neosim

LuSi Physiological Model

Josef X. Brunner and Thomas Riedel

Publisher:
neosim academy
c/o neosim AG
Susenbühlstrasse 12
CH-7000 Chur
Switzerland
www.neosim.ch

Authors:
Josef X. Brunner, PhD, Chur, c/o neosim AG, Susenbühlstrasse 12, CH-7000 Chur, Switzerland
Thomas Riedel, PD Dr. med. Department of Paediatrics, Cantonal Hospital Graubuenden, Chur and Division of Respiratory Medicine, Department of Paediatrics, Inselspital, University of Bern

This work is subject to copyright. All rights are reserved, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction and storage in data banks.
Product liability: The publisher can give no guarantee for information about drug dosage and application thereof contained in this book. In every individual case, the respective user must check accuracy.

ISBN 978-3-9524884-1-6
Year of publication: 2020
Printed in Switzerland

Contents

Purpose of this document 5

Systems overview 6

LuSi lungs and circulation 8

Scenario building and execution 9

LuSi^{LIFE} Overview 10

- Scenarios 10
- Base case 10
- Progressions 10

Physiological models: conceptual overview 11

- Numerical modelling concept 13

Real-time variables calculated every 5ms 14

- Spontaneous breathing 14
- Central Apnoea 14
- Sighs 14
- ECG 15
- Pulse oximeter sound 15
- Pulse oximeter plethysmogram 15
- Intrathoracic pressure swing and pulse pressure variation 16
- Pleural pressure 17
- Lung recruitment and collapse 18

Variables calculated once every breath 19

- Heart rate and bradycardia 20
- Dead space 21
- Lung recruitment 21
- Pulmonary gas exchange 24

Arterial blood gases 32
Haemodynamic models 33
Body position 33
Respiratory centre modelling 34
Effect of different settings for respiratory mechanics 36
High Frequency Ventilation modelling 37
CO_2 elimination 37
Oxygenation 37
Limitations of models used 38
Appendix: Scientific basis 40

Disclaimer

neosim does not warrant that the LuSi will work properly in all environments and applications, and makes no warranty and representation, either implied or expressed, with respect to the quality, performance, merchantability, or fitness for a particular purpose.

neosim has made every effort to ensure that this Manual is accurate; neosim disclaims liability for any inaccuracies or omissions that may have occurred. Information in this Manual is subject to change without notice and does not represent a commitment on the part of neosim. neosim assumes no responsibility for any inaccuracies that may be contained in this Manual. neosim makes no commitment to update or keep current the information in this Manual, and reserves the right to make improvements to this Manual and/or to the products described in this Manual, at any time without notice. If you find information in this manual that is incorrect, misleading, or incomplete, we would appreciate your comments and suggestion.

In no event shall neosim be liable for any special, direct, indirect, consequential, or incidental damages or any damages whatsoever, whether in an action of contract, negligence or other tort, arising out of or in connection with the use of LuSi or the contents of the Manual.

This Manual offers medical and physiological information and is designed for educational purposes only. You should not rely on this information as a substitute for, nor does it replace, professional medical advice, diagnosis, or treatment.

Purpose of this document

Model based simulators provide consistent simulation teaching yet are challenging to validate. Although a fundamental issue, little attention has been given to validation."The Comprehensive Textbook of Healthcare Simulation" edited by Adam I. Levine et.al. ISBN 978-1-4614-5992-7 covers the subject only on few pages, for example on page 567-570: Appendix: Design Paradigms in Physiologic Model Construction (Leisman et.al.). The authors conclude with ".....the onus is on all supervisors who run interactive simulations to be aware of the inaccuracies of the simulator .... and how these might cause negative learning".

The purpose of this document is to provide comprehensive information for these supervisors and trainers in order for them to assess the models built into LuSi for fitness of their training goals.

NOTE: the models presented in this document pertain to the firmware version as provided in the footnote. Deviations may occur. All scenario implementations need to be checked by the trainer prior to training.

Systems overview

LuSi is an artificial baby with lungs that respond to respiratory treatment. LuSi does actually breathe, can be intubated or fitted with nasal prongs and creates vitals signs that are displayed on a virtual monitor.

LuSi is a means to enable training on respiratory support devices.

The LuSi-System consists of a physical lung built into a silicone body and a Windows based control software LuSi^{LIFE} to control and monitor LuSi via a Bluetooth connection.

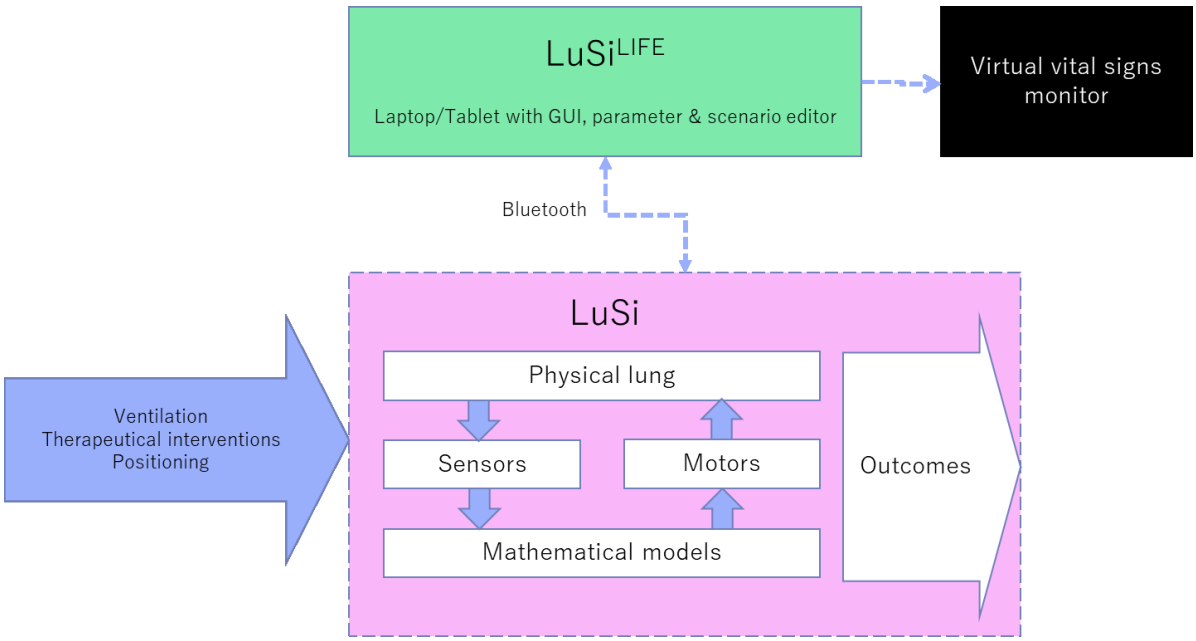

Figure 1: Overview LuSi System. LuSi is the "patient" of the learner and LuSi^{LIFE} is the tool of the trainer.

The purpose of LuSi is to enable training in the application of the following respiratory support therapies:

- Invasive mechanical ventilation
- nasal CPAP
- high-flow oxygen delivery
- resuscitation bag usage
- other respiratory support

The simulation shall be realistic, measurable and accountable (Figure 2).

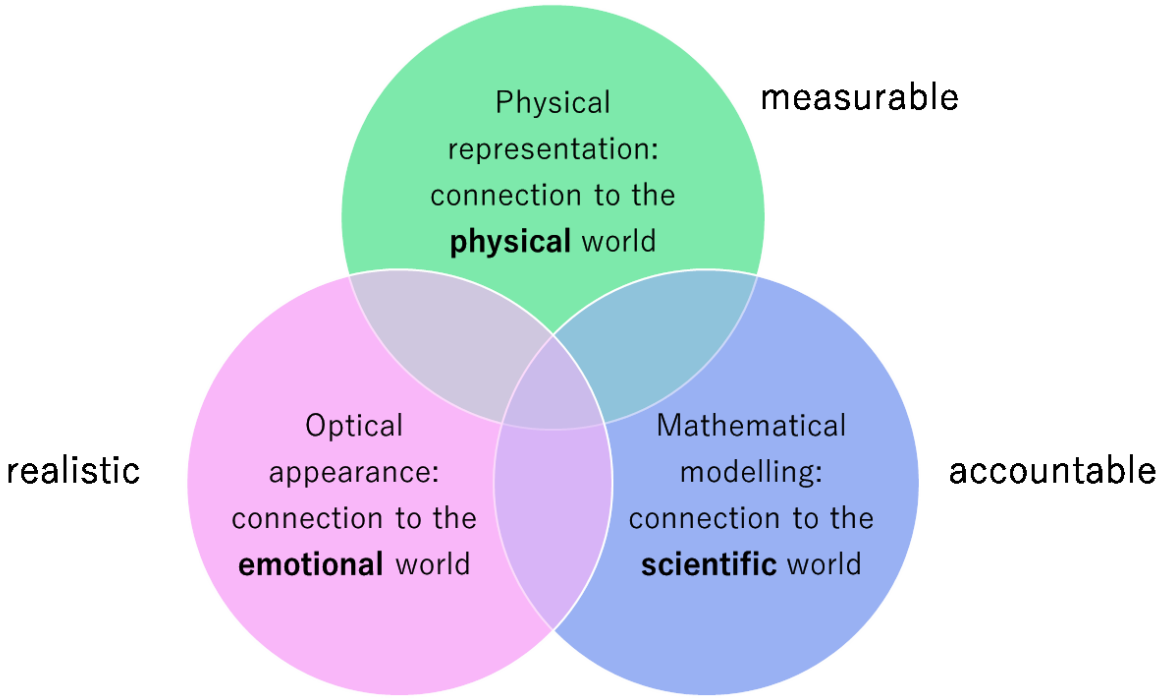

Figure 2: illustration of the concept LuSi.

