# Machine learning for automated discovery of clinically unstable episodes in paediatric intensive care patients with congenital heart disease: Aberration Detection

## ***Proposition of Adjustments***

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**Algorithmic adjustments:**

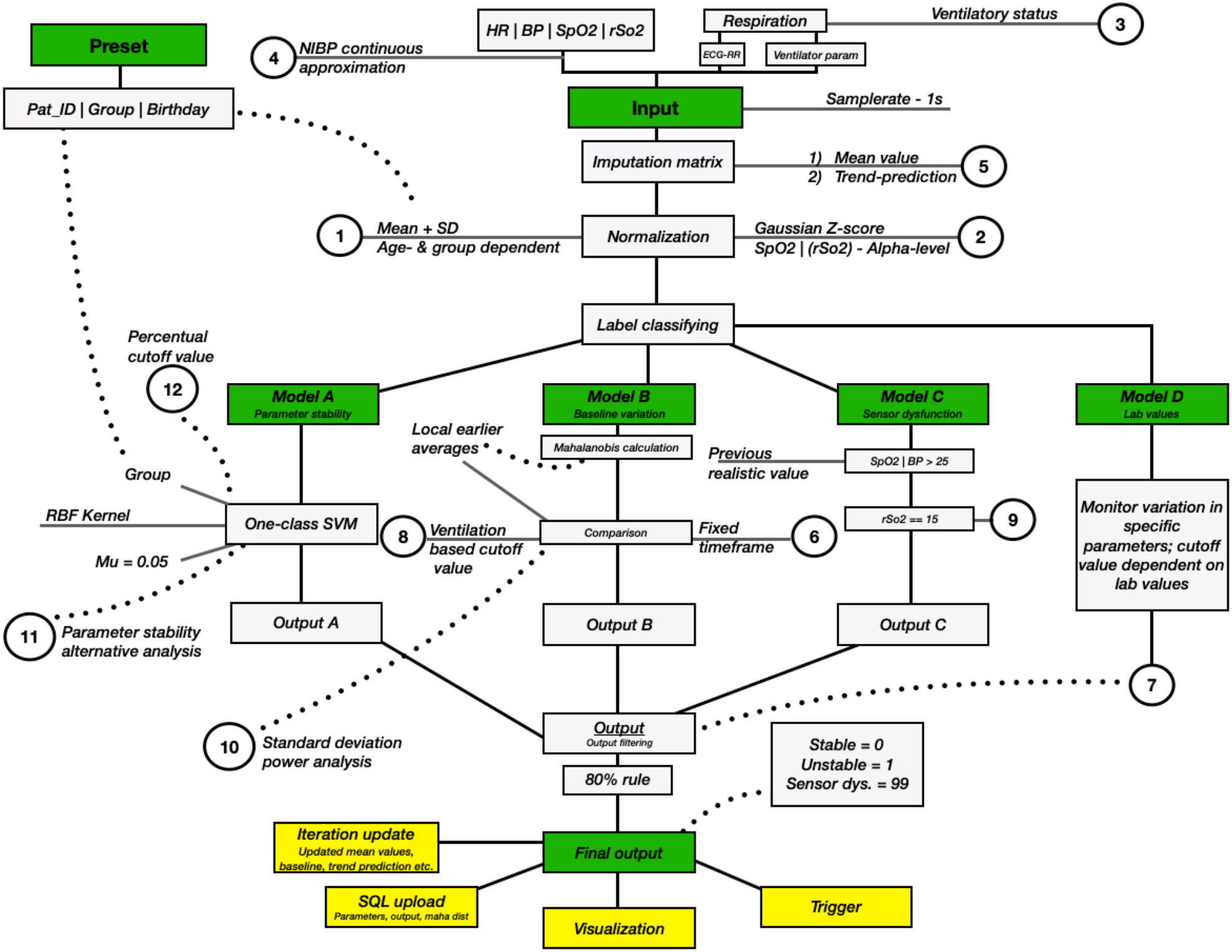
1) Age-specific normalization of parameters
2) SpO2 / rSo2-normalisation in assumption of clinically relevant negative development
3) Respiratory rate analysis
4) Non-invasive bloodpressure at times of unmeasured invasive BP
5) Missing value imputation
6) Sensitivity: Short vs long-term
7) Discontinuous data analysis – laboratory values
8) Vital function impaired variation during active ventilation
9) Sensor dysfunction rSo2
10) Standard deviation Mahalanobis – power analysis
11) SVM stability analysis – alternatives
12) Percentual cutoff value SVM

**Prospective approach – dataflow adjustments**

Currently, a retrospective approach is used in testing. For prospective validation, a different way of modeling is required. The main point of difference in this approach is the inability for overall processing (e.g., calculate baseline for entire admission, then proceed to comparison for entire admission) and the corresponding need for 'step-wise'-processing as no future data is known.

