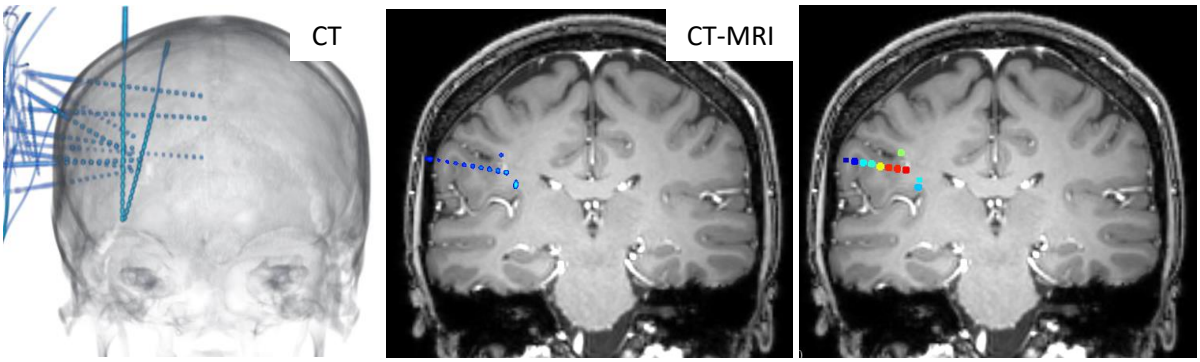
Detection of interictal epileptiform discharges in invasive EEG

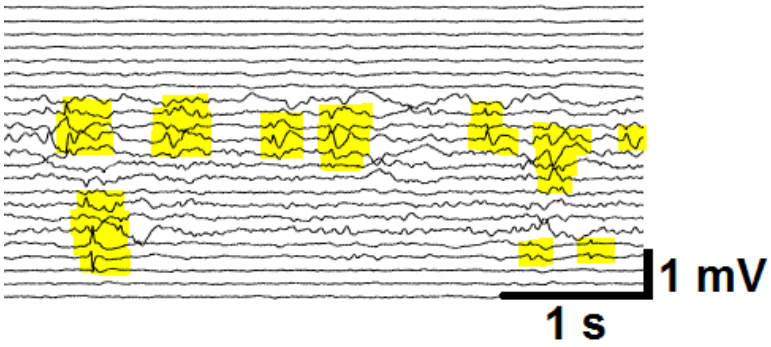
Introduction:

Epilepsy is a group of neurological disorders, that is characterised by the spontaneous epileptic seizures. It affects approximately 1% of the population in developed countries (in the Czech Republic 70-80 thousands of patients). Seizures can variate in semiology and intensity, from losing the vigilance, nausea, and auras to complex losing consciousness with myoclonus. Seizures generate abnormal neuronal populations (**epileptogenic zone/network**), that can generate electric activity, which distorts functionality of neighbour brain or closely connected areas to transform normal EEG to epileptic. Affecting of high functional eras leads to external manifestation with specific semiology e.g.: motor areas = spasms/myoclonus, hippocampus = memory loss, insula = pain, skin burning, sound hallucination, frontal = vocalization, occipital = lights/flashes...). These interconnected regions make an **epileptic network**, that produces specific abnormal activity also outside the seizure. A typical type is **interictal epileptiform discharges** (**IED**) composed of sharp transient and subsequent wave. The subnetwork, that generates IED is called the **irritative zone** (**IZ**).

Approximate 1/3 of patients do not sufficiently response to antiepileptic drugs, however around 10% of them can profit from epilepsy surgery treatment, that is based on resection or disconnection of pathological brain tissue without new cognitive deficits. Precise localization of epilepsy focus is not possible by imaging (MRI, PET, SISCOM) in all cases, therefore invasive EEG (**iEEG**) monitoring is required. Implantation of subdural electrocorticography electrodes (ECoG) or intracerebral stereotactical electrodes (SEEG) allows precise brain exploration by the up to 256 channels iEEG for long term recording and zones identifications. Many days continuous 24/7 monitoring produces enormous dataflow, that is impossible fully visually validated by clinicians. Therefore, signal processing and artificial intelligence are used to objective quantitative evaluation of EEG (**qEEG**).