For this reason, LuSi was designed to look “real”, be physically connectable to respiratory support devices, and respond dynamically, depending on the pathology set and the therapy administered.

LuSi is not a mannequin to train skills like CPR, general medical assessment, neurological assessment, catheterization, auscultation, fluid administration. LuSi is also not a tool to train intubation and endoscopy.

LuSi lungs and circulation

The physical lung built into LuSi is made of two silicone bellows mounted inside a PVC tube. The PVC tube is closed at the "cranial" side by

- an assembly of valves to simulate different airways resistances
- a valve to create a leak
- a pressure sensor to measure "alveolar" pressure
- a pressure sensor to measure "airway" pressure
- an oxygen sensor

The bellows are closed by a lid which is connected to a DC motor with a string. Pulling on the string creates ventilation. The DC motor is fitted with a decoder to measure the rotation of the motor. This rotation is converted to the bellows displacement thus volume can be measured in real-time. The DC motor is always pulling with a small force to keep the string in constant tension. This technique provides the capability to measure volumes and flows even if there is no "patient activity", e.g. in paralyzed patients.

A mechanical lever is located inside the bellows and is used to restrict the movement of the bellows. Such restriction creates

- changes in compliance
- lower inflection points
- lung collapse or recruitment

The lever is operated by a servo motor so that LuSi can respond to therapy based on its sensory input.

While LuSi's lungs are physically present, LuSi's circulation is simulated by the firmware built into LuSi. Virtual sensors measure arterial blood gases, ECG, blood pressure, exhaled CO2, etc. and the trainer can display these vital signs on a configurable monitor for the learners to see and act upon when executing a simulation session.

Scenario building and execution

The first phase in scenario building consist of

- deciding on the skills to be trained including the respiratory support devices
- setting measurable goals
- defining the role/pathology of the simulator (in this case LuSi)
- designing a scenario consisting of a base case and progressions (if needed)
- testing the scenario and adjusting it until it meets expectations
- releasing a scenario

The second phase is the execution which consists of

- preparation of the training venue, including set-up of all devices

Once all is ready, the actual simulation can be started.

- Welcome the learners: explain roles, goals and safety
- case briefing
- doing the simulation session
- debriefing
- review

LuSi^{LIFE} supports these phases.

LuSi^{LIFE} Overview

Scenarios

LuSi^{LIFE} is a scenario data base management system. Scenarios appear as tiles on the basic screen and are stored in folders which are accessible to the trainer. This way the trainer is free to organise the different scenarios and follow the building phases described above.

NOTE: Each scenario is a file which can be shared with other LuSi users.

Scenarios can be created, edited, modified and executed. When they are executed, a log file is created which stores all the information gathered during the simulation session, including notes taken by the trainer.

Base case

Each scenario consists of a Base Case which is often sufficient to run a simulation session. Progressions of the Base Case can be added to inject events or complications during the simulation session, if needed, or to account for different actions of the learner.

IMPORTANT: response to treatment does not need to be created by the trainer as it is done automatically by the physiological models.

Progressions

While a complete set of model parameters describes a Base Case, a second complete set of model parameters may lead to Progression 1, a third complete set of model parameters to Progression 2, and so forth. Once a parameter has changed, the model is recalculated to obtain the new steady-state values.

NOTE: The response time is thus faster than in reality. The transition time to change from Base Case to an Progression can be set to simulate slow phenomena, if desired.

Physiological models: conceptual overview

LuSi is built around physiological models which cover a large spectrum of lung physiology as depicted in Figure 3.

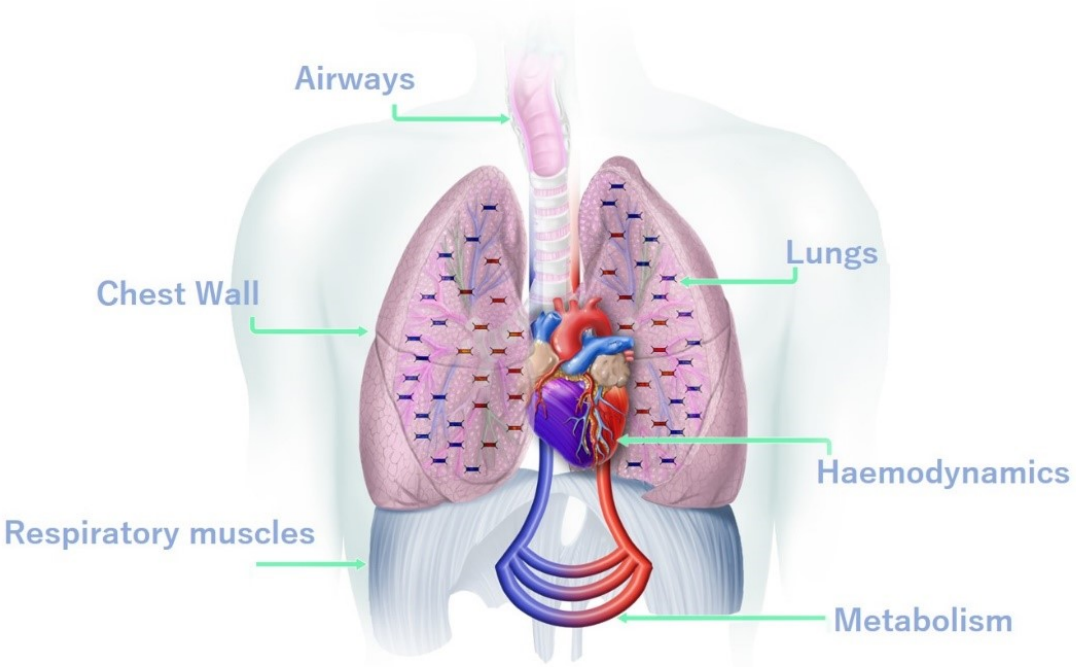

Figure 3: Summary of physiological models used in LuSi.

The airways of LuSi are modelled physically as baby nostrils, mouth and tubing leading to the entrance of the lungs.

NOTE: LuSi does not feature anatomically correct internal airways. Do not use for bronchoscopy or to train intubation.

The basic lung/chest-wall model follows the equation of motion, depicted in Figure 4.

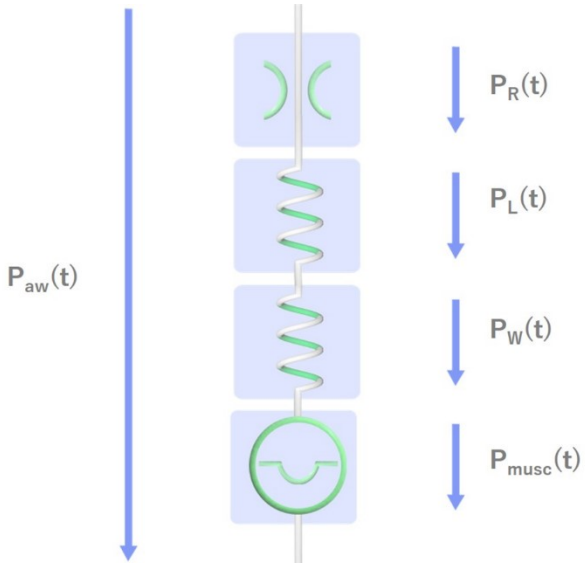

Figure 4: Mechanical model of the lungs: airway pressure P_{aw} is the sum of pressure drop across the airways P_R, pressure drop across the lungs P_L, pressure drop across the chest wall P_W and pressure created by the respiratory muscles P_{musc}.

The resulting equation of motion is known as:

$$P_{aw}(t) = \frac{dV_L(t)}{dt} \cdot R_{aw} + \frac{V_L(t)}{C_L} + \frac{V_L(t)}{C_w} + P_{musc}(t)$$

Pulmonary gas exchange is modelled according to the Riley model (see explanations further down).

Heart lung interaction is modelled phenomenologically and based on the clinical observation that pulse oximeter plethysmogram variation is caused by hypovolemia and preload/afterload deficiency of the heart, respectively.

Heart activity is modelled by ECG with standard QRS templates. Heart rate response to hypoxaemia is modelled phenomenologically.

Respiratory muscle activity is modelled either statistically or with a simple respiratory controller.

Metabolism is modelled by the trainer-set metabolic rate (CO_2 production and oxygen consumption). RQ is assumed to be 1. Exhaled levels of CO_2 are modelled mathematically and take the response time of CO_2 analysers into account (response time can be set by the trainer to show technical limitations of a given capnograph).

Arterial blood gases are modelled mathematically according to West and Wagner, assuming steady state conditions. This assumption leads to fast responses of the models which is physiologically incorrect yet very helpful in the context of simulation based training because results are readily available. If slower responses are needed, they can be created by manually adding a response time.

