ILSVRC) 2012
- ImageNet:
  - 15+ million labeled high-resolution images
  - 22000 categories ILVRC subset:
  - 1000 images per category
  - 1000 categories
  - 1.2 million training images | 50000 validation images | 150000 testing images

AlexNet Task

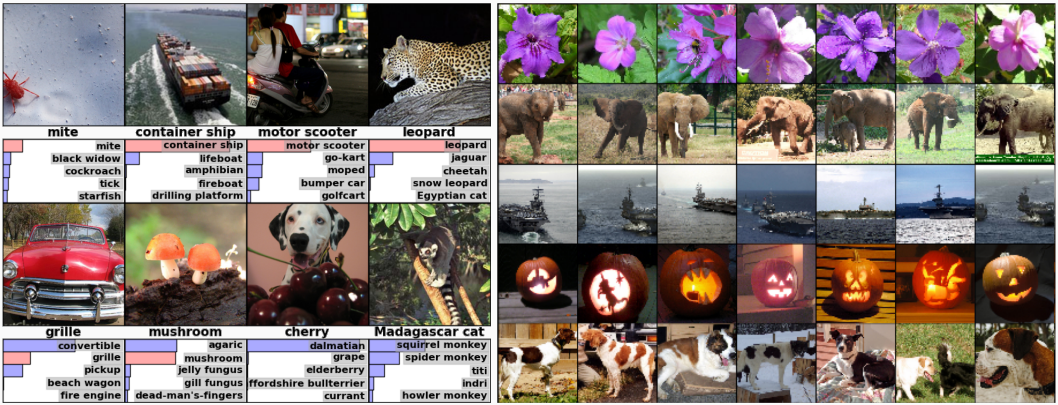


Figure 13: An illustration of the architecture of our CNN explicitly showing the delineation of responsibilities between the two GPUs. One GPU runs the layer-parts at the top of the figure while the other runs the layer-parts at the bottom. The GPUs communicate only at certain layers. The network's input is 150,528-dimensional, and the number of neurons in the network's remaining layers is given by 253,440–186,624–64,896–64,896–43,264–4096–4096–1000.

AlexNet Task

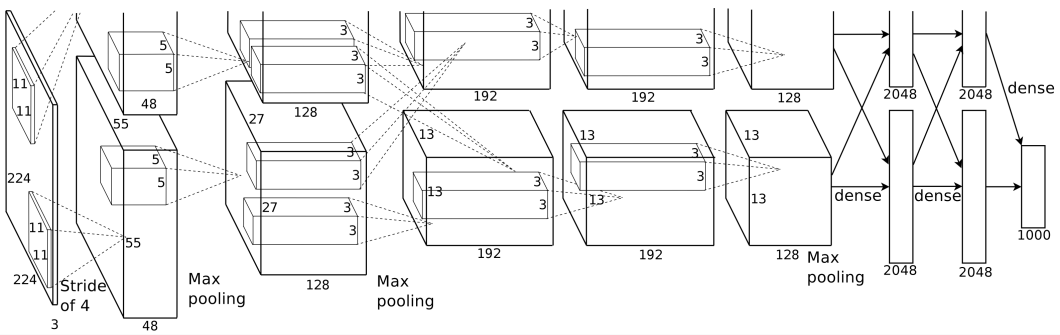


Figure 14: (Left) Eight ILSVRC-2010 test images and the five labels considered most probable by our model. The correct label is written under each image, and the probability assigned to the correct label is also shown with a red bar (if it happens to be in the top 5). (Right) Five ILSVRC-2010 test images in the first column The remaining columns show the six training images that produce feature vectors in the last hidden layer with the smallest Euclidean distance from the feature vector for the test image.