Invasive EEG has a bigger amplitude (physiological 50 uV, abnormal up to 1 mV) than scalp EEG, contains fewer artefacts, has wider bandwidth (DC – 2 kHz), is more focused (higher dynamic, inter-channel delay etc.). IED in iEEG is described as sharp discharges with 20-70 ms duration with amplitude 0.1-1 mV, that is often subsequent by slow wave (0.1-0.5 s). IED can be generated from more than one sources and propagated through the whole brain network. IED rate variated in patients and is influenced by drugs, sleep deprivation or circadian rhythms [1]. The maximal IED rate cross 100 min^{-1} only rarely, more often during the sleep with spreader propagation. The highest IED rate area often corresponds to the epileptogenic zone.





Five seconds sample of iEEG with marked IEDs. Morphology of waveforms variate in brain structures.

Aims:

1. Display multichannel iEEG signal
    a. Download the iEEG data „iEEG_bipolar_optimal.mat“
    b. Filter 50 Hz hum and isoline (<0.5 Hz)
    c. Show section of iEEG date in one window, with channel labels and *datenum* time axis
    d. Visually identify IEDs
2. Automated detection of IEDs
    a. Make the own function to detect IED in one channel, save the all IED positions
    b. Apply the algorithm to one selected channel from the irritative zone (indicated in „iz_bip“) and display iEEG with detection markers
    c. Apply the algorithm to all channels. Count IED rate per minute for each channel
    d. Divide the channels to a propagated area (low IED rate) and the irritative zone (high IED rate). Use decision rules based on: thresholding, statistical outliers, self-clustering algorithm k-means
3. Clinical validation agreement
    a. Compare your identified channels with clinical evaluation. Compute sensitivity (SEN) and positive predictive value (PPV)
    b. Compute the agreement in three epochs of the same patient: focal activity (focal), low activity (low) and multifocal activity (optimal).
    c. Apply clinically validated algorithm developed in CTU in Prague by ISARG [2] and compare agreement with your algorithm.

[1] Janca, Radek, et al. "The Sub-Regional Functional Organization of Neocortical Irritative Epileptic Networks in Pediatric Epilepsy." *Frontiers in neurology* 9 (2018): 184.

[2] Janca, Radek, et al. "Detection of interictal epileptiform discharges using signal envelope distribution modelling: application to epileptic and non-epileptic intracranial recordings." Brain topography 28.1 (2015): 172-183.

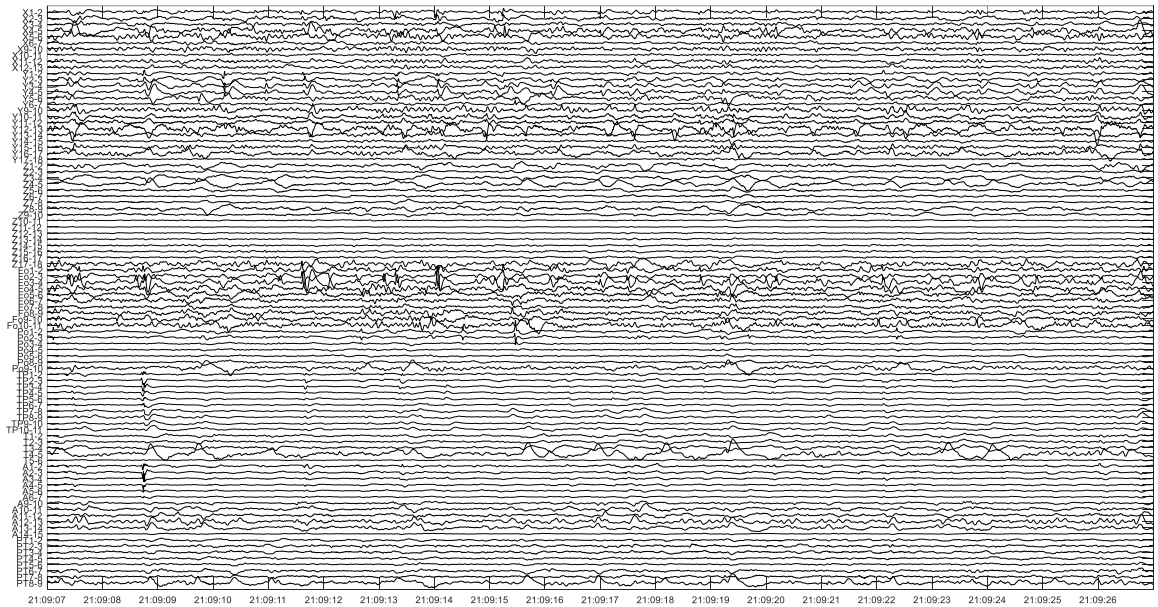
Data structures:

```
iEEG_bipolar_focal.mat
iEEG_bipolar_low.mat
iEEG_bipolar_optimal.mat

fs … sampling frequency (Hz)
iz_bip … irritative zone channels marked by clinicians
d … iEEG (uV) - iEEG in a bipolar montage (time, channels)
labels … CELL {label, [channels in referential montage]}
tabs … time vector in datenum format (contain data and time)
```