Numerical modelling concept

Modelling is done numerically, in two different time intervals: a fixed 5ms interval (fast rate) and variable breath interval (slow rate). ECG, pulse oximeter plethysmogram, intrathoracic pressure, pleural pressure and lung collapse and recruitment are considered real-time phenomena and calculated in 5ms intervals. Gas exchange and acid-base balance are considered "slow" phenomena and calculated every breath (see below). If no breath can be identified, for example in apnoea or if tidal volume is smaller than the dead space, calculations are done once every 5 seconds (Beck et.al).

Real-time variables calculated every 5ms

Spontaneous breathing

Spontaneous breaths are defined by timing and effort, Pmusc. The trainer can further determine the inspiratory waveform.

Timing is defined by respiratory rate with Ti being 30% of the total time (see Beck et.al., Garcia-Munoz Rodrigo et.al.). The rate can be set to vary randomly. The actual inspiratory time as measured externally by analysis of flow and pressure might be longer than the neural breath timing, depending on the measurement device employed (see Mortola et.al. who have determined Ti to be around 45% of total time).

Expiratory muscle tone can be set in percent of the inspiratory pressure level.

Central Apnoea

Trainer-set apnoea overrules the breathing pattern and stops the breathing activity altogether. In case an expiratory muscle tone is specified by the trainer, this muscle tone disappears completely during apnea.

Sighs

The inspiratory effort of a sigh is set to be twice the inspiratory effort of a breath. If the breath is set by the trainer, the Pmusc is 2*Pinsp. If the breaths are controlled by the respiratory control centre, then the Pmusc is double the previous Pmusc.

The sigh rate can be set by the trainer.

The duration of a sigh is double the Ttot set by the trainer (Ttot=60/RR) and the pressure curve form is linear increase and sinus decrease (Garcia-Munoz Rodrigo et.al.)

ECG

The ECG is modelled according to data provided by Dickinson et.el.. PQRST waves are represented. ECG wave form is a "typical" wave form and created by linear superposition of:

- Amplitudes of P, Q, R, S, T
- QRS duration (assumed to be constant at 90ms)
- PQ is taken as 100ms constant
- QT interval in sec according to Bazzet, with QT= 0.410 * $\sqrt{HR}interval$
- QRS duration was assumed to be constant 90ms

Pulse oximeter sound

The beep-sound of the pulse oximeter was modelled after a recommendation by Loeb et.al. A base frequency of 1000 Hz was chosen which changes with saturation according to the following formula:

$$f(Sat) = 132 * e^{0.0202*Sat}$$

The duration of a beep is 100ms (median of the extremes of observed by Loeb et.al.)

Pulse oximeter plethysmogram

The plethysmogram Pleth(t) in function of time is modelled by a train of 3 triangles and subsequently filtered by a low pass filter (cut-off at 100Hz).

Care is taken to avoid a notch in the signal as this is not common in neonates (Riedel).

Movement artefacts are modelled by adding the measured vertical position to the plethysmogram. To achieve this, the measured position needs to be high-pass filtered as follows:

$$y(i) = \alpha_{pos} \cdot y(i-1) + \alpha_{pos} \cdot \big(x(i) - x(i-1)\big)$$

with alpha being (RC is set to 2 seconds)

$$\alpha_{pos} = \frac{RC}{RC + \Delta t}$$

The amplitude of the Pleth(t) function is modulated by the intrathoracic pressure as described next.

Intrathoracic pressure swing and pulse pressure variation

The intrathoracic pressure that affect pulse-pressure amplitude and pulse-oximeter plethysmogram amplitude (Pleth), respectively, is calculated as $P_{cardio}(t)$ and as follows:

$$P_{cardio}(t) = \frac{V_L(t)}{C_w} - P_{musc}(t)$$

To make the Pleth in function dependent on pressure P_{cardio}, we write:

$$Pleth(t) = Pleth_{original}(t) \cdot \left(1 - k \cdot P_{cardio}(t)\right)$$

with $Pleth_{original}$ being the synthesized plethysmogram and k being a constant (which will be calculated further down below) and reflects the desired Pulse Pressure Variation.

The trainer entered parameter Pulse Pressure Variation PPV or Pulse Oximeter Plethysmogram variation POPv (in %) is defined as

$$POPv = \frac{Pleth_{max} - Pleth_{min}}{Pleth_{mean}}$$

$Pleth_{max}$ and $Pleth_{min}$ are maximal and minimal amplitudes, $Pleth_{mean}$ can be simplified and expressed as $(Pleth_{max}+Pleth_{min})/2$ – thus

$$POPv = \frac{Pleth_{max} - Pleth_{min}}{Pleth_{max} + Pleth_{min}} \cdot 2$$

The amplitude $Pleth_{max}$ is defined to be around a value of 75 (arbitrary units). The P_{cardio} shall now influence the $Pleth_{min}$ so that the PPV is reflected at a nominal tidal volume, say at 10ml for patients of 2500g weight.

$$Pleth_{min} = Pleth_{max} \cdot \frac{2-POPv}{2+POPv} \qquad \text{at} \qquad P_{cardio}(example) = \frac{10ml}{C_w}$$

for all $P_{cardio}(t)$larger than 0. For the P_{cardio}at the end of inhalation with 10ml delivered tidal volume and no muscular activity (example case), we can write

$$\left(1 - k \cdot P_{cardio}(example)\right) = \frac{2 - POPv}{2 + POPv}$$

$$1 - k \cdot \frac{10ml}{C_w} = \frac{2 - POPv}{2 + POPv}$$

$$1 - \frac{2 - POPv}{2 + POPv} = k \cdot \frac{10ml}{C_w}$$

$$k = \frac{C_w}{10ml} \cdot \frac{2 \cdot POPv}{2 + POPv}$$

or with PPV given in %

$$k = \frac{C_w}{10ml} \cdot \frac{2 \cdot POPv\%/100}{2 + POPv\%/100} = \frac{C_w}{5ml} \cdot \frac{POPv\%}{200 + POPv\%}$$

Implemented limits: Pleth will not fall below 10% of the maximal amplitude.

Implemented limits: Pleth will not be increased by spontaneous muscle efforts.

Pleural pressure

Pleural pressure $P_{pl}(t)$ is calculated as function of $V_L(t)$. Since $V_L(t)$ is referenced to FRC at ZEEP, increases in lung volume will be reflected by $P_{pl}(t)$.

Lung collapse decreases the baseline of $P_{pl}(t)$ proportionally to lung collapse as follows, with collapse volume calculated breath-by-breath (Note: $V_{collapse}$ is always positive).

$$P_{pl}(t) = \frac{V_L(t)}{C_w} - \frac{V_{collapse}(breath)}{C_w} - P_{musc}(t)$$

Cardiogenic oscillations are created as follows: a tenth of the pulse-oximeter plethysmogram is added to the $P_{pl}(t)$ signal, corresponding to a cardiogenic fluctuation of about +/-1mbar (Lichtwarck-Aschoff, JAP 2004, calculated with a volume +/-20ml in a compliance of 27ml/mbar given by their paper).

$C_w$is entred as a constant by the trainer, yet it is known that $C_w$depends on the body position (Ingimarsson et.al.). This dependency is not implemented yet.

Lung recruitment and collapse

The real-time recruitment activity is created based on the actually measured values of pressure and using the variables calculated at the slow-rate.

Recruitment happens as soon as P_{alv} > "Recruitability threshold" and is proportional to the alveolar pressure, e.g.

$$Recruitment \sim P_{alv}(i) \cdot C_r$$

$$V_{Lrec}(i) = V_{Lrec}(i-1) + \alpha_{rec} \cdot \left(P_{alv}(i) \cdot C_r - V_{Lrec}(i-1)\right)$$

V_{Lrec} is initially set to 0.

Collapse happens as soon as P_{alv}<"Collapse threshold" and as follows:

$$V_{Lrec}(i) = V_{Lrec}(i-1) - \alpha_{col} \cdot V_{Lrec}(i-1)$$

Recruitment and collapse happen throughout the breath, but the consequences for blood gases are calculated once per breath only (see below). Also the filter constants are calculated and re-calculated once per breath (see below).

Variables calculated once every breath

"Once per breath" also means "once per apnoea" in case of apnoea. Since apnoea is defined as “no-breath in 5 seconds”, the rate of calculation is at least once every 5 seconds. The following interrelationship-diagram depicts the connection between the different parameters and variables, entered by the trainer, calculated by the model or applied by the ventilator.