AlexNet kernels

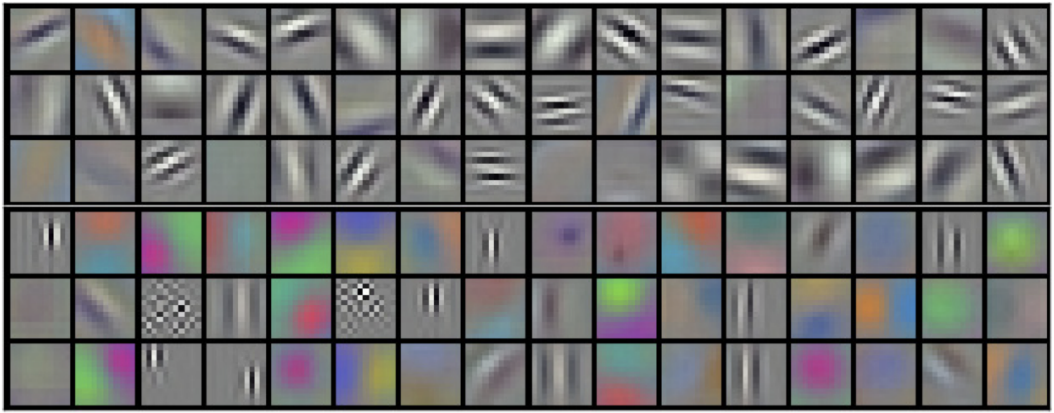


Figure 15: 96 convolutional kernels of size 11×11×3 learned by the first convolutional layer on the 224×224×3 input images. The top 48 kernels were learned on GPU 1 while the bottom 48 kernels were learned on GPU 2

Local Response Normalization LRN

AlexNet introduced LRN to mimic a form of **lateral inhibition** (biological inspiration). The idea is to encourage *competition* between neighboring feature maps at the **same spatial location**.:

- If several channels respond strongly at the same pixel, they **suppress** each other.
- This makes the most strongly activated feature maps stand out.

Motivation in 2012 context:

- ReLU activations can produce large responses.
- LRN provided extra **regularization/stabilization** when training deep CNNs on ImageNet.

Local Response Normalization (LRN)

AlexNet used a LRN technique.

Given an activation $a^i_{x,y}$ at position (x, y) in channel i, LRN outputs:

$$\underbrace{b^i_{x,y}}_{\text{normalized response}} = \underbrace{a^i_{x,y}}_{\text{activation (after ReLU)}} \Big/ \left(\underbrace{k}_{\text{bias}} + \underbrace{\alpha}_{\text{scaling}} \sum_{j \in \mathcal{N}(i)} (\underbrace{a^j_{x,y}}_{\text{neighboring channels}})^2 \right)^\beta$$

- N: number of channels (feature maps)$\mathcal{N}(i) = \{j : \ |j - i| \leq n/2\} \cap [0, N-1]$
- n: size of the local neighborhood across channels
- Typical AlexNet hyperparams: $k = 2$, $n = 5$, $\alpha = 10^{-4}$, $\beta = 0.75$

Effect in AlexNet

LRN is applied after ReLU in AlexNet (in the early conv layers).

Observed effect:

- Small but measurable improvement in ImageNet accuracy.
- Encourages **sparser / more selective** channel responses.

Trade-offs:

- Adds computation and extra hyperparameters.
- Later architectures (VGG/ResNet) largely dropped LRN in favor of better regularization and normalization (e.g., BatchNorm).

CNN explainer

See it at:

- https://www.youtube.com/watch?v=HnWIHWFbuUQ
- https://poloclub.github.io/cnn-explainer

from (POLO Club 2019; Wang et al. 2021)

Applications, general overview

In the domain of Bioinformatics

- **Biomedical imaging** (cells, tissues, organs)
- **High-content screening** and microscopy phenotyping
- **Computational pathology** whole slide image (WSI)
- **CNNs** 1D convolutions on sequences (Alipanahi et al. 2015; Zhou and Troyanskaya 2015)
- **CNNs** 1D convolutions on biomedical signals (ECG,EEG) (Alipanahi et al. 2015; Zhou and Troyanskaya 2015)

Biomedical imaging

Modality	Typical data	Key quirks	Common CNN strategy
Histopathology (WSI)	Gigapixel slides	stain variation, tiling, weak labels	MIL / tile CNN + aggregation
Microscopy	cells/tissues	illumination, blur, small objects	U-Net/Mask R-CNN, augmentations
Radiology (CT/MRI/X-ray)	2D/3D volumes	anisotropy, 3D context	2.5D/3D CNNs, careful splits
Physiological signals (ECG/EEG/EMG)	1D time series (multi-lead / multi-channel), sometimes transformed to time–frequency	nonstationarity, noise/artifacts (motion, baseline wander), variable length, subject/device variability, label ambiguity (event timing)	**1D CNN / TCN** on raw or filtered signals; windowing + stride; multi-channel convolutions; often add **spectrograms** (STFT/wavelets) -> 2D CNN; patient-wise splits, augmentation (jitter, scaling, time-warp), class-imbalance handling

Classification tasks in biomed (examples)

- Disease detection / grading (e.g., skin lesions, diabetic retinopathy, cancer subtyping)
- Cell phenotype classification (immune cell states, mitosis detection)
- Subcellular localization (protein patterns)
- Parasite/organism identification in microscopy
- Drug response phenotyping in screening plates