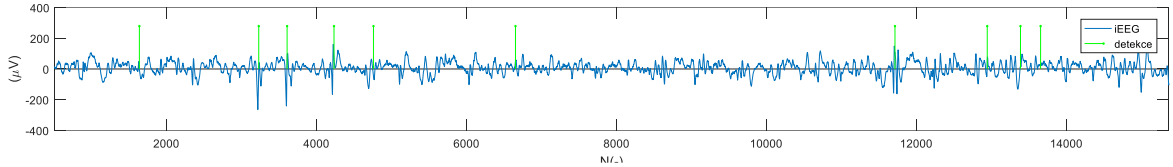
Useful functions: **`intersect, setxor, fitlfilt, repmat, butter, quantile`**

Help:

```
% load data to structure
data=load('iEEG_bipolar_optimal.mat');

% select i.e. 20 seconds for plotting
d=data.d(1:20*data.fs,:); % iEEG
t=data.tabs(1:20*data.fs); % absolute time

% filter 50 Hz and isoline!!!

% use inter-channel offset for multichannel plotting
offset=2*max(std(d)); % maximal S.D. of all channels
DC=linspace(0,-offset.*(size(d,2)-1),size(d,2)); % 1st channel = 0, 2nd
channel = -1*offset...

d=d+repmat(DC,[size(d,1) 1]); % add DC offset matrix to iEEG

plot(t,d,'k'); % iEEG
% 1st channel on top, that is bigger DC offset, therefore indexing from end
% Ytick corresponf with offset, YTickLabels add text
set(gca,'YTick',DC(end:-1:1),'YTickLabels',data.labels(end:-1:1,1))
% 10 values in x-axis
set(gca,'XTick',linspace(t(1),t(end),10))
% Time axis in datenum format can be showed in clock form
datetick('x','HH:MM:SS','keeplimits'); % read documentation
```

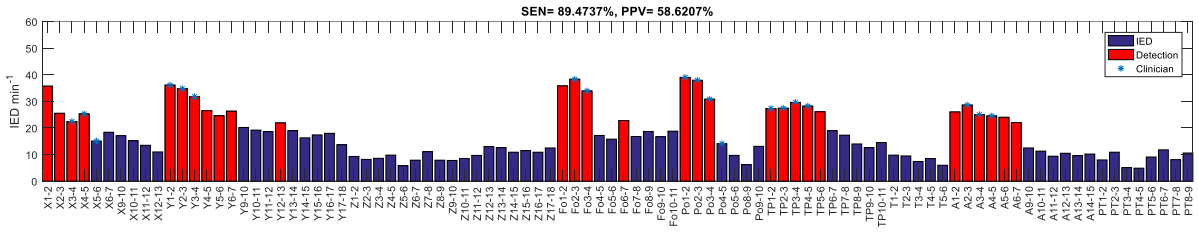


```
% Detection of IED:=========================================================
% modify algorithm for R-peak detection in ECG
% 1) filtering - band pass. Use frequency range extracted from IED
properties: discharges duration is between 20-70 ms (f=1/T)
% 2) energy
% 3) signal envelope (smoothing corresponds to discharges duration)
% 4) set detecting threshold
%   a) constant value?
%   b) statistical parameters (Have envelope Gaussian distribution?)?
%   c) Tukey's criteria of outlier in nonparametric distributions
%       q1=quantile(x,0.25); 1st quartile
%       q3=quantile(x,0.75); 3nd quartile
%       th=q3+k*(q1+q3);    (k=1.5 or stricter 3)

% example of one-channel detection
ch=data.iz_bip(1); % 1st channel of irritative zone
N=simple_IED(data.d(:,ch),data.fs); % your detector, N are detection
positions in samples

figure(2); clf
plot(data.d(:,ch)); xlim([1 30]*data.fs)
hold on
stem(N,max(data.d(:,ch))*ones(length(N),1),'g.')
xlabel('N(-)'); ylabel('iEEG (\muV)');
legend('iEEG','detekce')
```