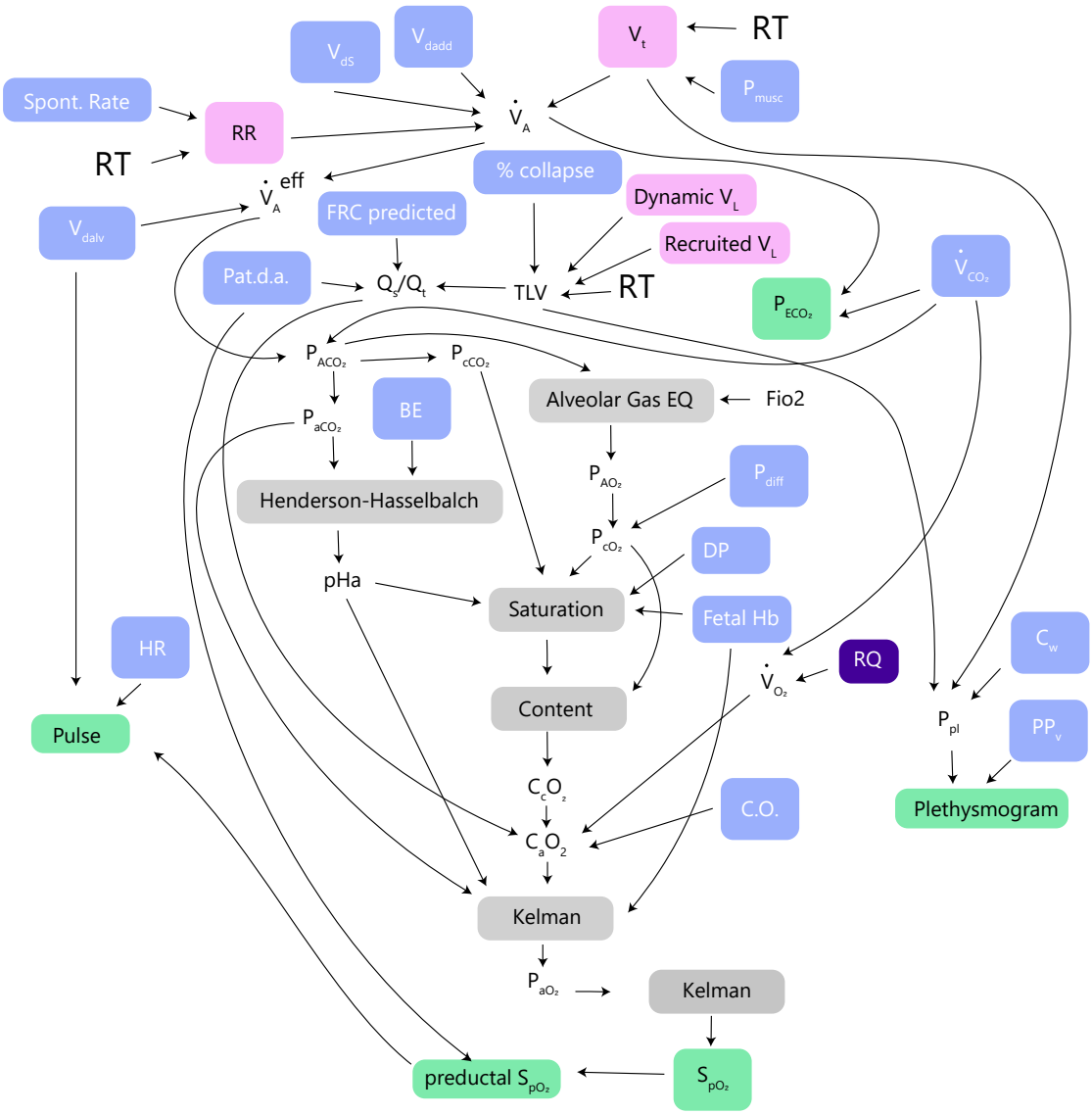

Figure 5: Interrelationship diagram of LuSi: Trainer set Parameter (light blue), measured values (pink), numeric function (grey, see literature), and calculated vital signs output (green). RT: influence of Respiratory Therapy methods such as ventilation, nCPAP, etc.

The formulas are based on steady-state conditions, albeit steady-state cannot be achieved within 5 seconds. To add some transitional appearance, results are averaged over the past 3 breaths (or apneas) and further low-pass filtered with a time constant of 20-30 seconds which yields a response time of 1-2 minutes. If slower response is needed, it is recommended to use the transition time setting on the Progression definition of LuSi^{LIFE}.

Heart rate and bradycardia

The baseline heart rate is entered by the trainer as Pulse Rate and can be set to vary randomly. This is the fundamental heart rate HRset.

Heart rate is made dependent on preductal oxygen saturation according to the model set by the user (available from Rev. 50 upward). Three response curves can be selected: linear drop, aggressive drop, conservative drop in heart rate with dropping oxygen saturation (see Figure below).

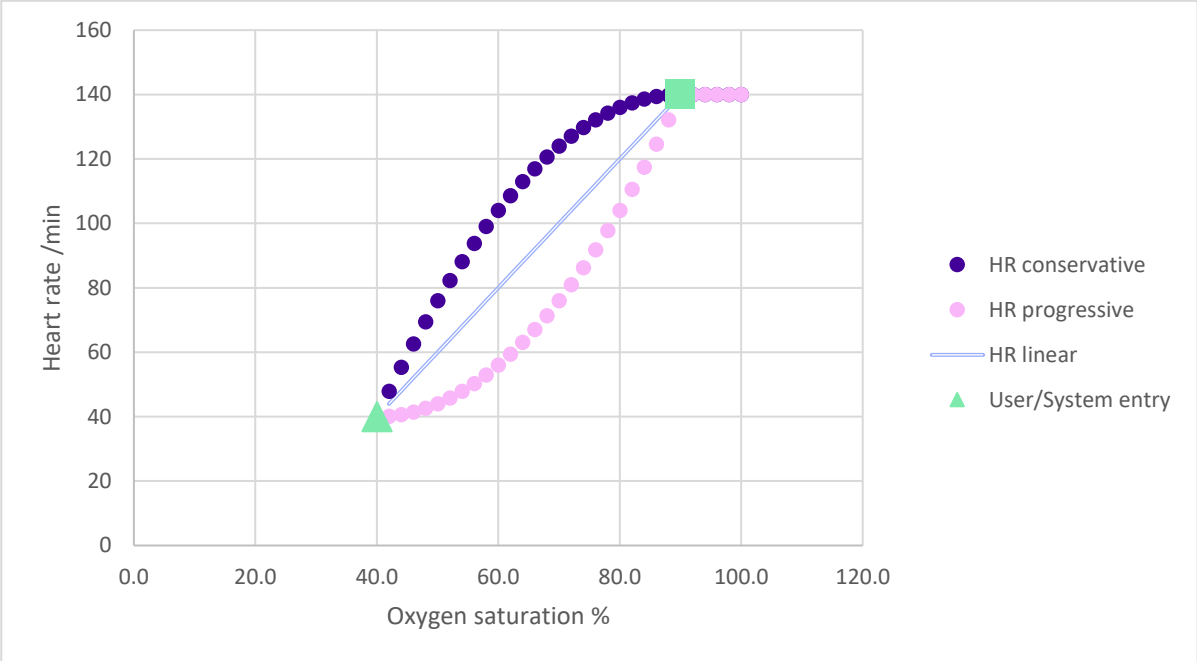

Figure 6: Heart rate as function of preductal oxygen saturation. The green rectangle (S_{pO2}^{crit} at HRset) is trainer adjustable, the green triangle is fixed at 40 /min at 40% oxygen saturation. Curves are second order polynomials for conservative or progressive drops with horizontal tangent at the green rectangle or the green triangle, respectively.

The trainer selects the following parameters:

- HRset, the basic heart rate with or without variations (vertical coordinate of green rectangle of the above Figure)
- S_{pO2}^{crit}, the oxygen saturation at which the heart rate starts to drop (horizontal coordinate of green rectangle in the above Figure)
- the characteristics of the drop, either linear, progressive or conservative

Heart rate will drop to a minimal value of 40 /min at a saturation of minimal 40% (green rectangle in the above Figure).

Heart rate is further made dependent on preductal saturation and lung expansion, i.e. breathing. If pre-ductal oxygen saturation drops and alveolar ventilation is less than 1, HR is reduced as follows:

$$HR = HRset \cdot S_{pO2}$$

with S_{pO2} being the pre-ductal value.

High intrathoracic pressures impede venous reflux and may lower the stroke volume. Clinically, the heart rate may increase to keep cardiac output constant. Such response is not implemented yet.

Dead space

Three different dead spaces are defined in LuSi: airway dead space, alveolar dead space and added dead space. All three dead spaces can be set by the trainer independent from each other.

NOTE: in neonates, the airway dead space was measured to be as low as 1.5 to 2ml/kg body weight (Thamrin et.al.) and appears to be smaller than usually predicted (2.2ml/kg predicted body weight).

Lung recruitment

The following LuSi parameters entered by the trainer govern lung recruitment and collapse:

- Expected FRC (ml):FRC_{pred}
- Degree of lung collapse (%):$\%FRC_{col}$
- Recruitability (ml/mbar): C_{rec}
- Recruitability threshold (mbar): P_{rec}
- Recruitment time constant (sec):RC_{rec}
- Lung collapse threshold (mbar):P_{col}
- Lung collapse time constant (sec):RC_{col}
- p/V curve (defined by the restrictor position)

The following variables describe the state of recruitment:

- End-expiratory lung volume $V_{bellows_EE}$ (ml), measured, adds to TLV
- Recruited Lung volume V_{Lrec} (ml), calculated
- Actual bellows restrictor position $RSTR_{act}$ (ADUs), calculated

The entered amount of collapsed lung ($\%FRC_{col}$) is related to the entered (initial) restrictor position $RSTR_{init}$:

$$V_{Lrec} = \%FRC_{col} \cdot FRC_{pred} \cdot \left(\frac{RSTR_{init} - RSTR_{act}}{RSTR_{init}}\right)$$

Initially, the restrictor position is set by the trainer, $RSTR_{init} = RSTR_{act}$, and the lung volumeTLV is reduced by the $\%FRC_{col}$, i.e. the collapsed volume. Consequently, the recruited lung volume is 0. If the lung is being recruited, the recruited lung volume grows and approaches its maximum which matches the amount of the original collapse. There is no further recruitment. In other words, the lungs cannot be recruited above FRC_{pred}.