Classification: patch/tiling vs whole-image

- Whole image works for modest-sized images (microscopy tiles, X-rays)
- Whole-slide images (WSI) require **tiling**
  - Extract patches at one or more magnifications
  - Run CNN per tile
  - Aggregate to slide/patient prediction (max/mean/attention/MIL)

Semantic vs instance segmentation

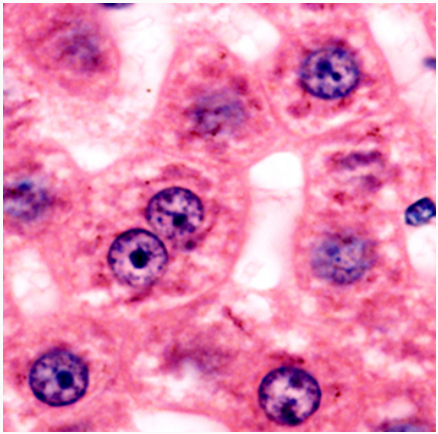
- **Semantic segmentation**: each pixel gets a class (cell vs background)
- **Instance segmentation**: separate objects (each cell/nucleus gets its own ID)
  - Mask R-CNN-style approach (He et al. 2017)
  - or post-processing on semantic maps (watershed, connected components)

Weak supervision for WSI (common)

- Labels often at **slide level**, not pixel/region level
- Strategy:
  - train tile encoder $f_\theta(x_i) \rightarrow z_i$
  - aggregate to slide score $\hat{y} = g(\{z_i\})$
- Practical aggregation choices:
  - top-k pooling, attention pooling, mean pooling
- Case study later: weakly supervised WSI pathology (Campanella et al. 2019)

Hematoxylin & Eosin (H&E) staining

- **H&E** most common *routine* stain in histology.
- It combines **two dyes**:
  - **Hematoxylin** (with a mordant) stains **basophilic** structures -> mainly **cell nuclei** (blue/purple)
  - **Eosin** stains **eosinophilic** structures -> mainly **cytoplasm** and **extracellular proteins** (pink)
- Viewing tissue structure under a light microscope shows strong **contrast** between nuclei vs cytoplasm/ECM so tissue architecture is easy to interpret.



Institute for Research and Innovation in Health

Histopathology specifics: stain & color

- Hematoxylin and eosin (H&E) staining accounts for over 80% of slides stained worldwide
- Stain variability (H&E) causes domain shift
- Common fixes:
  - color augmentation
  - stain normalization methods
  - multi-site training + validation
- Avoid “too-clean” preprocessing that removes diagnostic cues

Histopathology specifics: stain & color inference

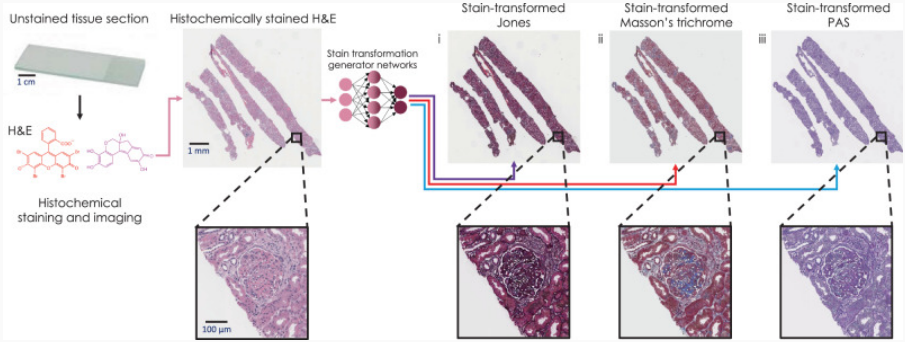


Figure 16: Histochemical staining of H&E is digitally transformed using a deep neural network into the special stains: (i) generation of JMS (purple arrow); (ii) generation of MT (Masson's Trichrome, red arrow); (iii) generation of PAS (Periodic acid–Schiff, blue arrow).