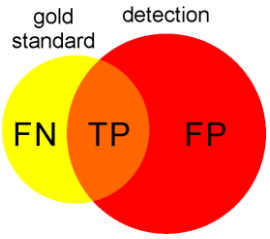



```
% 5) Apply the algorithm to all channels
...
N_IED(ch)=length(N);
...
```

```
% 6) Show "IED rate per minute" distribution for all channels.
figure(3);clf
bar(N_IED); ylabel('IED min^{-1}'); axis tight; ylim([0 60])
set(gca,'XTick',1:length(N_IED),'XTickLabels',data.labels(1:length(N_IED)))
xtickangle(90); % labels rotation

% 7) Identify the background (low rate) and irritative zone (high rate)
channels
%    a) What threshold?
%    b) Tukey's criteria k=1.5 or 3?
%    c) Clustering baseline/outlier (k-means)
[idx,C]=kmeans(N_IED(:),2,'replicate',10); % find two groups
[~,higher_C]=max(C); % centroid with higher value marks outlier
iz_det=find(idx==higher_C); % all outlier channels are detected irritative
zone (IZ)

hold on
bar(iz_det,N_IED(iz_det),'r'); % IZ channels by red
plot(iz_bip,N_IED(data.iz_bip),'*'); % clinical evaluation by stars
legend('IED','Detection','Clinician')
```



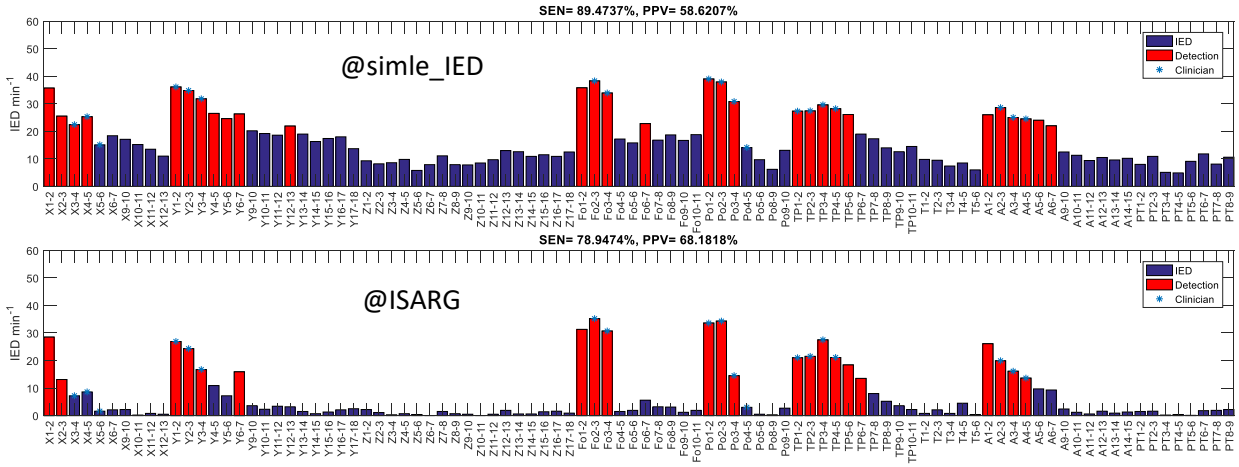

```
% 8) Clinical evaluation agreement
% TP ... true positive - correct channels (intersection of detector and
clinician)
TP=intersect(iz_det,iz_bip);
% FP ... false positive - incorrectly marked channels (all detections, that
are not TP)
FP=intersect(...,setxor(...));
% FN ... false negative - overlooked channels by the detector (all
undetected channels)
% use functions: intersect, setxor
FN=intersect(...,setxor(...));
```



$$SEN = 100 \cdot {}^{N_{TP}}/_{(N_{TP} + N_{FN})}$$

$$PPV = 100 \cdot {}^{N_{TP}}/_{(N_{TP} + N_{FP})}$$

```
SEN=100*length(TP)/(length(TP)+length(FN)); % sensitivity (%)
PPV=100*length(TP)/(length(TP)+length(FP)); % positive predictive value (%)

% 9) use clinically validated detector
[~, discharges]=spike_detector_hilbert_v23(data.d,data.fs);
N_IED=sum(discharges.MV>0);
```




```
% 10) Compare detector in different signals
```

	@Simple_IED		@ISARG	
Soubor:	**SEN:**	**PPV:**	**SEN:**	**PPV:**
iEEG_bipolar_low.mat				
iEEG_bipolar_focal.mat				
iEEG_bipolar_optimal.mat			78.9%	68.2%

What and where is the best agreement with clinician?