On the other hand, TLV can be increased without recruitment, for example by external pressure (PEEP) or by dynamic hyperinflation. Such TLV-growth is not influencing the venous admixture.

The amount of recruited lung volume V_{Lrec} depends on the alveolar pressure available and is calculated every 5ms.

Technical note: Low-pass filter constants are calculated breath-by-breath as using the general form of a simple numeric low-pass filter. Applied to input alveolar pressure PA with x being the measured value, the filtered output y becomes:

$$y(i) = y(i-1) + \alpha \cdot \big(x(i) - y(i-1)\big)$$

In LuSi, the time constant for recruitment enters the equation as follows

$$\alpha_{rec} = \frac{\Delta t}{RC_{rec} + \Delta t}$$

and for collapse as follows

$$\alpha_{col} = \frac{\Delta t}{RC_{col} + \Delta t}$$

End-expiratory lung volume can be augmented because of external PEEP distending the lungs, or due to actual recruitment of previously collapsed or atelectatic alveoli.

Pure distention is continuously measured by LuSi. The end-expiratory bellows volume is termed $V_{bellows_EE}$ and is added to the entered FRC. Thus the Total Lung Volume is calculated as

$$TLV(n) = FRC_{pred} - \frac{\%FRC_{col}}{100} \cdot FRC_{pred} + V_{Lrec}(n) + V_{bellows_EE}(n)$$

with n being the nth breath. The volume of collapsed lung is

$$V_{collapse}(n) = \frac{\%FRC_{col}}{100} \cdot FRC_{pred} - V_{Lrec}(n)$$

and the calculation of TLV can be expressed as

$$TLV(n) = FRC_{pred} - V_{collapse}(n) + V_{bellows_EE}(n)$$

Shunt is calculated based on the following reasoning:

a) if no part of the lungs is collapsed ($V_{collapse}(n)=0$), there shall be no venous admixture (except true shunt, independent parameter to model extra venous admixture, for example in Persistent Pulmonary Hypertension of the Newborn)

b) if all lung is collapsed ($V_{collapse}(n)=FRC_{pred}$), there shall be 100% venous admixture

mathematically:

$$\frac{Q_s}{Q_t}(n) = \frac{V_{collapse}(n)}{FRC_{pred}}$$

for values of FRC_{pred} greater zero.

The recruited volume shall not exceed the entered degree of lung collapse $\%FRC_{col}$ and Qs/Qt shall never be negative.

The position of the restrictor needs to follow the recruited lung volume as follows:

$$RSTR_{act} = RSTR_{init} \cdot \left(1 - \frac{V_{Lrec}}{\%FRC_{col} \cdot FRC_{pred}}\right)$$

The initial position of the restrictor $RSTR_{init}$ is set by the trainer and determines the pressure volume curve at zero airway pressure (without recruitment!).

The resulting restrictor position $RSTR_{act}$ determines the actual pressure volume curve (including recruitment).

Pulmonary gas exchange

The basis model is the classical Riley three-compartment model expanded by the notion of dead space ventilation, series or anatomic dead space, possibly added dead space (apparatus dead space) and "alveolar dead space ventilation" as a percentage of alveolar ventilation $\%V_{dA}$ (see equation down below).

The following parameters are user set:

- Metabolic rate V'_{CO2}.
- Blood flow Q_t
- Size of venous pool TBV
- Anatomical dead space V_{dS}
- Added dead space V_{dAdded}
- Alveolar dead space $\%V_{dAlv}$
- Base Excess BE
- pH

- P50 = 26.8, dP50=0;
- Foetal Hb in %; if 100% then P50 is shifted by 26.8-19=7.8, if lower then the shift is proportional

All other blood chemistry is assumed to be normal and constant according to physiological text books (see further down below).

All variables are re-calculated iteratively and based on breath-by-breath analysis which yields V_t, RR, Total Lung Volume (actual/current FRC minus series dead spaces=TLV) and effective alveolar ventilation V'_{eff}. Put in iterative form, they can be formulated as follows:

$$V_A(n) = V_t(n) - V_{dS} - V_{dAdded}$$

if larger than zero, else, V_A is set to zero. V_A is zero in Apnoea in ml/min.

$$V'_A(n) = \frac{V_A(n) \cdot 60}{T_{tot}(n)}$$

Alveolar dead space ventilation is entered with $\%V_{dAlv}$ parameter and is used to calculate the effective alveolar ventilation:

$$V'_{eff}(n) = V'_A(n) \cdot \frac{100 - \%V_{dAlv}}{100}$$

Volume measurements are reported in BTPS so the actually measured volumes need to be converted into STPD. The gas equations can be formulated as follows:

$$V_{STPD} = V_{BTPS} \cdot \frac{(P_B - P_{H2O}) \cdot 273}{1013 \cdot T} = V_{BTPS} \cdot k_{STPD}$$

For Barometric Pressure of 970mbar and Temperature of 37 Degrees Celsius, the factor becomes 0.8. Thus, the volumes measured by LuSi are first converted to STPD conditions. Water Vapour is taken into account virtually, also in the blood gas calculations.

Specific gas volumes are expressed in ml-STPD.

Partial pressures P_{CO2}, P_{O2} are used instead of fractions.

Metabolism is defined by the consumption of oxygen and production of CO_2. In neonates, the relationship of V'_{CO2} to V'_{O2} varies and is about 0.9 to 1.0 (Zoppi, 1998). NOTE: the implemented model does not simulate CO_2 elimination by other paths than

the respiratory path. The oxygen flow from arterial blood to the cells (V'_{O2}) is thus assumed to equal V'_{CO2}.

The production of CO_2 is entered by the trainer, V'_{CO2}. The CO_2 flow into the venous pool and the oxygen uptake from the venous pool is assumed to be constant (metabolic rate=constant).

The arterial blood flows into the blood pool of the size given by the Total Blood Volume TBV (entered by the trainer), 86.5ml/kg in neonates (Russel et al, Simpson et al).

It is assumed that TBV is forming the venous pool.

Initial values are needed for all the partial pressures – starting values are normal values:

$P_{aCO2}=P_{ACO2}=P_{cCO2}=40mmHg$

$P_{AO2} = P_{cO2} = P_{aO2} = 100mmHg$

pHa = 7.4

To calculate the blood contents, the following constants are used (not adjustable by trainer):

$Hb = 15g/100ml_{blood}$

$Hb_{O2} = 1.34\ ml_{O2}/g_{Hb}$

Hcrit = 50%;

Oxygen solubility = $0.0030ml_{O2}/mmHg/100ml_{blood}$ (NOTE: the solubility is actually dependent on temperature but since this is only a small effect it is neglected here)

The present implementation assumes quasi steady-state.

The arterial P_{CO2} partial pressure is determined by the effective alveolar ventilation $V'_{eff}(n)$ converted to STPD:

$$P_{aCO2} = P_{ACO2} = \frac{V'_{CO2}}{V'_{eff}}$$

The arterial values of CO_2 may be affected by venous admixture. However, in normal breathing the V/Q line of CO_2 is flat and little affected by venous admixture (see Riley and Cournand, JAP 1949).

Metabolic factors which influence recirculation time are not taken into account. With V'_{CO2} and the arterial P_{CO2}, it is possible to calculate mixed venous P_{CO2}. However, a simpler approach is used according to data by McEvoy et.al. which suggeted the following relationship:

$$P_{vCO2} = \frac{P_{aCO2}}{0.8}$$

The end-tidal CO2 may be lower, depending on the degree of alveolar dead space ventilation:

$$P_{etCO2} = \frac{V'_{CO2}}{V'_A}$$

with V'_A in STPD.

The partial pressure of carbon dioxide during exhalation is termed Capnogram. LuSi creates this capnogram using the actual exhaled volume and the end tidal CO_2 (P_{etCO2}).

If the exhaled volume is smaller than the airways dead space, the exhaled CO_2 is zero.

Once the exhaled volume is larger than the airways dead space, the exhaled CO_2 approaches P_{etCO2}.

The slope of phase II is created with the response time of CO_2 analysers in mind. To achieve such an effect, CO_2 is filtered by a low-pass filter. The bandwidth is determined by the rise time (10-90%). The trainer can set different rise times to represent the effect of slow CO_2 analysers. In a pure RC circuit, the output risetime (10% to 90%) is approximately equal to 2.2 RC. The following equations are used:

The general form of a simple numeric low-pass filter applied to a variable x is used:

$$y(i) = y(i-1) + \alpha \cdot \big(x(i) - y(i-1)\big)$$

The time constant for CO_2 analysers enters the equation as follows

$$\alpha \quad = \frac{\Delta t}{RC_{CO2} + \Delta t}$$

and the expiratory CO_2 curve is filtered accordingly using the expected expiratory partial pressure as x(i).

NOTE: the actual P_{etCO2} is dependent on the alveolar dead space and the time constant of the CO_2 analyser. This double dependency is reality and part of the clinical challenge to interpret end-tidal values.