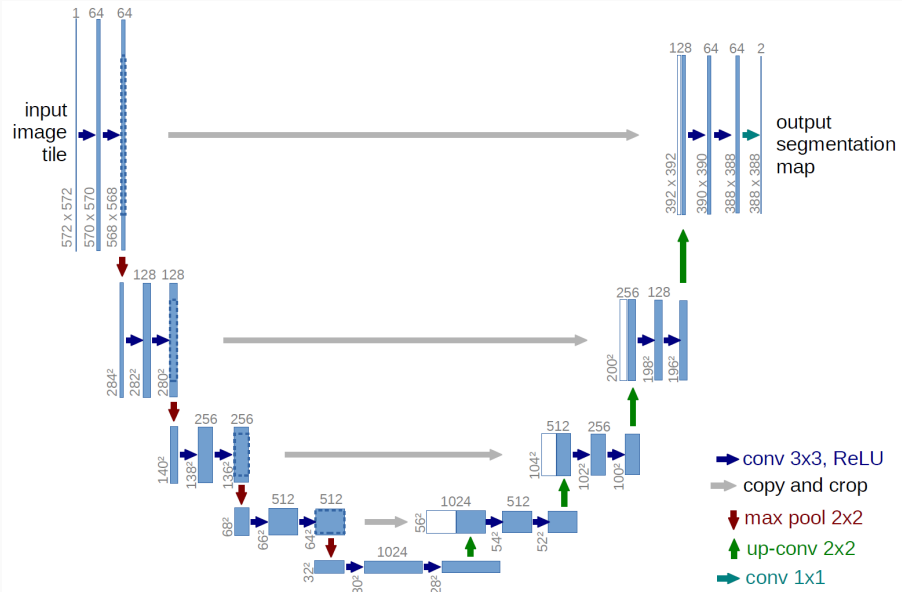
from (Haan et al. 2021)

U-Net for biomedical segmentation

U-Net: Convolutional Networks for Biomedical Image Segmentation

- Dense, *pixelwise* prediction with precise localization from limited labeled data (Ronneberger, Fischer, and Brox 2015a, 2015b).
- Key idea: **encoder–decoder with skip connections** that transfer *high-resolution* features directly to matching decoder stages.
- Practical focus:
  - strong data augmentation (esp. elastic deformations),
  - careful handling of borders and class imbalance,
  - fast inference on full images via tiling/overlap.

Architecture (the “U”)



Skip connections as multiscale feature fusion

Let the encoder feature map at level ℓ be $E_\ell \in \mathbb{R}^{H_\ell \times W_\ell \times C_\ell}$ and the decoder feature map before fusion be $D_\ell \in \mathbb{R}^{H_\ell \times W_\ell \times C'_\ell}$.

- Upsample decoder features: $\tilde{D}_\ell = \mathrm{Up}(D_{\ell+1})$
- Fuse via channel-wise concatenation:

$$F_\ell = \mathrm{Concat}(E_\ell,\ \tilde{D}_\ell)$$

- Then refine:

$$D_\ell = g_\ell(F_\ell)$$

  where $g_\ell(\cdot)$ denotes the conv block at level ℓ.

Concatenation preserves fine spatial cues in E_ℓ while $\tilde{D}_\ell$ carries semantic context from deeper layers, improving boundary localization (Ronneberger, Fischer, and Brox 2015a).

Pixelwise prediction + weighted loss for borders

For each pixel x and class k, logits $a_k(x)$ produce softmax probabilities:

$$p_k(x) = \frac{\exp(a_k(x))}{\sum_{k'=1}^{K} \exp(a_{k'}(x))}$$

U-Net uses a **weighted** pixelwise cross-entropy to emphasize difficult regions (notably touching objects / borders):

$$\mathcal{L} = -\sum_{x \in \Omega} w(x) \log\left(p_{y(x)}(x)\right)$$

where $y(x)$ is the ground-truth class at pixel x, and $w(x)$ is a precomputed weight map that upweights separation boundaries (Ronneberger, Fischer, and Brox 2015a, 2015b).

U-Net Training & inference details

- **Data augmentation:** heavy geometric + photometric augmentation; elastic deformations are highlighted as especially effective for biomedical imagery (Ronneberger, Fischer, and Brox 2015a).
- **Valid vs. same padding:** original U-Net uses *valid* convolutions, shrinking spatial size; output is produced for the central region of a larger input patch.
- **Inference on large images:** tile the image, predict per tile, and blend overlaps to reduce boundary artifacts.
- Strong benchmark performance on ISBI-style biomedical tasks and robust results with few training images (Ronneberger, Fischer, and Brox 2015a).

Pitfalls and others

Main pitfalls (the stuff that breaks papers)

- **Data leakage**
  - tiles from same WSI across train/test
  - slices from same patient across splits
- **Batch/site effects**
  - scanner differences, staining labs, acquisition protocols
- **Annotation noise**
  - weak labels, inter-rater variability, ambiguous boundaries
- **Hidden stratification**
  - model “works” overall but fails on rare clinically important subtypes

Questions

References

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Extra slides !!

- Slides extra which are always nice to have