Therefore, structural adjustments are necessary. A corresponding dataflow requires efficient processing, where the total time of calculation must be less than the chosen time-interval in order to remain 'on time'.
This approach requires limitation of processing, where repeated measurements are kept to a minimum and local variables need to be updated in order to keep this runtime down.

On the next page, a first version of structural dataflow adjustments are depicted including propositions as described further in detail.


Preset
Pat_ID | Group | Birthday
HR | BP | SpO2 | rSo2
Respiration
ECG-RR
Ventilator param
Ventilatory status
3
4
NIBP continuous approximation
Input
Samplerate - 1s
Imputation matrix
1) Mean value
2) Trend-prediction
5
1
Mean + SD
Age- & group dependent
Normalization
Gaussian Z-score
SpO2 | (rSo2) - Alpha-level
2
Label classifying
Percentual cutoff value
12
Model A
Parameter stability
Model B
Baseline variation
Model C
Sensor dysfunction
Model D
Lab values
Local earlier averages
Mahalanobis calculation
Previous realistic value
SpO2 | BP > 25
Group
RBF Kernel
One-class SVM
8
Ventilation based cutoff value
Comparison
Fixed timeframe
6
rSo2 == 15
9
Monitor variation in specific parameters; cutoff value dependent on lab values
Mu = 0.05
11
Parameter stability alternative analysis
Output A
Output B
Output C
7
10
Standard deviation power analysis
Output
Output filtering
80% rule
Stable = 0
Unstable = 1
Sensor dys. = 99
Iteration update
Updated mean values, baseline, trend prediction etc.
Final output
SQL upload
Parameters, output, maha dist
Visualization
Trigger

# Algorithmic adjustments

## 1) Age-specific normalization of parameters

Problem:

Currently, parameter values are normalized on mean and standard deviation derived from infants with a mean age of 7-9 days. Parameter values however differ depending on age, where lower values can be seen. When the AD-algorithm is used on infants with a higher age than where normalizing-parameters where derived from, prediction may be inaccurate.

Proposition:

Normalizing towards specific, age-related, cutoff values while (if possible) maintaining the standard deviation in both groups. Consider, when enough data, to calculate standard deviations in each of these subgroups of varying age. Also take power analysis into account, as will be discussed at point 10.

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## 2) SpO2 / rSo2-normalisation in assumption of clinically relevant negative development

Problem:

When normalizing parameters using Gaussian normality, any value above- or below the respective mean is considered a negative development in the calculation of Manhattan distance as it utilizes absolute values. However, considering SpO2 & rSo2, any value above the respective mean may not necessary be consider a clinical negative development.

Proposition:

Utilizing alpha-level distribution for SpO2 / rSo2, then normalizing each parameter (gaussian or not) towards a 0-1 curve. Point of note: include vector of parameter means in calculating Mahalanobis, as it is currently centered around 0 since z-score was used.

Pitfall: breaking correlation with SpO2 / rSo2 due to different distributions, consequently be considered unstable by the SVM -> proposition needs additional revising and testing.

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## 3) Respiratory rate analysis

Problem:

Respiratory rate analysis may be more accurately estimated when utilizing ventilatory machine-parameters, rather than singularly using ECG-derived respiratory rate (which may be faulty at times).

Proposition:

Taking a new approach to respiratory capacity analysis using ventilatory monitor data (tidal volume, breaths/min, EtCo2 for example).

Pitfall: When using different methods of estimating respiratory capacity (ecg-derivation vs ventilator-derived), future research-related data may be difficult to compare as different standards are considered. Additional revising is necessary to ensure equal scores between, for example, an ECG-derived RR of 35- and a ventilator set at 35 breaths/min both for medical- as well as research purposes.

### 4) Non-invasive blood pressure when invasive BP is not measured.

Problem:

Currently, only invasive blood pressure is used. NIBP may be measured on a discontinuous scale, while other parameters are continuously being monitored. However, by definition, this BP is 'outdated' as soon as the value is known due to constant fluctuations. We therefore need to find a way to implement the powerful source of (discontinuous) information, as is the BP, to accurately work together with continuous data streams.

Proposition:

1) Predict *changes* in BP, knowing the starting point through NIBP, by using AUC of pulse oximetry-derived heart rate as proxy for peripheral vascular resistance, combined with the heart rate as proxy for Cardiac output (assuming cardiac load to remain similar).
2) Take approximations of BP in time, through correlation- / co-integration effects measured with (for example) Heart-rate and SpO2 (more difficult in high-spo2-group, where it is less prone to changes of BP). rSo2 is discouraged as tool since the regulatory capacity of Cerebral bloodflow (autoregulation) may have a too severe effect for accurate prediction.

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### 5) Missing value imputation

Problem:

Missing values occur frequently, and result in an overall missing value of the Mahalanobis due to its structure (Mahalanobis requires all values to be present). Therefore, up to two missing values may be imputed to maintain a continuous approach as often not all parameters are observed to be missing.