Transcutaneous P_{CO2} is expected to represent arterial P_{CO2} yet can be quite different from the real arterial P_{CO2}. Normally, there is a bias of about 1-3 mmHg (PtcCO2 higher than the arterial, 1.30 + 3.95 mm Hg according to Palmisano and Severinghaus. This component can be adjusted.

$$P_{tcCO2} = P_{aCO2} + \text{"}skin\ bias\text{"}$$

Transcutaneous CO_2 measurements may drift over time. However, according to Storre et.al., drift is very slow (around 0.1, -0.5 mmHg/h) and insignificant for the simulation experience. Therefore, drift is NOT modelled.

Transcutaneous CO_2 measurement responds slowly to changes in arterial P_{CO2}. The step response is at least 77.9 seconds (10-90%) plus a 16.8 second lag time (Kesten et.al.), but can be up to 240 seconds (Schuhmacher et. al.). The values in LuSi are low-pass filtered to create the slow response time of the mean value of 77.9 and 240 seconds plus 16.8 seconds lag time. The low-pass filter time constant RC_{tc} is roughly half the T_{90} response time, thus:

$RC_{tc} = (T_{90mean}+T_{lag})/2 = 88$ seconds

Please note that this is a rough simplification because lag time and rise time are, strictly speaking, different phenomena.

Extreme hypercapnia

LuSi employs models of steady-state, with the exception of extreme values. If arterial P_{CO2} rises above a maximum value $P_{ACO2max}$ (due to hypoventilation), it is assumed that P_{aCO2} approaches the mixed venous P_{CO2} which means, that CO_2 elimination comes to a halt. The assumption is further, that this effect starts when $P_{ACO2} > P_{vCO2}$.

The maximal arterial partial pressure P_{CO2} may be up to 150mmHg. In the literature, such spread is documented (Kaiser JR et al.)). That maximum value of 150mmHg is not achieved instantaneously but depends on many factors, including re-circulation loading with CO_2.

The turnover time of blood can be calculated as:

$$TO_{circ} = \frac{TBV}{Q_t} \times 60 \times k$$

However, equilibration for the entire body takes much longer (Gruber 1995) because not only the blood but also other body fluid compartments need to be equilibrated and, according to Gruber, takes about 3.5minutes (210seconds). If we interpret TO_{circ} as kind of time constant, the state 210 seconds correspond to about 3 time constants and one time constant is thus 210/3=70 seconds. TBV/Qt*60 is about 20seconds in normals and the factor k is used to adapt the response pragmatically.

Consequently, the TO_{circ} is used to model extreme hypoventilation responses as follows.

$$P_{vCO2}(n) = P_{vCO2}(n-1) + \alpha_{circ} \cdot \left(\frac{P_{aCO2}(n)}{0.8} - P_{vCO2}(n-1) \right)$$

In LuSi, the recirculation turno-over TO_{circ} enters the equation as follows

$$\alpha_{circ} = \frac{T_{tot}}{TO_{circ} + T_{tot}}$$

The maximum value of P_{vCO2} is 150/0.8=187.5mmHg, the minimum value is set to 10 mmHg for computational reasons.

For P_{aCO2} less than 0.8* P_{vCO2}, P_{aCO2} calculation is governed by ventilation, i.e. by the formulas given above this box.

For P_{aCO2} higher than 0.8* P_{vCO2}, P_{aCO2} calculation is governed by P_{vCO2}, i.e. set to 0.8* P_{vCO2}.

The process can be expedited by resetting the values as provided by $LuSi^{LIFE}$.

P_{AO2} is calculated according to the alveolar gas equation

$$P_{AO2} = (P_B - P_{H2O}) \cdot F_{iO2} - \frac{P_{ACO2}}{RQ}$$

With R being close to 1 in neonates, and water vapour pressure simulated, not being present, the equation becomes

$$P_{AO2} = P_{O2measured} - P_{H2O} - P_{ACO2}$$

If diffusion of oxygen across the alveolo-capillary barrier is limited, capillary blood is not equilibrating with the alveolar blood. To simulate such effects, a Diffusion Limitation factor is introduce, P_{diff}.

$$P_{cO2} = P_{AO2} \cdot \frac{100}{P_{diff}}$$

and finally the partial pressure to saturate capillary blood becomes

$$P_{cO2} = (P_{O2measured} - P_{H2O} - P_{ACO2}) \cdot \frac{100}{P_{diff}}$$

This actual capillary oxygen partial pressure is converted to a "virtual" oxygen partial pressure according to Kelman for use in a standard dissociation curve:

$$P_{O2virt1} = Kelman(P_{cO2}, P_{aCO2}, pH, Temp)$$

Shifts of the dissociation curve such as caused by an increased red cell concentration of 2,3-DPG can be accommodated by the equation derived from Roughton et.al. as follows:

$$P_{O2virt} = P_{O2virt1} \cdot \frac{26.8}{26.8 + DP50}$$

Oxygen saturation is calculated using the formula of Severinghaus:

$$S_{cO2} = \frac{100}{\frac{23400}{P_{O2virt}^3 + 150 \cdot P_{O2virt}} + 1}$$

The P50 of this saturation curve is at 27mmHg. In foetal haemoglobin, the P50 is at 19.2mmHg. Such a left-shift of the curve can easily be obtained by replacing the factor 23400 by 10000. With the percentage of neonatal haemoglobin entered by the trainer

($\%Hb_{fetal}$), the oxygen dissociation curve can be shifted proportionally using the following formula:

$$S_{cO2} = \frac{100}{\frac{23400 - \%Hb_{fetal} \cdot 134}{P_{O2virt}^3 + 150 \cdot P_{O2virt}} + 1}$$

Capillary blood is diluted by venous blood due to ventilation/perfusion inequalities and, possibly true right-left shunt. To calculate the arterial saturation in steady-state, the shunt equation can be used:

$$Q_s/Q_t = \frac{(C_{cO2} - C_{aO2})}{(C_{cO2} - C_{vO2})}$$

Shunt due to ventilation/perfusion inequalities is assumed to be proportional to atelectatic lung parts and calculated according to the following formula, using the actual collapsed lung volume and the predicted FRC (see chapter on Lung recruitment for calculation of $V_{collapse}(n)$):

$$Q_s/Q_t\,(preductal) = \frac{V_{collapse}(n)}{FRC_{pred}}$$

Qs/Qt is limited to 0, of course. In other words, if TLV is larger than the predicted FRC, shunt is assumed to be zero. This shunt pertains to the pre-ductal blood stream.

The post-ductal blood stream can be affected by partially patent ductus arteriosus in presence of pulmonary hypertension (Broadhouse et.al.). In that case, Qs/Qt is increased and the shunt becomes

$$Q_s/Q_t\,(postductal) = 1 - \frac{TLV}{FRC_{pred}} + \frac{\%TrueShunt}{100}$$

with %TrueShunt being the entered value.

The mixed venous content is unknown, yet can be calculated by using oxygen consumption V'_{CO2} as follows:

$$V'_{O2} = (C_{aO2} - C_{vO2}) \cdot Q_t = C_{aO2} \cdot Q_t - C_{vO2} \cdot Q_t$$

and C_{vO2}

$$C_{vO2} = \frac{C_{aO2} \cdot Q_t - V'_{O2}}{Q_t}$$

Combination with the shunt formula yields

$$C_{aO2} = C_{cO2} - \frac{Q_s/Q_t}{\left(1 - Q_s/Q_t\right)} \cdot \frac{V'_{O2}}{Q_t}$$

Thus knowing shunt and metabolic rate, one can calculate the arterial content of oxygen and saturation.

$$S_{aO2} = \frac{C_{aO2} - P_{aO2} \cdot Oxygen_{solubility}}{\frac{Hb \cdot Hb_{O2}}{100}}$$

A random number between +/-0.5 is added to the calculated saturation S_{aO2} to enhance realism.

The pre-ductal SpO2 is calculated with a simplified formula as follows:

$$S_{pO2} = S_{aO2} + (100 - S_{aO2}) \cdot \frac{\%TrueShunt}{100}$$

A random number between +/-1 is added to S_{aO2} and preductal S_{pO2} do add realism.

Arterial blood gases

Since P_{aO2} is not readily available, it needs to be calculated by iteration using the C_{aO2} value.

P_{aCO2} is set equal to the ideal alveolar P_{ACO2}.

pH is calculated iteratively from the P_{aCO2} and the entered BE value using the following equation:

$$BE = 0.02786 \cdot P_{aCO2} \cdot 10^{(pH-6.1)} + 13.77 \cdot pH - 124.58$$

The trainer enters BE to model the fundamental metabolic state:

- metabolic alkalosis: BE >2 mEq/L
- metabolic acidosis: BE < - 2mEq/L

Haemodynamic models

Cardiac output is assumed to be constant in a given Base Case or Escalation. Variations in cardiac output need to be done manually.

Blood pressures are also entered manually and remain constant throughout a given Base Case or Progression.

Body position

Body position of LuSi is measured as Pitch and Roll with the following quantitative assignments.

Position	Pitch	Roll
Supine	between +/-0.3	<-2
Right lateral	between +/-0.3	-1.5
Left lateral	between +/-0.3	1.5
Prone	between +/-0.3	>2
Upright	>1	any number
Heads down	<-1	any number

Simplified table:

Position	Pitch	Roll
Supine	between +/-0.3	<-2
Lateral (right or left)	between +/-0.3	-2 .. +2
Prone	between +/-0.3	>2
Upright	>1	any number
Heads down	<-1	any number

Remark: -1.1 is ambiguous, can be right lateral or left lateral.

Respiratory centre modelling

The respiratory centre is modelled as a double feedback controller working on inspiratory pressure to maintain a target volume and working on the respiratory rate to maintain a trainer-set P_{aCO2} value.

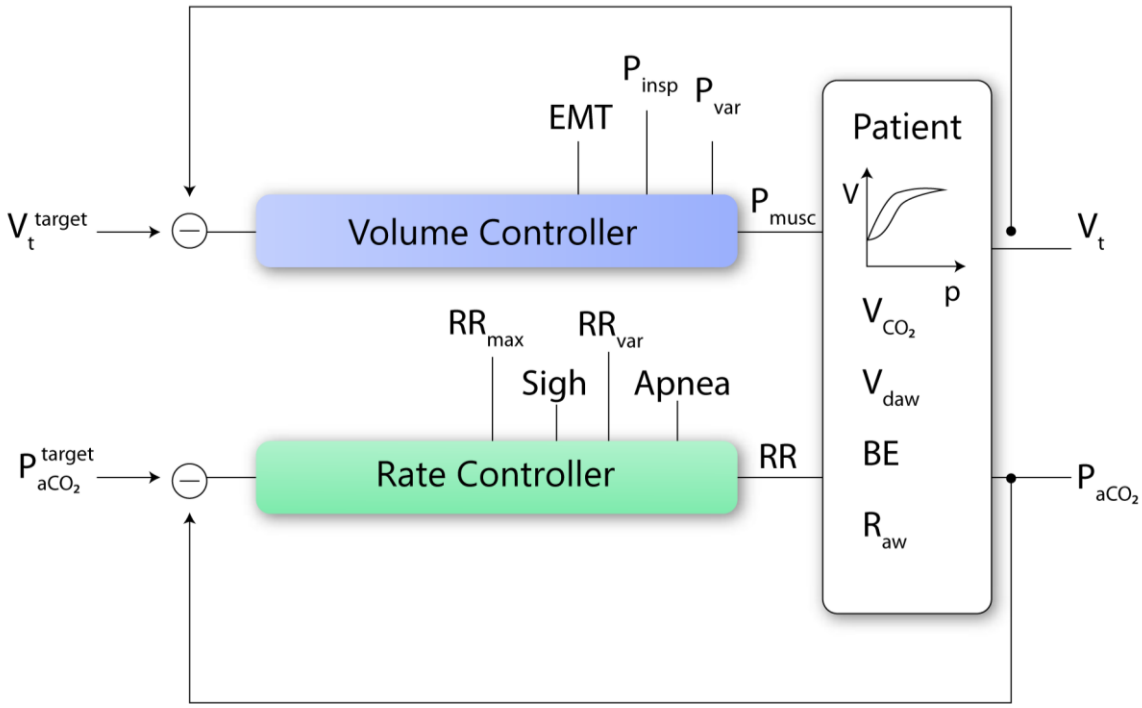

*Figure 7: Respiratory control centre: Vt target is 3*Vd, P_{aCO2} target is trainer set (Special effects menue). EMT is trainer-set Expiratory Muscle Tension, Pinsp is the trainer-set maximum pressure the controller can reach, Pvar is the trainer-set muscular pressure variation. RRmax is the trainer-set respiratory rate which is taken to be the maximum rate.*

Trainer-set values are taken to govern the control of breathing if the respiratory centre is set to "PaCO2" according to the following table:

Table 1: Central respiratory control: User Set or PaCO2

Parameter	Central respiratory control set to "User set"	Central respiratory control set to "PaCO2"
Inspiratory effort Pinsp (Respiratory Control)	Used as set	Used as maximal value to achieve the target Vt
Respiratory Rate (Respiratory Control)	Used as set	Used as maximal value to achieve the target PaCO2
PaCO2, also used for resp. control (Respiratory Control)	Not used	Used as target PaCO2
Airways dead space (Gas Exchange)	Used to calculate alveolar ventilation	Used to calculate the target Vt (target Vt=3*Vdaw, see Polgar et.al.) and alveolar ventilation

**may vary with the version of LuSi^{LIFE} used.

The controllers are I-controllers with an acceptance band of +/-1ml and +/-2mmHg for the volume and CO2 controller, respectively. The changes in the controller output are +/-C_{outVt} mbar and +/-C_{outRR} bpm for the volume and CO2 controller, respectively, with both values being between 0 and 1, randomly distribued, equal distribution.

The target value for tidal volume is set to 3 times the anatomical dead space according to Polgar et al. Rationale: predicted Vd is about 2ml/kg, tidal volumes range between 5 and 8ml/kg or 2.5-4 times Vd.

The target value for value for P_{aCO2} needs to be selected by the trainer.

The maximum muscular pressure that LuSi can develop is the trainer set value of Pinsp.

LuSi can reduce the inspiratory effort if breaths are supported by pressure support. However, the minimum muscular pressure is 3mbar.

The trainer can add variability to Pinsp – this variability is applied only if the controlled variable is within the Vt target band.

LuSi will control the arterial P_{aCO2} by varying respiratory rate up to the trainer-set spontaneous rate. Thus: set the rate high enough to enable LuSi to control P_{aCO2}. If the respiratory rate is set too low, hypercapnia will result.

The minimum respiratory rate is set to 2 bpm.

The trainer can add variability to respiratory rate – this variability is applied only if the controlled variable is within the CO2 target band.

The response time of the controller is about 1 Minute.

Effect of different settings for respiratory mechanics

The volume controller will try to achieve the set target volume (3*Vd) even if the lung mechanics change. At normal values with about 1.8ml/mbar compliance, a tidal volume of 16.5ml will be achieved with about 10mbar. If the lungs are made to collapse to reach 0.8ml/mbar compliance, the same tidal volume will need inspiratory pressures of at least 20mbar. If the setting for Pinsp is set to values below 20mbar, the tidal volume target will not be achievable and thus P_{aCO2} will rise. In response, the controller increases the respiratory rate until the set P_{aCO2} is reached.

If the respiratory rate approaches the trainer-set spontaneous respiratory rate, the controller stops increasing the rate and the trainer-set P_{aCO2} will not be achieved, resulting in respiratory acidosis.

High Frequency Ventilation modelling

CO_2 elimination

Respiratory rates between 5 and 20 per second, called HFV, are said to invoque special gas exchange mechanisms. While there is still debate about both, the clinical effectiveness as well as the physics involved, one common hypothesis is that tidal volumes less than the airway dead space create effective alveolar ventilation in HFV. The model used in LuSi follows as described by Boynton et.al.:

Conventional ventilation: Below 300 /min, alveolar ventilation is calculated as

$$V_A(n) = V_t(n) - V_{dS} - V_{dAdded}$$

High frequency ventilation: Above 300 /min, alveolar ventilation is calculated as

$$V'_A(n) = f_{HFV} * V_t{}^2(n) * k_{HFV}$$

where f_{HFV} denotes the frequency in Herz (/s) and k_{HFV} is a empirical constant set by the trainer to convert the units from ml^2/s to ml/min and to represent the response of the baby to HFV.

Babies respond to HFV in different ways and as a result, HFV is effective for some and not for others. With the trainer-set factor k_{HFV} (DCO2 for HFV factor) this response can be adjusted and “responders” as well as “non-responders” can be created.

Finally, the present model assumes that the alveolar ventilation provided by HFV is effective, i.e. that there is no alveolar dead space ventilation.

$$V'_{eff}(n) = V'_A(n)$$

For example, setting a high alveolar dead space will create hypercapnia with conventional ventilation and improved CO_2 elimination during HFV.

Oxygenation

Apart from CO_2 elimination effects, HFV will certainly create elevated mean alveolar pressures and those elevated pressures will create lung recruitment according to the recruitment models described above. In the end, HFV will have effects on both, CO_2 elimination and oxygenation of arterial blood, depending on the parameters set by the trainer.

Limitations of models used

Physiological models are limited per-se, yet there are further limitations of the physiological models as implemented. The following is a list of known limitations. The overall work-around is to create Progressions which implement responses manually, or, alternatively, to adjust the parameters during the simulation session.

First of all, blood composition is standard and constant and cannot be changed by the user. The values are set as follows:

- Hb = $15g/100ml_{blood}$
- Hb_{O2} = $1.34\ ml_{O2}/g_{Hb}$
- Hcrit = 50%;
- Oxygen solubility = $0.0030ml_{O2}/mmHg/100ml_{blood}$
- P_{H2O} = 47mmHg
- RQ=1

Second, a number of simplifications were made which are described in the following table along with possible work-around.

NOTE: While the table provides a list of the most important limitations, it is not a complete list of limitations. Others may apply depending on the circumstances used.