Proposition:

1) Mean value of longer period of time (e.g. mean value of last minute as imputation for a maximum duration of X seconds)
2) Trend-prediction over preceding period of time

Pitfalls: Prediction remains an estimation of an unknown value, possibly breaking correlation which may result in inaccurate prediction.

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### 6) Sensitivity: Short vs long-term baseline

Problem:

A reduced sensitivity was observed for model-labeling at later moment of admission rather than at start of measurements. This may be due to a shifting percentual impact of later values, as baseline calculations are based on aggregate values. Due to this shifting percentual impact, labeling may be inaccurate and non-uniform at different stages of admission.

Proposition:

Calculate baseline deviations based on a fixed value of X hours preceding T.

Future: Percentual changes regarding earlier days may be noted somewhere, yet are not alarm-worthy. Perhaps once on a standard basis at each day, mention to the medical team the shift in baseline regarding earlier days.

### 7) Discontinuous data analysis – Laboratory values

Problem:

Currently, laboratory values are not implemented yet may be of use as additional stream of information.

Proposition:

Use lab-values as a means to widen/tighter the allowed variation in certain parameters.
*Example:* Any K+-value considered too high may reduce the variation-detection cutoff value of the Heart rate in order to stay increasingly vigilant for cases of arrythmia. When the k-value again falls in normal ranges, the variation can be increased to allow for less false positive detections.

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### 8) Vital function impaired variation during active ventilation

Problem:

At times of active ventilation, patients are deemed in an iatrogenic fixed state where parameter variation is reduced. Currently, 20% penalty in Mahalanobis is given at times of active ventilation. Two problems arise when actively ventilated:

1) At times of normal ventilation (±35 breaths/min), a reduced variation of parameters can be observed. This reduced variation makes the baseline-model insensitive when utilizing the same cutoff value between stable- and unstable as non-ventilated patients.

   Proposition: Lower the cutoff value regarding active ventilation. Either in the form of a percentual increase in Mahalanobis, or by lowering the cutoff value and leaving the Mahalanobis intact.
   Pitfall: Future research-related comparison between ventilated- and non-ventilated patients may be difficult to compare when using different scales; therefore additional revision of choices to make is required.

2) At times of *heavy* ventilation (±50 breaths/min) however, the algorithm becomes *too* sensitive. This comes following the observation that the RR distance to its mean in these heavy cases, is almost singularly capable of triggering the cutoff value, resulting in an increase of false-positive triggers. Additionally, false triggers may be seen due to the SVM detecting broken correlation regarding RR with other parameters.

   Proposition: Use additional, ventilator-derived, information more accurate representing current respiratory status (as discussed in point 3). Additionally, RR could altogether be excluded as information source due to its fixed nature, where stability analysis will rely on alternate parameter variation. This variation is reduced, as discussed above, where the same solution might be applicable.
   An alternate option maybe to exclude SVM-analysis, singularly faring on baseline-analysis of parameter variation.
   Pitfall: Exclusion of an important source of information.

### 9) Sensor dysfunction rSo2

Problem:

Sensory dysfunction of rSo2 is currently implemented as a static 15- or 95 value. However, a single testing patient showed a relatively high rSo2 of around 90-95. This consequently resulted in various (incorrect) sensor dysfunction triggers, as the rSo2 at times reached 95 which can be deemed as a representative value for the patient's condition instead of a sensorical dysfunction.

Proposition:

Deem only sensorial dysfunctions of rSo2 at lower bound (15). Upon further testing, analyze how many sensor dysfunctions were 'missed' in this approach. When more dysfunctions are missed than deemed acceptable, the model could also be triggered when rSo2 is *statically* high (or low) during a fixed period of X minutes in a row.

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### 10) Standard deviation Mahalanobis - power analysis

Problem:

Currently, to determine the cutoff-value separating stable from unstable patient status for each group, standard deviations are calculated. However, at this time, no power analysis was performed to account for statistical backup.

Proposition:

Calculate power analysis to statistically support the calculated standard deviations and include as many patients as possible.

### 11) SVM parameter stability alternatives

Problem:

At this time, parameter stability analysis is performed by training of a single-class Support Vector Machine (SC-SVM). However, SC-SVM does not support the assignment of different weights to each parameter. Therefore, alternative options may be investigated if the effect of weights will result in a decrease of false positive triggers.

Proposition:

Train different variants of artificial neural networks, such as Multi-layer perceptron, which allows weighted parameters. A semi-prospective approach, where no real-time analysis is performed yet detailed records of (minute-specific) (un)stable episode-timing is kept, could allow for detailed analysis between models aimed for optimal clinical efficiency.

### 12) Percentual cutoff value SVM

Problem:

When evaluating results from the algorithm, more false-negative than false-positive triggers were seen. This reducing sensitivity may be seen partially due to a high percentual cutoff-value in Mahalanobis when selecting parameter-combinations for training purposes.

Proposition:

Lower the percentual cutoff value (80% -> 75% for example) to allow for less margin in parameter variation deemed stable, increasing false positive yet decreasing false negatives.