Limitation	Explanation/counter measure
The response time is significantly shortened compared to physiology.	This was done on purpose to allow the trainer to show steady state effects quickly. In real life, steady state may take minutes or even hours and is often not visible. The transit-times from one Escalation to another can be used to manually created longer response times of desired.
Oxygen solubility is not made dependent on body temperature.	Error is small since saturation dominates in the critically ill patient
Spontaneous Ti is fixed at 30% of total breath	According to Beck et.al. this is a reported phenomena.
Simplified venous admixture model: Qs/Qt is the quotient of Collapsed-Lung volume and expected FRC	True shunt can be added, for example, to model venous admixture through the ductus arteriosus in presence of pulmonary hypertension. This true shunt fraction remains uneffected by therapy!
Simplified model for true shunt contribution	Use for illustration only
Simplified Heart Rate response to low saturation and apnoea.	Because the main use of LuSi is to simulate lung function, less emphasis was put on the modelling of cardiovascular response. If such response needs to be simulated this can be done manually.
Pulse Pressure Variation effect on pulse oximeter plethysmogram is phenomenological only.	Pulse oximeters invariably employ sophisticated and proprietary gain-adjustment technology to obtain optimal measurement results. These gain adjustments influence amplitude variation. Since they are proprietary, modelling is virtually impossible.
Cardiac output is constant	Although the heart rate is variable, cardiac output is assumed to be constant. Cardiac output influences the shunt calculation and the lack of variability might introduce some inconsistencies. If these are not acceptable, please implement appropriate values manually, e.g. using different Progressions.

Appendix: Scientific basis

NOTE: Papers not cited above are listed because they provide reference data for neonates.

Bazett HC (1920) An analysis of the time-relations of electrocardiograms. Heart 7:353-370.

Beck J, Reilly M, Grasselli G, Qui H, Slutsky AS, Dunn MS, Sinderby CA. Characterization of neural breathing pattern in spontaneously breathing preterm infants. Pediatr Res. 2011 Dec;70(6):607-13. doi: 10.1203/PDR.0b013e318232100e. PubMed PMID: 21857389; PubMed Central PMCID: PMC3210880.

Boynton BR, Hammond MD, Fredberg JJ, Buckley BG, Villanueva D, Frantz III ID: Gs exchange in healthy rabbits during high-frequency oscillatory ventilation. J. Ppl. Physiol. 66(3):1343-1351, 1989

Broadhouse KM, Price AN, Durighel G, Cox DJ, Finnemore AE, Edwards AD, Hajnal JV, Groves AM. Assessment of PDA shunt and systemic blood flow in newborns using cardiac MRI. NMR Biomed. 2013 Sep;26(9):1135-41. doi: 10.1002/nbm.2927. Epub 2013 Feb 15. PubMed PMID: 23412748.

Dickinson DF. The normal ECG in childhood and adolescence. Heart 2005;91:1626–1630

García-Muñoz Rodrigo F, Urquía Martí L, Galán Henríquez G, Rivero Rodríguez S, Hernández Gómez A. Neural breathing patterns in preterm newborns supported with non-invasive neurally adjusted ventilatory assist. J Perinatol. 2018 Sep;38(9):1235-1241. doi: 10.1038/s41372-018-0152-5. Epub 2018 Jun 18. PubMed PMID: 29910465.

Gruber P, Kwiatkowski T, Silverrnan R, Flaster E, Auerbach C: Time to Equilibration of OxygenSaturation Using Pulse Oximetry. Acad. Emerg. Med. 1995; 2:810-815.

Ingimarsson J, Thorsteinsson A, Larsson A, Werner O. Lung and chest wall mechanics in anesthetized children. Influence of body position. Am J Respir Crit Care Med. 2000 Aug;162(2 Pt 1):412-7. PubMed PMID: 10934062.

Kaiser JR, Gauss CH, Pont MM, William DK. Hypercapnia during the first 3 days of life is associted with severe intraventricular hemorrhage in very low birth weight infants. J Perinatol 2006;26:279-285

Kelman GR. Digital computer subroutine for the conversion of oxygen tension into saturation. J Appl Physiol. 1966 Jul;21(4):1375-6. PubMed PMID: 5916678.

Kesten S, Chapman KR, Rebuck AS. Response Characteristics of a Dual Transcutaneous Oxygen/Carbon Dioxide Monitoring System. Chest 1991; 99:1211-15

Kingdon CC, Mitchell F, Bodamer OA, Williams AF. Measurement of carbon dioxide production in very low birth weight babies. Arch Dis Child Fetal Neonatal Ed. 2000 Jul;83(1):F50-5. PubMed PMID: 10873173; PubMed Central PMCID: PMC1721102.

Latzin P, Roth S, Thamrin C, Hutten GJ, Pramana I, Kuehni CE, Casaulta C, Nelle M, Riedel T, Frey U. Lung volume, breathing pattern and ventilation inhomogeneity in preterm and term infants. PLoS One. 2009;4(2):e4635. doi: 10.1371/journal.pone.0004635. Epub 2009 Feb 27. PubMed PMID: 19247491; PubMed Central PMCID: PMC2645689.

Lanteri CJ, Sly PD. Changes in respiratory mechanics with age. J Appl Physiol (1985). 1993 Jan;74(1):369-78. PubMed PMID: 8444716.

Leisman S, Gilpin K, Hanss, B: Simulation in Basic Education. in Levine A.I. et.al. (eds.), The Comprehensive Textbook of Healthcare Simulation, Springer Science+Business Media New York 2013, 557-571,DOI 10.1007/978-1-4614-5993-4_40

Lichtwarck-Aschoff M, Suki B, Hedlund A, Sjöstrand UH, Markström A, Kawati R, Hedenstierna G, Guttmann J. Decreasing size of cardiogenic oscillations reflects decreasing compliance of the respiratory system during long-term ventilation. J Appl Physiol 96: 879–884, 2004.

Lui K, Lloyd J, Ang E, Rynn M, Gupta JM. Early changes in respiratory compliance and resistance during the development of bronchopulmonary dysplasia in the era of surfactant therapy. Pediatr Pulmonol. 2000 Oct;30(4):282-90. PubMed PMID: 11015127.

Loeb RG, Brecknell B, Sanderson PM, The sounds of desaturation: a survey of commercial pulse oximeter sonifiactions. Anesth Analg 2016;122:1395–403

McEvoy JDS, Jones NL, Campbell EJM. Mixed venous and arterial PCO2. Brit Med J 1974, 687-690

Mortola JP, Fisher JT, Smith B, Fox G, Weeks S: Dynamics of breathing in infants. J Appl Physiol. 1982, 52(2):1209-1215

Palmisano BW, Severinghaus JW. Transcutaneous PCO2 and PO2: a multicenter study of accuracy. J Clin Monit 1990;6:189-195

Polgar G, Weng TR: The functional development of the respiratory system. Am Rev Respir Dis 1979, 120:625-695

Riley RL, Cournand A. "Ideal" alveolar air and the analysis of ventilation/perfusion relationships in the lung. J Appl Physiol 1949; 1: 825–847.

Roughton. Transport of oxygen and carbon dioxide. Handbook of Physiology, ect. 3, Vol.1, Ch.31, Respiration, Washington, DC, Am Physiol Soc. 1964, 767-825

Russel SJM: Blood volume studies in healthy children. Arch Dis Child 1949 88-98

Schumacher PM, Caruso ALG, Hartwich V, Luginbuehl M, Bouillon TW: Dynamic Properties of a New Transcutaneous CO2 Sensor: Fast Enough for Early Detection of Apnea? Anesthesiology 2006; 105: A477

Severinghaus JW. Simple, accurate equations for human blood O2 dissociation computations. J Appl Physiol Respir Environ Exerc Physiol. 1979 Mar;46(3):599-602. PubMed PMID: 35496.

Simpson J, Stephenson T:Regulation of extracellular fluid volume in neonates Early Human Development 34(3)1993, 179-190

Snepvangers Y, Peter de Winter JP, Burger H, Brouwers H, Van der Ent CK. Neonatal respiratory mechanics and development of bronchial hyperresponsiveness in preterm infants. Early Hum Dev. 2004 Jul;78(2):105-18. PubMed PMID: 15223115.

Stenson BJ, Glover RM, Parry GJ, Wilkie RA, Laing IA, Tarnow-Mordi WO. Static respiratory compliance in the newborn. III: Early changes after exogenous surfactant treatment. Arch Dis Child Fetal Neonatal Ed. 1994 Jan;70(1):F19-24. PubMed PMID: 8117122; PubMed Central PMCID: PMC1060982.

Stocks J, Quanjer PH. Reference values for residual volume, functional residual capacity and total lung capacity. ATS Workshop on Lung Volume Measurements. Official Statement of The European Respiratory Society. Eur Respir J. 1995 Mar;8(3):492-506. Review. PubMed PMID: 7789503.

Storre JH, Magnet FS, Dreher M, Windisch W. Transcutaneous monitoring as a replacement for arterial PCO2 monitoring during nocturnal non-invasive ventilation. Respiratory Medicine (2011) 105, 143-150

Thamrin C, Latzin P, Sauteur L, Riedel T, Hall GL, Frey U. Deadspace estimation from CO2 versus molar mass measurements in infants. Pediatr Pulmonol. 2007 Oct;42(10):920-7. PubMed PMID: 17722053.

West J, Wagner PD. Chapter 5 in Bioengineering Aspects of the Lung (Lung biology in health and disease Volume 3), ISBN-13: 978-0824763787

Zoppi G, Luciano A, Cinquetti M, Graziani S, Bolognani M. Respiratory quotient changes in full term newborn infants within 30 hours from birth before start of milk feeding. Eur J Clin Nutr. 1998 May;52(5):360-2.

neosim AG

Susenbühlstrasse 12

CH-7000 Switzerland

www.neosim.ch

LuSi is a trademark of neosim AG

Patent pending